CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050803Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Gary Chiang, MD, MPH
Review Completion Date	June 25, 2010
Established Name	Clindamycin phosphate and Tretinoin
(Proposed) Trade Name	(Veltin® Gel) Trade Name
Therapeutic Class	Antimicrobial and Retinoid
Applicant	Stiefel, a GSK Company
Formulation(s)	Gel
Dosing Regimen	Once a day
Indication(s)	Treatment of acne vulgaris
Intended Population(s)	Patients 12 years and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Stiefel, a GlaxoSmithKline Company, has submitted a complete response to the Not-Approvable Letter issued on June 10, 2005 for a topical combination product Veltin Gel, containing clindamycin phosphate 1.2% and tretinoin 0.025%. The combination product is indicated for the once daily topical treatment of acne vulgaris in patients 12 years and older.

The applicant has demonstrated that Veltin Gel is safe and effective for the treatment of acne vulgaris in subjects 12 years and older when used once daily for 12 weeks, and from a clinical perspective, it is recommended that the application be approved.

Both active ingredients have been approved individually in various formulations for marketing in the United States. Additionally, this combination is currently marketed in the United States as Ziana™ Gel (clindamycin phosphate 1.2% and tretinoin 0.025%) approved on November 7, 2006. Since the Veltin Gel application originated prior to the approval of Ziana™ Gel, this product was not considered to be a generic product, and the application is filed under section 505 (b)(2) of the Act.

1.2 Risk Benefit Assessment

Safety assessments for this application are based on clinical trial results as well as marketing experience for the two components of the proposed Veltin Gel product. This combination is currently marketed in the United States as Ziana™ Gel (clindamycin phosphate 1.2% and tretinoin 0.025%) by Medicis and was originally approved under NDA 50-802 on November 7, 2006. There is extensive safety experience with each active ingredient which is available in various approved formulations.

The most common adverse events associated with Veltin Gel in the clinical trials were dry skin, skin exfoliation, erythema, and burning. There were no deaths and no serious adverse events which were considered to be related to the proposed product.

The proposed product labeling includes warnings and precautions statements concerning antibiotic associated colitis occurring with the use of oral and topical clindamycin and the need for avoidance of ultraviolet light exposure. The label also includes information regarding the teratogenic effects of tretinoin and its effects on pregnancy. Both of these issues are contained in labeling for previously approved products.

No new safety concerns were identified in the clinical trials performed with Veltin Gel as compared to previously approved formulations of topical tretinoin, topical clindamycin phosphate or in combination.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for REMS or additional risk management steps beyond product labeling.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarketing requirements or commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed topical product, Veltin Gel, is a topical combination product consisting of clindamycin phosphate 1.2% (antimicrobial) and tretinoin 0.025% (retinoid) in an aqueous gel-based formulation, developed to treat acne vulgaris.

The original submission for this application (original proposed trade name Velac Gel) was received on August 23, 2004 by Connetics Corporation under (b) (4). Velac Gel failed non-clinical assessments for carcinogenicity (b) (4) A Not Approvable letter was issued by the Agency on June 10, 2005. The applicant re-formulated their product (b) (4) and satisfactorily completed carcinogenicity assessments for the currently proposed, to be marketed Veltin Gel formulation.

The proposed indication for Veltin Gel is for the treatment of acne vulgaris in patients 12 years and older, and is intended for once daily application. The duration of treatment in the pivotal clinical trials was 12 weeks.

2.2 Tables of Currently Available Treatments for Proposed Indications

Clindamycin and tretinoin are approved topical agents in the treatment of acne vulgaris. Depending on the severity, there are a number of other topical and systemic drugs available for the treatment of acne vulgaris. These include topical as well as oral antibiotics, retinoids of various strengths, and a combination of these drugs. The oral formulation of isotretinoin is also available for severe, recalcitrant, nodulo-cystic acne.

Table 1: Retinoids (Topical and Oral)

Medications	Dose	List of Preparations
Topical Retinoids		
Tretinoin	Once daily, at bedtime	**Creams:** 0.025%, 0.05%, 0.1% **Gels:** 0.01%, 0.025%, 0.05% **Microsphere gels:** 0.04%, 0.1% **Prepolyolprepolymer gel:** 0.025%
Adapalene	Once daily, at bedtime	**Cream:** 0.1% **Gels:** 0.1%, 0.3%
Tazarotene	Once daily, at bedtime	**Creams:** 0.05%, 0.1% **Gels:** 0.05%, 0.1%
Oral Retinoid		
Oral isotretinoin	0.5mg/kg/day, increasing to 1mg/kg/day; total dose 120 to 150mg/kg over 20 weeks	**oral**

Source: Adopted from a review of UpToDate Online 18.1 Acne Medications 2; 2010

Table 2: Topical Antimicrobials

Medications	Dose	List of Preparations
Benzoyl peroxide†	Twice daily	Multiple 2.5% to 10% gels, lotion, creams, pads, masks, cleansers
Clindamycin	Twice daily	1% gel, lotion, solution, foam
Erythromycin	Twice daily	2% gel, solution
Dapsone	Twice daily	5% gel
Sodium sulfacetamide (KLARON®)	Twice daily	10% lotion, wash, suspension, pad plus 10% urea

Source: Adapted from a review of UpToDate Online 18.1 Acne Medications 2; 2010
† Benzoyl peroxide is non-prescription

Table 3: Topical Combination Products

Medications	Dose	List of Preparations
Benzoyl peroxide 5% - Clindamycin 1% (BENZACLIN® and DUAC®)	Twice daily	Gel
Benzoyl peroxide 5% - Erythromycin 3% (BENZAMYCIN®)	Twice daily	Gel
Benzoyl peroxide 2.5% - Clindamycin 1.2% (ACANYA®)	Once daily	Gel
Clindamycin 1.2% - Tretinoin 0.025% (ZIANA®)	Once daily, at bedtime	Gel
Benzoyl peroxide 2.5% - Adapalene 0.1% (EPIDUO®)	Once daily	Gel
Azelaic acid (FINACEA® and AZELEX®)	Twice daily	20% cream, 15% gel

Source: Adapted from a review of UpToDate Online 18.1 Acne Medications 2; 2010

Table 4: Oral Antibiotics

Medications	Dose
Tetracycline	500mg twice daily
Doxycycline	50 to 100mg twice daily or 150mg once daily
Minocycline	50 to 100mg twice daily or 1mg/kg.day or the extended release formulation
Erythromycin	500mg twice daily
Trimethoprim-sulfamethoxazole	160mg/800mg once to twice daily
Azithromycin [a]	Intermittent dosing due to long drug half life; optimum regimen unknown

Source: Adapted from a review of UpToDate Online 18.1 Acne Medications 2; 2010
Note: Antibiotics are frequently used in clinical practice, but may not be approved for the indication.
[a] Katsambas A, Dessinioti C. New and emerging treatments in dermatology: acne. Dermatol Ther. 2008;21(2):86-95.

Table 5: Hormonal Agents

Medications	Dose
Combination oral contraceptives (estrogen/progestin)	Once daily
Spironolactone	25 to 200mg/day; doses of 50 to 100mg/day may be as effective as higher doses and reduce side effects

Source: Adapted from a review of UpToDate Online 18.1 Acne Medications 2; 2010

2.3 Availability of Proposed Active Ingredient in the United States

Topical clindamycin phosphate 1% was first approved in 1980 and topical tretinoin 0.025% in 1975. Clindamycin phosphate was approved as a topical gel formulation in 1987 under the trade name Cleocin® T at a strength of 1% (base equivalent), while tretinoin was

approved in a topical formulation in 1982 (Retin-A®); both were approved for the topical treatment of acne vulgaris.

Clindamycin is indicated systemically in oral and intravenous formulations for the treatment of serious infections caused by anaerobic bacteria and for susceptible strains of streptococci, staphylococci, and pneumococci, while topical clindamycin is indicated only for acne vulgaris.

Tretinoin has since been marketed for a variety of dermatoses at strengths ranging from 0.025% to 0.1% topical formulations. Topical tretinoin is indicated for the treatment of acne vulgaris and as adjunctive agent for the use in the mitigation of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin. Oral tretinoin has also been approved for use in patients with acute promyelocytic leukemia.

2.4 Important Safety Issues with Consideration to Related Drugs

The adverse event profile of each of the active ingredients is well-established through extensive historical clinical experience. Antibiotic associated colitis is a potentially serious concern with the use of clindamycin. Orally and parenterally administered clindamycin has been associated with severe colitis which may result in patient death and use of the topical formulation may result in the absorption of the antibiotic from the skin surface, and cases of antibiotic associated colitis have been reported with topical use.[1,2] Studies indicate that the toxin produced by *Clostridium difficile* is the primary cause of antibiotic associated colitis.

Topical tretinoin is labeled as a Pregnancy Category C and previously approved labeling mentions that animal teratogenicity tests have generated equivocal results. Thirty human cases of temporally associated congenital malformations have been reported during two decades of clinical use of Retin-A®. Although no definite patterns of teratogenicity and no causal association has been established from these cases, five of the reports describe rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not definitively known.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This product was developed under IND 65,369.

On August 26, 2002, a Pre-IND meeting was held with the sponsor during which the Agency provided guidance advice regarding the non-clinical and clinical development plans for their drug product. The sponsor was informed that if they wanted to rely upon the Agency's finding of safety and efficacy of a listed drug(s), they must submit an application as described under Section 505(b)(2) of the Act. In addition to the two Phase 3 clinical trials, they would to assess bioequivalence to the referenced drug(s). Finally, the Agency advised that referencing the

1 Parry MF, Rha CK. Pseudomembranous colitis casued by topical clindamycin phosphate. Arch Dermatol 1986; 122 (5): 583-4.
2 Milstone EB, McDonald AJ, Scholhamer Jr CF. Pseudomembranous colitis after topical application of clindamycin. Arch Dermatol 1981; 117 (3): 154-5.

safety data from the original European studies would be limited since the formulation in those studies was different from the US studies.

Following the Pre-IND meeting, on October 10, 2002, the sponsor submitted a protocol entitled: "A Phase III, Multicenter, Randomized, Double-Blind, Active- and Vehicle- Controlled Study of the Safety and Efficacy of Velac Gel for the Treatment of Acne Vulgaris" to open IND 65,369. This protocol was reviewed and comments were provided to the sponsor

On May 27, 2004, a Pre-NDA meeting was held to discuss further development plans for the combination drug product. A review of the trial designs for a fixed combination product for purposes of demonstrating 'proof of effectiveness' appeared to support the filing of a marketing application. The sponsor was informed that due to the chronic nature of acne vulgaris, long-term safety data would be needed in reference to the ICH E1A guidelines.

The original NDA was submitted on August 23, 2004. The applicant proposed trade name for the combination product was Velac Gel (clindamycin 1% - tretinoin 0.025%). The PDUFA date was determined to be June 25, 2005 for a standard review and a partial waiver was granted for children less than 12 years of age. The waiver was not evaluated by PeRC.

On January 27, 2005, the completed statistical evaluation of study AA81EW.7D8T.BTL: 26-Week Dermal Carcinogenicity Study in Tg.AC Mice, concluded there was statistically significant higher tumor incidence, for both genders, in each of the four dose groups compared to the untreated group. These results were brought to the Executive Carcinogenicity Assessment Committee (ECAC) on March 29, 2005.

March 29, 2005: Executive CAC Meeting

ECAC Recommendations and Conclusions:

1) The Committee noted that positive results in the Tg.AC assay indicate that a substance may be either a promoter or a complete carcinogen and concurred that the vehicle of Velac Gel alone caused a statistically significant increased incidence of skin papillomas compared to the untreated controls and that clindamycin in Velac Gel caused further significant dose-related increases in papillomas relative to the vehicle controls and untreated animals.
2) The applicant argued that the site irritation led to papilloma formation. However, the Committee is aware of other studies in Tg.AC mice in which irritation alone was not sufficient to cause papillomas. Therefore, the Committee cannot concur with the applicant's position that the increase in papillomas with vehicle and clindamycin represents a nonspecific response to irritation.

By June 2, 2006, all primary reviews were completed. A summary conclusion of the primary reviews will be presented.

Statistical Review and Evaluation of Clinical Studies (4/25/2005):

Velac Gel was studied in two Phase 3 safety and efficacy clinical trials for the treatment of acne vulgaris. Velac Gel was found to be superior to each of its active components and

vehicle. Determination of superiority of Velac Gel to its components and vehicle gel was assessed by winning on two of three lesion counts and on the Investigator's Global Assessment (IGA). The local safety profile of Velac Gel is similar to that of tretinoin with increasing levels of local skin reaction to drug product in the first two weeks of treatment followed by a reduction in skin irritation after two weeks of using the drug product. No serious adverse events or deaths attributable to the drug product were reported by study investigators.

Clinical Pharmacology and Biopharmaceutics Review (4/26/2005):

To characterize the percutaneous absorption of clindamycin phosphate and tretinoin following daily application of Velac Gel (clindamycin 1%/tretinoin 0.025%) , the applicant conducted a Phase 1, multiple dose study under maximal exposure conditions in 15 evaluable male and female patients with acne vulgaris, ages 12 to 20 years. 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 post dose, 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 pre dose 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.

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

Clinical Microbiology Review (5/09/2005):

Microbiology studies were not performed during the clinical studies. *Propionibacterium acnes* are strictly anaerobic gram-positive bacillus that has been associated with acne vulgaris. Review of the literature shows in vitro susceptibility of *P. acnes* to clindamycin; an MIC_{90} of 0.125 mg/mL for clindamycin against *P. acnes* has been reported. The results of the clinical studies, VLC.C.304 and VLC.C.305, show that Velac Gel met the primary and secondary efficacy evaluation criteria. From a microbiology perspective, the product is approvable.

Pharmacology/Toxicology Review (5/16/2005):

Topical application of Velac Gel vehicle caused an increase in papilloma formation in all treatment groups, including the vehicle control, when compared to the untreated controls in a

Tg.AC mouse model for carcinogenicity. These findings indicate the drug product is, at best, a tumor promoter, and at worst, a complete carcinogen. A 2-year mouse dermal carcinogenicity study would distinguish between the two, but neither is acceptable for a topical drug for acne, where application to initiated skin can be expected. The recommendation was not approvable based on a positive signal in the Tg.AC mouse carcinogenicity study.

Chemistry Review (6/02/2005):

Approvable action from the standpoint of chemistry, manufacturing, and control (CMC) is recommended for NDA 50-803.

Clinical Review (6/07/2005):

The reviewer found Velac Gel to be safe and efficacious. The conclusions were derived from the review of two phase 3 clinical trials and six European studies (with an older formulation of Velac gel). However, due to the positive signal in the Tg.AC mouse carcinogenicity study, the risk-benefit profile this topical acne drug that has the potential to cause cutaneous cancers does not lend itself to product approval. A Not-Approvable action was recommended for Velac Gel in the treatment of acne vulgaris because of component(s) of the vehicle that may be a carcinogen.

Not Approvable Action:

On June 10, 2005 a Not-Approvable Letter was issued to Connetics Corporation for NDA 50-803, Velac Gel (clindamycin 1% - tretinoin 0.025%). The applicant was told to reformulate the product so that the choice of vehicle will be safe and not carcinogenic. Also, a safety update as described in 21 CFR 314.50(d)(5)(vi)(b) would be required and should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

Subsequent to the Not-Approvable Letter, a guidance meeting was held on August 17, 2005 to discuss further development of their drug product for approval. (b) (4)

The applicant agreed that application of SUPAC logic for a Level 3 change is appropriate for consideration of this modification to the vehicle and that full carcinogenicity data from the reformulated product would be required prior to approval.

In order to establish clinical comparability/bioequivalence of the modified formulation to the original product, the applicant agreed to conduct a PK study comparing the systemic exposure, allowing reference to the safety and efficacy data from the original clinical trials.

Connetics Corporation was acquired by Stiefel in December of 2006. A change in ownership letter was provided to the Agency dated January 9, 2007.

On October 3, 2005, a Special Protocol Assessment (SPA) for a phase 3 study with the newly reformulated product was submitted to IND 65,369 for Agency review. In reaction to the Agency SPA comments, a meeting was held on December 18, 2007 to discuss the continued development plans for this drug product. It was concluded that a 3-arm non-inferiority design with a 7% margin would not be practical given the sample size. The applicant concluded that a 4-arm study was preferable and would submit a revised phase 3 protocol for the Agency to review. The Agency informed the sponsor that the optimal co-primary endpoint of absolute change in lesion counts is recommended rather than percent change, in line with the current acne guidance.

On July 22, 2009, the Agency received a letter to inform that Stiefel laboratory was acquired by GlaxoSmithKline.

Reviewer's comment: The applicant chose to conduct a single 4-arm trial without the original formulation, citing a trial design with a 7% non-inferiority margin would be a massive study to conduct. In addition, the main ethical flaw, associated with the non-inferiority study design is that subjects would intentionally apply a potential carcinogen in two arms of the trial(active Velac Gel and the Velac Gel vehicle). While a small study was conducted to assess the relative bioavailability of the original Velac Gel and reformulated Veltin Gel products, the Agency concurred that a large bridging study exposing subjects to a potentially carcinogenic product should not be conducted given the safety and ethical circumstances This reviewer agrees that the design of the currently conducted Phase-3 clinical trial with the reformulated drug product is sufficient, provided that efficacy and safety determinations were consistent with the findings of the original application.

October 15, 2009: Complete Response

This current submission is a Complete Response to the Not-Approvable Letter issued for NDA 50-803. The following studies were conducted with the reformulated product: a 2-year dermal carcinogenicity study in mice, a bioavailability study, a pivotal phase 3 safety and efficacy clinical study, two phase 1 safety studies and one phase 1 tolerability study.

The applicant's resubmission did not include an Integrated Summary of Efficacy (ISE) as required under 21 CFR 314.50(d)(5)(v). Efficacy data from clinical trials VLC.C.304 and VLC.C.305 for the original Velac Gel formulation were not included in the resubmission for review and are not re-reviewed in this document.

2.6 Other Relevant Background Information

Acne vulgaris is a chronic disease of pilosebaceous follicles that is multi-factorial in etiology and is characterized by the formation of two major types of acne lesions: non-inflammatory (open and closed comedones) and inflammatory (papules, pustules, and in severe

cases, nodules/nodulo-cystic lesions).[3] Acne vulgaris has its onset in puberty, but may persist past the third decade of life; severity is greater in male patients and it affects all races.

In clinical practice, effective management of acne involves the use of therapeutic agents that combat both follicular hyperproliferation and inflammation caused by *Propionibacterium acnes*. Topical retinoids are effective in the treatment of comedonal acne due to their ability to normalize follicular hyperkeratosis and prevent formation of the microcomedones. Topical retinoids also improve inflammatory acne due to a combination of intrinsic anti-inflammatory properties. In addition to targeting several aspects of acne lesion pathophysiology, it has been postulated that topical retinoids may influence skin permeability and thereby enhance penetration of the topical antibiotic. Topical retinoids can be used as monotherapy in individuals with exclusively comedonal acne, however; patients will frequently present with an inflammatory component that will benefit from the addition of concomitant antimicrobial therapy.[4] Inflammation surrounding such lesions may be produced in part by colonization with bacteria such as *Propionibacterium acnes* and *Staphylococcus epidermidis* with which clindamycin is useful in treating.

The current submitted trade name, Veltin Gel, for this combination was proposed with the assistance of the DMETS review of the original proposed trade name Velac Gel.

Velac Gel was approved for marketing in France, but was never marketed due to Yamanouchi's (original sponsor) corporate business decisions. (b) (4) [redacted]. No further information is provided in this resubmission for the French product.

Connetics was acquired by Stiefel on December 28, 2006. Stiefel is now a Glaxo Smith Klein Company.

3 Ethics and Good Clinical Practices

The Division of Scientific Investigators (DSI) was not consulted to review the conduct of the single pivotal trial (W0265-03). The clinical team, in consultation with the biostatistics reviewer, concluded that there were no irregularities in the data requiring DSI consultation.

3.1 Submission Quality and Integrity

Overall, the quality of the application is acceptable.

3.2 Compliance with Good Clinical Practices

The studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and the International Conference on Harmonization (ICH) harmonized tripartite guidelines for Good Clinical Practice and the compliance with local and FDA

3 Gollnick HP, Zouboulis CC, Akamatsu H, Kurokawa I, Schulte A. Pathogenesis and pathogenesis related treatment of acne. J Dermatol 1991;18:489-99.
4 Feldman S, Careccia RE, Barham KL, Hancox J. Diagnosis and treatment of acne. Am Fam Physician. 2004;69(9):2123-30.

regulatory requirements. The protocol and Informed Consent Forms were reviewed by the Investigational Review Board (IRB) associated with the trial sites or by consulting central IRB. Written informed consents were obtained from subjects at the first (baseline) visit.

3.3 Financial Disclosures

All investigators reported no financial interest or arrangements with the applicant.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The proposed product, Veltin Gel, is a yellowish, opaque, aqueous gel containing two commercially available, USP grade, active pharmaceutical ingredients: clindamycin phosphate (1.2% equivalent to 1% of clindamycin) and tretinoin (0.025%). Both clindamycin phosphate and tretinoin are fully solubilized in the formulation.

The CMC data have been extensively reviewed by the ONDQA reviewer, Dr. Shulin Ding. Her review concludes: This NDA has provided sufficient stability information to assure the identity, strength, purity, and quality of the drug product during the expiration dating period. All outstanding CMC deficiencies have been adequately addressed by the applicant through amendments. The NDA contains no pending CMC deficiencies. All facilities involved are in compliance with cGMP, and labels/labeling have adequate information required.

There are no recommendations for phase 4 (post-marketing) commitments or agreements necessary. Therefore, from a CMC perspective, this NDA is recommended for "Approval".

(b) (4)

This reviewer concurs with the CMC review of the carton and container labels dated June 22, 2010. The carton and container labels are presented in ***Appendix 9.4****.*

4.2 Clinical Microbiology

Microbiological studies were not performed by the applicant for clindamycin phosphate and tretinoin as a fixed-combination product. No microbiological data were submitted with this application and the applicant will not pursue an antibacterial claim for this product. The applicant, however, provided sufficient information from the literature on the clinical use of clindamycin and tretinoin as a fixed combination product for the treatment of acne. The

applicant also provided a published paper describing an *in vitro* study that involved tretinoin-clindamycin as a combined product.

The significant clinical safety issue related to topical clindamycin is the development of resistance of *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *S. aureus* for patients who may require subsequent treatment for these organisms. Consequently, the three fold increase in the presence of clindamycin resistant *S. aureus* after 12 weeks of treatement for severe inflammatory acne is of concern as this drug may not be useful to these patients should they develop uncomplicated skin and skin structure infections or community acquired pneumonia at a later date.

The Microbiology review recommends placement of this information in the Warnings and Precautions section of the Veltin Gel label. The long term goal of the Division of Anti-Infective and Ophthalmology Products is to add similar warnings to the entire class of clindamycin products which includes oral and parenteral formulations as well as topical products.

Reviewer's comment: Labeling for inducible clindamycin resistance has not yet been requested of any other approved clindamycin product to date. Since the exposure to parenteral and oral products is much greater than levels seen in topical acne products, the clinical review team recommends noting the association with antimicrobial resistance to P. acnes in the current Veltin label, but awaits consistent language to be incorporated into systemic clindamycin products before listing this as a Warning in topical clindamycin labeling. Once the specific language for oral and parenteral clindamycin product labeling is agreed upon, the entire class of topical clindamycin acne products, which would include Veltin Gel upon approval of this application, could be updated with labeling supplements at the same time for consistency across the indication. Please see Labeling Recommendations in ***section 9.2****.*

4.3 Preclinical Pharmacology/Toxicology

The non-clinical findings that formed the basis for the Not Approvable action letter (June 10, 2005) for Velac Gel (1% clindamycin, 0.025% tretinoin), was the determination of equivocal clastogenic activity in a chromosome aberration assay. When tested in a 26-week dermal carcinogenicity study in Tg.AC mice, the vehicle alone caused a statistically significant increase incidence of skin papillomas compared to untreated controls. Clindamycin in the Velac Gel vehicle caused further significant dose-related increases in papillomas relative to the vehicle controls and untreated animals.

The applicant has subsequently reformulated the original Velac Gel, (b) (4) and (b) (4) polyoxyethylene 4 monolauryl ether (POE 4) (b) (4) (b) (4) The reformulated clindamycin 1% - tretinoin 0.025% gel (Veltin Gel) contains the same concentration of active ingredients found in the previous formulation and, with (b) (4) POE 4, is identical to Velac Gel.

Given the similarities between Velac Gel and the newly reformulated Veltin Gel, the pharmacology, pharmacokinetics, and toxicology are expected to be similar and the supportive non-clinical information previously reviewed for Velac Gel (chronic toxicology, genetic

toxicology, reproductive and developmental toxicology) stands in support of the reformulated Veltin Gel.

The non-clinical deficiencies noted in the 2005 action letter, specifically the positive carcinogenicity signal in the Tg.AC mouse dermal carcinogenicity model, have been addressed by reformulation (b) (4). Clindamycin at the clinical concentration (1%) in the reformulated vehicle has been tested in a 2-year dermal carcinogenicity study (NPB00012) with adequate negative results. Consistent with the Agency's guidance (FDA Minutes of the Post-Action Meeting, September 12, 2005), the applicant has obtained the right of reference to a 27-week dermal carcinogenicity study of clindamycin phosphate (0, 0.5, 1, and 2%) in a different gel-formulation to provide evidence that clindamycin does not display carcinogenic potential across a range of concentrations bracketing the clinical concentration of the Veltin Gel product. The testing of the clinical clindamycin concentration in the vehicle and the long history of safe use of clindamycin are considered to be sufficient to support its use in the Veltin Gel.

The conclusion of the non-clinical review team is that Veltin Gel for the treatment of acne vulgaris is approvable from a pharmacological/toxicological perspective.

4.4 Clinical Pharmacology

After the "Not Approvable" action letter dated June 10, 200, the applicant proposed to establish a clinical bridge between Veltin Gel (new formulation) and Velac Gel (old formulation) in order to reference the previously submitted safety data. This was to be completed through a pharmacokinetic study to show bioequivalence of the two products. 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 Veltin Gel or Velac Gel. The results showed that with Veltin Gel, the exposure of clindamycin and clindamycin sulfoxide increased about two times while the exposure of tretinoin was comparable with Velac Gel. This study concluded that Veltin Gel was not bioequivalent to Velac Gel.

These findings were evaluated by the review teams, and it was determined that the non-clinical studies were dosed at sufficient excess levels to support this increase in bioavailability of clindamycin and clindamycin sulfoxide. There were no adverse events suggestive of systemic toxicity reported by any subjects in this study or in the phase 3 (W0265-03) safety and efficacy study. Hence, this suggests that an increase in clindamycin and clindamycin sulfoxide exposure with Veltin Gel should not result in any clinically meaningful safety concerns above the reference treatment. Indeed the clinical trial safety information supports this conclusion.

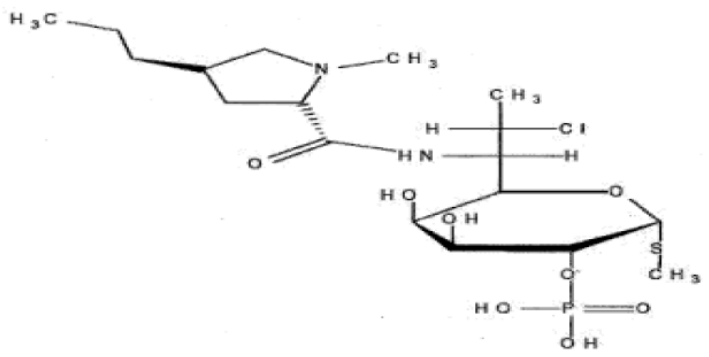
From a Clinical Pharmacology standpoint, the applicant met the requirements under 21 CFR 320 and the application is acceptable provided the recommended labeling comments are adequately addressed by the applicant.

4.4.1 Mechanism of Action

Veltin 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

bactericidal antibiotic belonging to the class of lincosamides with anti-inflammatory activity that is used to treat inflammatory lesions of acne caused by *Propionibacterium acnes* and *Staphylococcus epidermidis*. The chemical structure of clindamycin phosphate is shown in **Figure 1**.

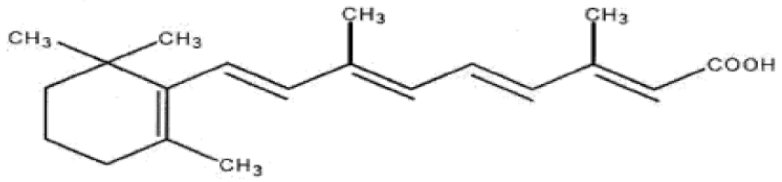
Figure 1: Structure of clindamycin phosphate



Clindamycin inhibits bacterial protein synthesis by irreversibly binding to the 50S subunit of the bacterial ribosome. Clindamycin phosphate is biologically inactive and is rapidly hydrolyzed to active clindamycin sulfoxide *in-vivo*.

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

Figure 2: Structure of tretinoin



Tretinoin (all-trans-retinoic acid) is a natural oxidative metabolite of vitamin A (retinol). It is normally found at low concentrations (4-14 nmol/L) in the human circulation and bound to albumin. Tretinoin is a comedolytic agent and its effectiveness has been attributed to its ability to reduce follicular hyperkeratinization and inhibit inflammatory reactions. It has also been reported that tretinoin not only normalizes hyperkeratinization, but also promotes drainage of pre-existing comedones and inhibits the formation of new ones. Follicles become unplugged and the environment within the follicles becomes less favorable for the growth of *P. acnes* and the consequent production of proinflammatory mediators.

4.4.2 Pharmacodynamics

The activity of clindamycin, clindamycin sulfoxide (active metabolite), and tretinoin have well characterized mechanism of actions. Please see above **section 4.4.1** for these descriptions.

4.4.3 Pharmacokinetics

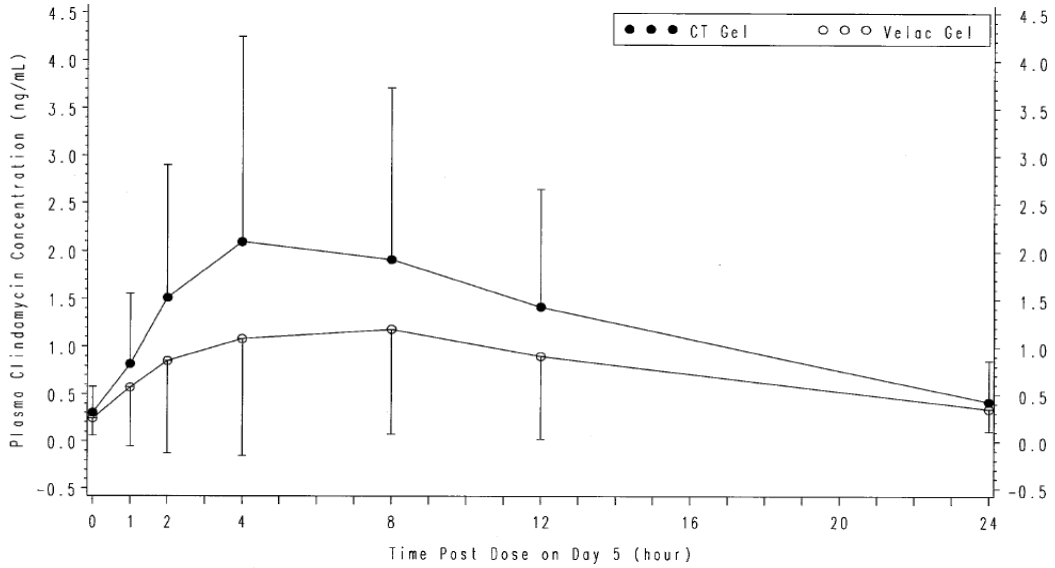
The bioavailability of clindamycin and tretinoin in product gel vehicle was evaluated individually in subjects with acne vulgaris following multiple applications of Veltin Gel or Velac Gel under maximal use conditions in clinical study W0265-02. This was a single-center, randomized, open-label, comparative bioavailability study in male and female subjects 12 years of age or older with acne vulgaris. Thirty-four subjects were enrolled and randomized 1:1 (Veltin 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).

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 Veltin 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.

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 Veltin 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 3**.

Figure 3: **Plasma clindamycin concentration (Mean ± SD) vs. time pre-dose and post-dose on day 5**



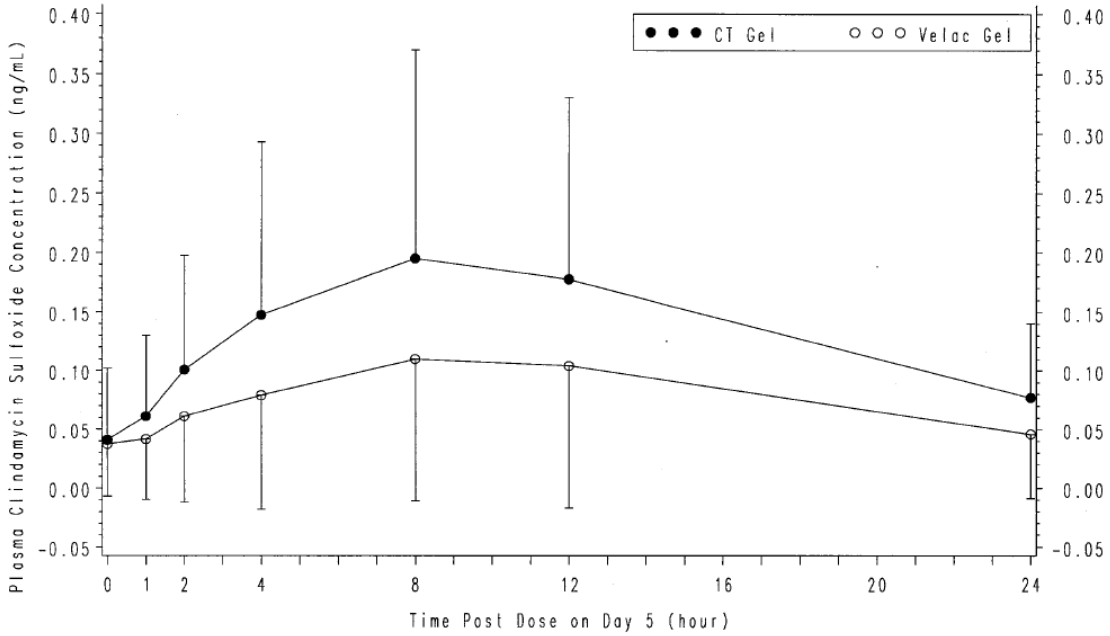
Source: Applicant's submission

After 5 daily applications, in the Veltin 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, within Velac Gel group, all plasma clindamycin concentrations were ≤ 4.93 ng/mL.

Plasma Concentrations of Clindamycin Sulfoxide:

The plasma clindamycin sulfoxide concentrations were much lower than plasma clindamycin concentrations. There were 2 subjects in the Veltin 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. Plasma concentrations peaked around 8 to 12 hours post dose. The average clindamycin sulfoxide exposure with Veltin Gel was found to be two times higher than the one obtained following Velac gel exposure. **Figure 4** below shows the average clindamycin sulfoxide concentrations pre and post dose on day 5.

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

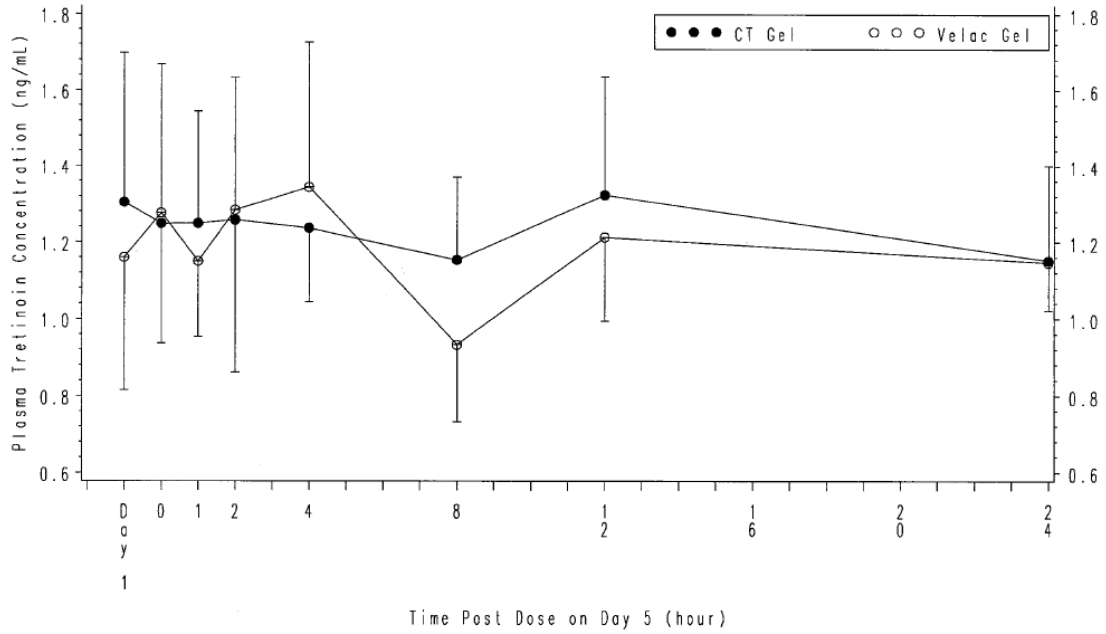


Source: Applicant's submission

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



Source: Applicant's submission

Statistical Analysis of Pharmacokinetic Parameters:

The specific aim of this analysis was to show that the levels of clindamycin, clindamycin sulfoxide and tretinoin were not different between Veltin Gel and Velac Gel.

However, the results showed that the overall systemic exposure to clindamycin and clindamycin sulfoxide is about two times higher with Veltin 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 6** 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 the higher clindamycin and clindamycin sulfoxide exposure with Veltin Gel, the Pharmacology/Toxicology team was asked to comment on the adequacy of the submitted non-clinical data with regards to the greater exposure of clindamycin and clindamycin sulfoxide. The 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 non-clinical studies were dose at sufficient excess to cover this increase in bioavailability."*

Table 6: 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

Source: Clinical Pharmacology Review by Chinamy Shukla Ph.D

Furthermore, in this study (Study W0265-02), 1 subject in the Veltin Gel group reported 2 mild adverse events. 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.

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.

Reviewer's comment: The studies conducted for the development of Veltin Gel were considered appropriate from a Clinical Pharmacology perspective. Additionally, the increase in clindamycin and clindamycin sulfoxide exposure does not result in any clinically meaningful safety concern for Veltin Gel, and no excess adverse events was demonstrated in the clinical trial with the reformulated drug product (see ***section 7.5****, Other Safety Explorations).*

5 Sources of Clinical Data

Efficacy of Veltin Gel is derived from the conduct of one pivotal safety and efficacy trial (W0265-03) conducted in sites across the US (27 sites), Canada (3 sites), and Belize (2 sites). Efficacy is supported by the two previously submitted phase 3 trials (VLC.C.304 & VLC.C.305) with the original formulation of Velac Gel, which differs from the to be marketed Veltin Gel (b) (4) [redacted]. This phase 3 trial enrolled 1,656 subjects randomized to Veltin Gel, clindamycin gel, tretinoin gel, or vehicle gel.

The safety of Veltin Gel is based on results of one phase 1 tolerability and comparability study, two phase 1 dermal safety studies, a phase 2 bioavailability study, and a phase 3b tolerability study with benzoyl peroxide. In addition, the safety profile will include the

experience from the previously reviewed Velac Gel formulation that includes two US phase 3 trials (VLC.C.304 & VLC.C.305), along with several European studies.

5.1 Tables of Studies/Clinical Trials

Table 7: Listing of Studies Conducted with Veltin Gel

Type of Study	Study Identifier	Title & Design	Total Number of Subjects	Duration of Treatment
Safety and Efficacy (Phase 3)	W0265-03	Multicenter, Randomized, Double-blind, Active and Vehicle-controlled Study of the Safety and Efficacy of Clindamycin-Tretinoin Gel versus Clindamycin Gel versus Tretinoin Gel versus Vehicle Gel in Subjects with Acne Vulgaris	1656	12 Weeks
Bioavailability (Phase 2)	W0265-02	A Randomized, Open Label Study to Evaluate the Bioavailability (Absorption) of Clindamycin Phosphate and Tretinoin in Subjects with Acne Vulgaris Using Veltin Gel or Velac Gel	34	5 Days
Tolerability (Phase 1)	CTG.103	Multicenter, Open-Label Study of Irritation Potential of Clindamycin 1%-Tretinoin 0.025% Gel in subjects with Mild to Moderate Facial Acne Vulgaris	30	8 Weeks
Tolerability (Phase 3b)	W0265-306	Multicenter, Assessor-blinded Study of the Tolerability of Clindamycin 1%-Tretinoin 0.025% Gel Used in Conjunction with Benzoyl Peroxide 4% Wash in Subjects with Mild-to-Moderate Facial Acne Vulgaris	61	4 Weeks
Safety (Phase 1)	W0265-103	Evaluator-Blinded, Randomized, Placebo-Controlled, Phase 1 Clinical Trial Evaluating the Phototoxic Potential of Topical Applied Clindamycin 1.0% Tretinoin 0.025% Gel (Veltin Gel) in Healthy Volunteers	37	24 Hours
Safety (Phase 1)	W0265-104	Single-Center, Evaluator Blinded, Randomized, Placebo-Controlled, Phase 1 Clinical Trial Evaluating the Photoallergic Potential of Topically Applied Clindamycin 1.0% Tretinoin 0.025% Gel (Veltin Gel) in Healthy Volunteers	64	7 x 24 Hours

Source: Applicant's submission

Table 7 lists all studies conducted with the reformulated Veltin Gel. Additionally, two phase 3 clinical trials previously conducted with the previous formulation, Velac Gel, will supplement the safety database for the review of Veltin Gel.

Table 8: Phase 3 Trials Conducted with Velac Gel (Old Formulation)

Type of Study	Study Identifier	Title & Design	Total Number of Subjects	Duration of Treatment
Safety and Efficacy	VLC.C.304	Randomized, Double-Blind, Parallel Group, Active- and Vehicle-Controlled Multicentered Evaluation of the Safety and Efficacy of Velac Gel in the Treatment of Acne Vulgaris	1083	12 Weeks
Safety and Efficacy	VLC.C.305	Randomized, Double-Blind, Parallel Group, Active- and Vehicle-Controlled Multicentered Evaluation of the Safety and Efficacy of Velac Gel in the Treatment of Acne Vulgaris	1136	12 Weeks

Source: Applicant's submission

5.2 Review Strategy

This review of efficacy for the newly formulated, Veltin Gel, will focus on the one pivotal phase 3 trial (W0265-03) with 1,656 subjects. Five other supporting studies; including three phase 1 safety studies, a phase 2 bioavailability study, and a phase 3b tolerability study are completed with the newly formulated Veltin® Gel and will be review separately.

The previous formulation, Velac Gel, review evaluated two pivotal phase 3 trials (**Table 8**) conducted in the United States (VLC.C.304 & VLC.C.305) and six safety and efficacy European studies conducted by the previous sponsor (Yamanouchi) in Europe. The Velac Gel efficacy will not be reviewed in this document, as it has been previously reviewed during the 2005 original cycle, but will be referenced for supporting evidence in the review of Veltin Gel.

The safety database will include all subjects exposed to the combination product of either formulation. The safety outcomes in the Veltin Gel trial were similar to the outcomes in the Velac Gel trials and the three trials had similar design and enrolled similar subject populations.

The applicant has submitted non-clinical and clinical literature references in support of the use of clindamycin and tretinoin in acne vulgaris. These are literature reports that discuss safety, efficacy, pharmacokinetics of both products, and compare the use of these products to other products used to treat acne vulgaris. This submitted literature forms the basis for a 505(b)(2) application.

5.3 Discussion of Individual Studies/Clinical Trials

Phase 3 Clinical Trial W0265-03

Title: A Phase 3 Multicenter, Randomized, Double-Blind, Active and Vehicle-Controlled Study of the Safety and Efficacy of Clindamycin – Tretinoin Gel versus Clindamycin Gel versus Tretinoin Gel versus Vehicle Gel in Subjects with Acne Vulgaris.

A total of 32 investigators screened and enrolled subjects in 27 centers located in the United States, 3 centers in Canada, and 2 centers in Belize. A total of 1,656 subjects were enrolled and 1,649 were analyzed in the intent-to-treat (ITT) analysis set.

Study population: Male and female subjects who were at least 12 years of age with acne vulgaris.

Inclusion Criteria

1. Male or female subjects 12 years of age or older in good general health.
2. An ISGA score of 2 or greater at baseline (**Figure 7**).
3. Subjects must have had both:
   - A minimum of 17 but no more than 40 facial inflammatory lesions (papules plus pustules), including nasal lesions;
   - A minimum of 20 but not more than 150 facial non-inflammatory lesions (open and closed comedones), excluding nasal lesions.
4. Females must have had a negative pregnancy test prior to enrollment in the study. If sexually active, 1 of the following combinations of contraception must have been practiced from baseline to the last study visit:
   - Hormonal contraception started more than 12 weeks prior to baseline/day 1;
     OR
   - Two forms of non-hormonal contraception.

   Hormonal contraception included oral contraception, injectables or implantable methods. Non-hormonal contraception included intrauterine devices or properly used barrier contraception (e.g., condoms or cap). A barrier contraceptive with spermacide was considered 2 forms of non-hormonal contraception. A woman of childbearing potential was defined as one who was biologically capable of becoming pregnant. Abstinence was considered a medically acceptable form of contraception.
5. The ability and willingness to follow all study procedures, attend all scheduled visits, and successfully complete the study.
6. The ability to understand and sign written informed consent form, which must have been obtained prior to applying the study product. Subjects under the legal age of consent in the state where the study was conducted must have provided assent and have had the written informed consent of the parent or guardian.

7. In the US, the ability to understand and sign a Heath Insurance Portability and Accountability Act authorization form which permitted the use and disclosure of the subject's individually identifiable health information.

Exclusion Criteria

1. Any subject who had participated in any previous phase 1 through 3 Velac Gel study.
2. Any nodulo-cystic lesions at baseline.
3. Pregnant or breast-feeding.
4. History or presence at entry of regional enteritis or inflammatory bowel disease (e.g., ulcerative colitis, pseudomembranous colitis, chronic diarrhea, or a history of antibiotic associated colitis, bloody diarrhea) or similar symptoms.
5. Used topical antibiotics on the face or used of systemic antibiotics within the previous 2 weeks.
6. Used topical corticosteroids on the face or used systemic corticosteroids within 2 weeks prior to entry. Use of inhaled, intra-articular or intra-lesional steroids other than for facial acne was acceptable.
7. Used systemic retinoids within the previous 3 months.
8. Treatment with estrogens, including oral, implanted, and topical contraceptives, androgens, or anti-androgenic agents for 12 weeks or less immediately prior to starting application of the study product. Subjects who had been treated with estrogens, as described above, androgens, or anti-androgenic agents for more than 12 consecutive weeks prior to starting application of the study product were allowed to enroll as long as they did not expect to change dose, drug, or discontinue use during the study.
9. Used topical anti-acne medications (e.g., benzoyl peroxide, retinoids, azelaic acid, resorcinol, salicylates, etc) within the 2 weeks prior to entry.
10. Used astringents, toners, and skin cleansers for less than 2 weeks prior to the start of the study. The subject must have had an established regimen for at least 2 weeks prior to enrollment that was not anticipated to change during the conduct of the entire study.
11. Concomitant use of the following types of facial products: abradants; facials; peels containing glycolic or other acids; masks; washes or soaps containing benzoyl peroxide or salicylic acid; non-mild facial cleansers; or moisturizers that contained retinol, salicylic acid or α- or β- hydroxy acids.
12. Concomitant medications that are reported to exacerbate acne (e.g., mega-doses of certain vitamins, such as vitamin D [>2000 IU every day] and vitamin B12 [>1000 mcg every day], haloperidol, halogens such as iodide and bromide, lithium, hydantoin, and phenobarbital) as these may have impacted efficacy assessments, Multivitamins, iron supplements, and folate were acceptable.
13. Facial procedures (blue light, chemical or laser peel, midrodermabrasion, etc) performed by an esthetician, beautician, physician, nurse, or other practitioner, within the 4 weeks prior to entry or during the conduct of the study.
14. Concomitant use of tanning booths or sunbathing.
15. Known hypersensitivity or previous allergic reaction to any of the active components, lincomycin, retinoids, or excipients of the study product.

16. A significant medical history of or were currently immunocompromised.
17. Used any investigational therapy with in the 4 weeks prior to entry.
18. Current drug or alcohol abuse at the time of entry (drug screening was not required).
19. Any other condition which, in the judgment of the investigator, would have put the subject at unacceptable risk for participation in the study.

Study Plan

All eligible subjects were randomized (2:2:2:1) to received Veltin Gel, clindamycin gel, tretinoin gel, or vehicle gel. Subjects applied the study product every evening for the duration of the study. Subjects were instructed to wash their faces with a mild soap and allow the areas to dry fully before applying study product. The study product was to have been applied prior to the application of any other skin products that the subject habitually used. Subjects were instructed to apply the study product in sufficient quantity to cover the entire face (including the forehead, nose, cheeks, and chin) and were allowed to use their assigned products on the neck, upper chest, and/or upper back if desired, although these areas were not evaluated. Subjects were instructed to continue study product daily to entire face until the end of the 12-week period even in the event that a subject's facial acne cleared prior to the week 12 visit.

Concomitant Medications

Other than the study product, no concomitant treatments for acne (facial or other body areas) were allowed. Astringents and toners may have been used as long as the subject had been using the same regimen for at least 2 weeks prior to the start of the study and they continued the same regimen during the conduct of the study. The use of medications for other medical conditions (e.g., hypertension, diabetes, acute bacterial or viral infections, etc.) and of multivitamins, iron supplements, and folate was allowed during this study. Subjects may have taken systemic antibiotics (with the exception of clindamycin, erythromycin, tetracycline, minocycline, and doxycycline) for up to 4 consecutive weeks for reasons other than the treatment of acne. Subjects also may have taken a short course (7 days) of systemic non-steroidal anti-inflammatory drugs for reasons other than the treatment of acne.

Figure 6: Schedule of Assessments

Visit	Visit 1 Baseline	Visit 2 Week 2	Visit 3 Week 4	Visit 4 Week 8	Visit 5 Week 12 / Early Termination [a]
Day	1	15±3	29±5	57±5	85±5
Written informed consent	X				
Medical history / review of systems	X				
Vital signs	X				X
Height and weight	X				
Concomitant medications	X	X	X	X	X
Adverse events [b]	X	X	X	X	X
Lesion counts [c]	X	X	X	X	X
Local tolerability assessments [c,d]	X	X	X	X	X
Investigator's Static Global Assessment [c]	X	X	X	X	X
Subject Global Assessment	X	X	X	X	X
Urine pregnancy test [e]	X				X
Weigh and dispense study product	X	X	X	X	
Collect and weigh study product		X	X	X	X

[a] For subjects who discontinued early from the study, the visit 5 procedures were completed.
[b] AEs were captured from the time the subject provided consent to the time the subject administered the last application of study product, inclusive. Study product-related AEs and serious AEs that were ongoing at the end of the application period were followed as described in section 9.5.3.
[c] The same investigator or designee performed all acne assessments for each subject at every visit whenever feasible.
[d] The investigator graded and recorded the severity of the signs (erythema, dryness, and scaling) and recorded the subject's assessment of the symptoms (burning and itching) of local tolerability at each visit.
[e] Pregnancy testing was mandatory for all female subjects regardless of childbearing potential.

Efficacy Measurements

The evaluation of co-primary endpoints is the proportion of subjects who had a minimum 2-grade improvement in the ISGA score from baseline from baseline to week 12 (end of study) and the absolute change in lesion counts (total, inflammatory, non-inflammatory) from baseline to week 12.

Investigator's Static Global Assessments (ISGA) and lesion counts were performed by the same investigator for each individual subject if feasible. The assessors were trained to conduct the ISGA and lesion counts to ensure consistency within and across investigational centers.

Figure 7: Investigator's Static Global Assessment (ISGA) Scale

0	Normal, clear skin with no evidence of acne vulgaris.
1	Skin almost clear: rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red) requiring no further treatment in the Investigator's opinion.
2	Some non-inflammatory lesions are present, with few inflammatory lesions (papules and pustules only, no nodulo-cystic lesions).
3	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be 1 small nodulo-cystic lesion.
4	Inflammatory lesions are more apparent: many comedones and papules/pustules, and there may or may not be a few nodulo-cystic lesions.
5	Highly inflammatory lesions predominate: variable number of comedones, many papules/pustules, and nodulo-cystic lesions.

Lesion counts were conducted at baseline and weeks 2, 4, 8, and 12, by trained study personnel. They assessed the inflammatory (pustules, papules, nodules) and non-inflammatory (open and closed comedones) for each subject. Each type of lesion was counted separately; the lesion counts were taken from the face defined as the hairline edge to the mandibular line; inflammatory lesions on the nose were included in the evaluation while non-inflammatory lesions on the nose were excluded. Total lesions were calculated as the sum of the inflammatory and non-inflammatory lesion counts.

Secondary measurements included percentage change in lesion counts from baseline to week 12, proportion of subjects with a Subject Global Assessment (SGA) score of 0 to 1 at week 12, and proportion of subjects with an ISGA score of 0 or 1 at weeks 12.

Figure 8: Subject Global Assessment (SGA) Scale

0	My face is basically free of acne, with only an occasional blackhead and/or whitehead.
1	My face has several blackheads and/or whiteheads and small pimples, but there are no tender deep-seated bumps or cysts.
2	My face has several to many blackheads and/or whiteheads and small to medium-sized pimples, and may have one deep-seated bump or cyst.
3	My face has many blackheads and/or whiteheads, many medium to large-sized pimples, and perhaps a few deep-seated bumps or cysts.
4	My face has blackheads and/or whiteheads, and several to many medium to large-sized pimples and deep-seated bumps or cysts dominate.

Tertiary endpoint measured the proportion of subjects who had a minimum 2-grade improvement in ISGA score from baseline to weeks 2, 4, and 8. Additionally, measurements of time to 50% reduction in total lesion counts, percentage and absolute change in lesion counts

from baseline to weeks 2, 4, and 8, and the proportion of subjects who had SGA and ISGA scores of 0 or 1 at weeks 2, 4, and 8 will encompass the tertiary endpoint assessments.

Safety Assessments

Safety assessments included adverse events (AE), changes from baseline to week 12 in vital signs (blood pressure, pulse, and temperature), subject local tolerability assessments (scaling, dryness, erythema, burning and itching), and application duration and reason for study withdrawal. All AEs that occurred during the study were recorded and classified using the Medical Dictionary of Regulatory Activities (MedDRA *version* 11.0).

Subject local skin tolerability assessments were completed at the baseline and all subsequent study visits (weeks 2, 4, 8, and 12). Each assessment was graded on a scale from 0 to 5, 0 being normal and 5 being prominent and dense. Itching and burning was also assessed from a scale of 0 to 5.

Scaling, Erythema, Dryness

None	0	Normal
Trace	1	Mild and localized
Mild	2	Mild and diffuse
Moderate	3	Moderate and diffuse
Marked	4	Moderate and dense
Severe	5	Prominent and dense

Itching and Burning

None	0	Normal, no discomfort
Trace	1	An awareness, but no discomfort and no intervention required
Mild	2	A noticeable discomfort that causes intermittent awareness
Moderate	3	A noticeable discomfort that causes continuous awareness
Marked	4	A definite discomfort that causes continuous awareness and interferes occasionally with normal daily activities.
Severe	5	A definite continuous discomfort that interferes with normal daily activities.

Data Analysis

Sample size was determined based on the true effect of Velac Gel phase 3 trials (VLC.C.304 and VLC.C.305). Using these estimates, 472 subjects in each of the active study product groups and 236 subjects in the vehicle gel product group were considered sufficient to demonstrate significance in the co-primary endpoints with 80% power using a 2-sided *Type I error* rate of 0.05.

Subjects evaluated their facial acne at baseline and weeks 2, 4, 8, and 12 (**figure 8**).

In order to demonstrate success,Veltin Gel must have been superior to clindamycin gel, tretinoin gel, and vehicle gel (2-sided, $P<0.05$ for each comparison) at week 12 in the co-primary outcomes. The tests for superiority were based on an analysis of covariance (ANCOVA) model with terms for treatment, center, baseline evaluation, and treatment-by-center interaction.

6 Review of Efficacy

Efficacy Summary

The efficacy of Veltin Gel was demonstrated in a pivotal, phase 3 clinical trial (W0265-03) conducted with the reformulated drug product in the US, Canada, and Belize. The results are supported by the statistical determination of efficacy with the Velac Gel formulation in the original review cycle.

The clinical trial with Veltin Gel (W0265-03) consisted of 1,649 subjects enrolled in 25 investigational centers. Eligible subjects included males and females who were 12 years of age and older. The protocol-defined co-primary efficacy endpoints included the absolute change in 2 out of 3 lesion counts (total, inflammatory, and non-inflammatory) from baseline to week 12 (end of treatment); and the proportion of subjects who have a minimum 2-grade improvement in their ISGA score from baseline to week 12 (Please refer to **section 5.3** for a detailed description of the study design). In order to demonstrate success, Veltin Gel must have been superior to clindamycin in vehicle gel, tretinoin in vehicle gel, and vehicle gel alone (2-sided, $P<0.05$) at week 12 in both these outcomes.

Overall, 1,649 subjects were included in the analysis of all randomized subjects in clinical trail W0265-03. The last observation carried forward method (LOCF) was used for imputation of missing lesion count data and baseline values were carried forward for subject who did not have post-baseline data. Veltin Gel was statistically superior to each monad and vehicle gel for the percent of ISGA successes and the absolute change in total lesion counts. For the comparison of inflammatory lesions counts, Veltin Gel was superior to tretinoin gel and vehicle gel, but did not reach statistical significance to clindamycin gel ($P= 0.1797$). For non-inflammatory lesion counts, Veltin Gel was superior to clindamycin gel and vehicle gel, but did not reach statistical significance to tretinoin gel ($P= 0.2541$).

In regards to ISGA improvement, Veltin Gel demonstrated superiority to each monad and vehicle gel for total lesions [clindamycin gel ($P= 0.0018$), tretinoin gel ($P= <0.001$), and vehicle gel ($P= <0.001$)]. Given these outcomes, the co-primary endpoint was met and the trial demonstrated positive efficacy of Veltin Gel in the treatment of acne vulgaris when applied once daily for 12 weeks.

In the review of the original formulation, two multi-centered, phase 3 clinical trials were conducted with Velac Gel to demonstrate safety and efficacy. Due to the positive carcinogenicity signal observed, Velac Gel was reformulated (b) (4) . The efficacy of Velac Gel demonstrated in the two previous clinical trials were comparable to the efficacy demonstrated in the clinical trial conducted with Veltin Gel.

6.1 Indication

Veltin (clindamycin 1% - tretinoin 0.025%) Gel is a combination product developed for the treatment of acne vulgaris. It contains clindamycin 1%, as clindamycin phosphate 1.2% and tretinoin 0.025%, formulated in an aqueous gel base. It has been developed to treat the multi-factorial origin of acne, i.e., both comedones (keratolytic activity of retinoids – tretinoin) and inflammed lesions (antibiotic – clindamycin). Both active ingredients are marketed in the US for the treatment of acne vulgaris in single and in combination. The proposed indication of Veltin Gel is once daily topical treatment for acne vulgaris in patients 12 years or older.

6.1.1 Methods

In the evaluation of efficacy, the following criteria were used to establish the efficacy of Veltin Gel for study W0265-03:

IGA: Success = week 12 score of 0 or 1 with at least a two grade improvement. The objective for assessing IGA success was to establish the:

- superiority of Veltin Gel over each monad; clindamycin gel, tretinoin gel, and vehicle.

Lesion Counts: The absolute change from baseline to week 12. The objective for assessing lesion counts was to establish the:

- superiority of Veltin Gel over clindamycin gel for total and non-inflammatory lesions,
- superiority of Veltin Gel over tretinoin gel for total and inflammatory lesions, and
- superiority of Veltin Gel over vehicle gel for total, inflammatory, and non-inflammatory lesions.

Testing was performed at the two-sided $\alpha = 0.05$ significance level. Analysis of the ISGA success rates was performed using CMH stratified on analysis centers. Comparison of the absolute changes was conducted using ANCOVA with terms for analysis centers and treatment and baseline counts as the covariate.

In addition to establishing the efficacy of Veltin Gel in clinical trial W0265-03, a summary evaluation of the cross trial data from the previously conducted two phase 3 clinical trials with Velac Gel (VLC.C.304 and VLC.C.305) will provide comparability and consistency of data across clinical trials. This is done in order to demonstrate that the three clinical trials with the same active components (clindamycin phosphate 1.2% - tretinoin 0.025%), but different excipient, did not differ in efficacy.

6.1.2 Demographics

Protocol W0265-03 is a four-arm (Veltin Gel, clindamycin gel, tretinoin gel, and vehicle gel) trial to evaluate the efficacy and safety of Veltin Gel in the treatment of acne. The trial enrolled a total of 1,649 subjects of which 476 were randomized to Veltin Gel, 467 were

randomized to clindamycin gel, 464 were randomized to tretinoin gel, and 242 were randomized to vehicle gel. Subjects were enrolled from 32 investigative centers with the average enrollment of 51.5 subjects per center. Centers were located in the United States (27 centers), Canada (3 centers), and Belize (2 centers). The first subject was enrolled on April 1, 2008 and the last subject completed the trail on April 7, 2009.

In this study, the mean age of all subjects in the ITT analysis set was 20.4 years, half of the subjects (51%) were less than 18 years of age, while half (49%) were 18 up to 65 years of age. Females (58%) out numbered males (43%) and the population was majority White (73%), and not Hispanic or Latino. No imbalances for any of the demographic characteristics were observed across the four treatment arms (**Table 9**).

Baseline disease characteristics were similar across the study groups. While all subjects were required to have facial acne, substantial proportions of subjects in each study group also had acne on their backs (28-33%), chest (17%-22%), and necks (12%-17%). The majority of subjects had an ISGA score of 3 (66.5% of subjects) and 52.5% had a subject's global score of 2. Overall, the mean number of total lesions present at baseline was 70.9 of which the mean number of inflammatory lesions was 25.5 and non-inflammatory lesions 45.5. Distributions across the treatment arms for these prognostic factors were roughly balanced.

Table 9: Baseline Demographics for W0265-03 (ITT)

	Veltin Gel (N=476)	Clindamycin Gel (N=467)	Tretinoin Gel (N=464)	Vehicle Gel (N=242)	All Combined (N=1649)
Age					
n	476	467	464	242	1649
mean (SD)	20.8 (8.5)	20.2 (8.1)	20.2 (7.7)	20.6 (8.4)	20.4 (8.1)
Age Category, n (%)					
< 18	230 (48)	247 (53)	243 (52)	127 (52)	847 (51)
18 to <65	246 (52)	220 (47)	221 (48)	115 (48)	802 (49)
Sex, n (%)					
Male	207 (43)	201 943)	200 (43)	89 (37)	697 (42)
Female	269 (57)	266 (57)	264 (57)	153 (63)	952 (58)
Race, n (%)					
American Indian or Alaska Native	4 (1)	4 (1)	4 (1)	3 (1)	15 (1)
Asian	8 (2)	8 (2)	11 (2)	5 (2)	32 (2)
Black	94 (20)	85 (18)	103 (22)	51 (21)	333 (20)
Multiracial	12 (3)	16 (3)	19 (4)	5 (2)	32 (2)
Native Hawaiian/Other Pacific Islander	0	4 (1)	2 (<1)	1 (<1)	7 (<1)
White	358 (75)	349 (75)	324 (70)	176 (73)	1207 (73)
Missing	0	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Ethnicity, n (%)					
Hispanic or Latino	110 (23)	105 (220	100 (22)	60 (25)	375 (23)
Not Hispanic or Latino	366 (77)	362 (78)	364 (78)	182 (75)	1274 (77)

Source: Applicant's submission section 15.1

6.1.3 Subject Disposition

Overall, 1,649 subjects were randomized in the trial and 203 (12.3%) subjects discontinued from the trial (**Table 10**). Seven subjects who were excluded in the ITT analysis set were randomized to, but did not apply the study product (2 subjects randomized to Veltin Gel, 2 subjects randomized to clindamycin gel, and 3 subjects randomized to tretinoin gel).

Table 10: Disposition of Subjects W0265-03 (ITT)

Disposition, n (%)	Veltin Gel (N=476)	Clindamycin Gel (N=467)	Tretinoin Gel (N=464)	Vehicle Gel (N=242)
Completed	414 (87)	416 (89)	405 (87)	211 (87)
Discontinued	62 (13)	51 (11)	59 (13)	31 (13)
		Reasons for Discontinuation		
Adverse event	6 (1)	0	5 (1)	0
Lost to follow-up	26 (5)	19 (4)	17 (4)	11 (5)
Lack of efficacy	1 (<1)	2 (<1)	2 (<1)	2 (<1)
Subject non-compliance	3 (1)	3 (1)	3 (1)	1 (<1)
Withdrawal of consent	19 (4)	18 (4)	26 (6)	13 (5)
Other	7 (1)	9 (2)	6 (1)	4 (2)

Source: Applicant's submission section 15.1.
Seven subjects (2 in Veltin Gel, 2 in the clindamycin gel, and 3 in tretinoin gel groups) who were randomized were not included in the ITT, as they did not apply study product.

The most common reasons for discontinuation across all study product groups were withdrawal of consent (76 subjects) and lost to follow-up (73 subjects). Additional reasons for discontinuation included other (26 subjects), AE (11 subjects), non-compliance (10 subjects), and lack of efficacy (7 subjects). For those that discontinued the trial and listed the reason as other, the rationale for discontinuing included the following: unable to attend all visits, did not satisfy entry criteria, did not use study drug, use of prohibited drug, pregnancy, incarcerated, and personal reasons.

Reviewer's comment: Subjects that withdrew consent were not associated with an adverse event. Exploration of safety due to adverse events can be found in section 7.3, Major Safety Results.

Table 11: Analysis Population for Clinical Trial W0265-03

Analysis Set, n (%)	Veltin Gel (N=478)	Clindamycin Gel (N=469)	Tretinoin Gel (N=467)	Vehicle Gel (N=242)	Total (N=1656)
ITT Population	476 (99.6)	467 (99.6)	464 (99.4)	242 (100)	1649 (99.6)
PP Population	402 (84.1)	404 (86.1)	389 (83.3)	206 (85.1)	1401 (84.6)
All Randomized	478 (100)	469 (100)	467 (100)	242 (100)	1656 (100)

Source: Applicant's submission section 15.1.

The Per-Protocol (PP) population excluded subjects who missed more than a total of 16 applications of study medication during the treatment period, and/or subjects who did not have efficacy evaluations at the baseline and week 12 visits, and/or subjects who used prohibited medications at anytime during the study period. A total of 1446 (87.7%) of subjects were included in the PP analysis population.

In this trial, 255 subjects were excluded from the PP analysis because of 286 protocol deviations, 217 subjects (13%) failed to have the required efficacy evaluations, 19 subjects (1%) missed more than 16 applications of study product, 16 subjects (1%) used a prohibited concomitant medication, 12 subjects (1% had their final efficacy evaluations conducted more than 5 days after the last application of study product, and 10 subjects (1%) had a positive pregnancy test result during the study. Additional deviations included not having an application onset date (7 subjects; <1%), failing to meet eligibility requirements (2 subjects <1%), and other (3 subjects; <1%).

6.1.4 Analysis of Co-Primary Endpoint(s)

The co-primary endpoints included the proportion of subjects who had a minimum 2-grade improvement in ISGA score from baseline to week 12 and the absolute change in lesion counts (inflammatory, non-inflammatory, and total) from baseline to week 12. To draw positive inferences, significant outcomes in all 3 pair wise comparisons between treatment groups were required in the ISGA analysis and in 2 of 3 lesion count types.

The protocol defines a success on the ISGA scale as a week 12 score which is at least 2 grades improved from the baseline ISGA score. As an alternate definition and a secondary analysis, one can define success as both a week 12 ISGA score of 0 or 1 combined with at least a two grade reduction from baseline to week 12, which ensures that all subjects who reach an ISGA score of 0 or 1 also had an improvement of the ISGA score of 2 grades. Using both definitions of ISGA success, Veltin Gel was superior to each of its monads and vehicle gel based upon the two-sided $\alpha = 0.05$ level **(Table 12**).

In regard to lesion counts, an ANCOVA model fit the absolute change in total lesion counts with factors for treatment, 'analysis center', and the respective baseline total lesion count as a covariate. Veltin Gel was superior to each monad and vehicle on the basis of the absolute change in total lesion counts with a treatment effect of 4.7, 2.7, and 10.6 lesions when comparing to clindamycin gel, tretinoin gel, and vehicle gel, respectively.

Similar investigation of 'analysis center' with respect to the baseline of inflammatory and non-inflammatory lesions counts as a covariate was performed. Veltin Gel was superior to tretinoin gel and vehicle gel in inflammatory lesion counts, but failed to show significance when compared to clindamycin gel for inflammatory lesions. The observed treatment effects were 1.0, 1.6, and 4.4 lesions when comparing Veltin Gel to clindamycin gel, tretinoin gel, and vehicle gel, respectively.

Additionally, Veltin Gel was found to be superior to clindamycin gel and vehicle gel in non-inflammatory lesion counts, but failed to show significance when compared to tretinoin gel for non-inflammatory lesions. The observed treatment effects were 3.7, 1.1, and 6.2 lesions when comparing Veltin Gel to clindamycin gel, tretinoin gel, and vehicle gel, respectively.

Table 12: Efficacy Summary (ITT/LOCF); Study W0265-03

	Veltin Gel (N=476)	Clindamycin Gel (N=467)	Tretinoin Gel (N=464)	Vehicle Gel (N=242)
ISGA Success: 0 or 1 with a Two Grade Improvement				
Success (%)	158 (33.2)	112 (24.0)	105 (22.6)	43 (17.8)
p-value†	-	0.0018	< 0.001	< 0.001
Success: ISGA Two Grade Improvement				
Success (%)	173 (36.3)	124 (26.6)	121 (26.1)	49 (20.2)
p-value†		0.0015	< 0.001	< 0.001
Absolute Change Total Lesions				
Mean Change (SD)	38.7 (26.8)	34 (25.2)	36 (28.3)	28.1 (27.7)
p-value‡	-	0.0028	0.037	< 0.001
Absolute Change Inflammatory Lesions				
Mean Change (SD)	15.5 (10.3)	14.5 (9.4)	13.9 (11.1)	11.1 (11.7)
p-value‡	-	.01797	0.0022	< 0.001
Absolute Change Non-Inflammatory Lesions				
Mean Change (SD)	23.2 (20.4)	19.5 (19.7)	22.1 (21.7)	17.0 (20.6)
p-value‡	-	0.001	0.2541	< 0.001

†CMH stratified by 'analysis center' (Source: Biostatistical reviewer's analysis)
‡p-value is based on an ANCOVA models with terms for treatment and 'analysis center' with covariate for the baseline lesion count (Source: Biostatistical reviewer's analysis)
Source of table: Statistical Review and Evaluation by Mat Soukup, Ph.D.

Reviewer's comment: Based upon the study defined primary co-endpoints, the combination product Veltin Gel proved superior to its monads and vehicle gel in the treatment of mild-moderate acne vulgaris. The efficacy data of the pivotal clinical trial (W0265-03) will be presented separately from the supportive clinical trials data conducted with the previous formulation (VLC.C.304 and VLC.C.305).

6.1.5 Analysis of Secondary Endpoints(s)

The following are the protocol defined secondary endpoints.

- Percentage change in lesion counts (total, inflammatory, non-inflammatory) from baseline to week 12 (end of study).
- The proportion of subjects who had a Subject Global Assessment (SGA) score of 0 or 1 at week 12.
- The proportion of subjects who had an ISGA score of 0 or 1 at week 12.

No secondary endpoints have been proposed by the applicant to be included in product labeling. As such, no further analyses are conducted on secondary clinical endpoints assessed during the clinical trial.

6.1.6 Other Endpoints

The following are the protocol defined tertiary endpoints.

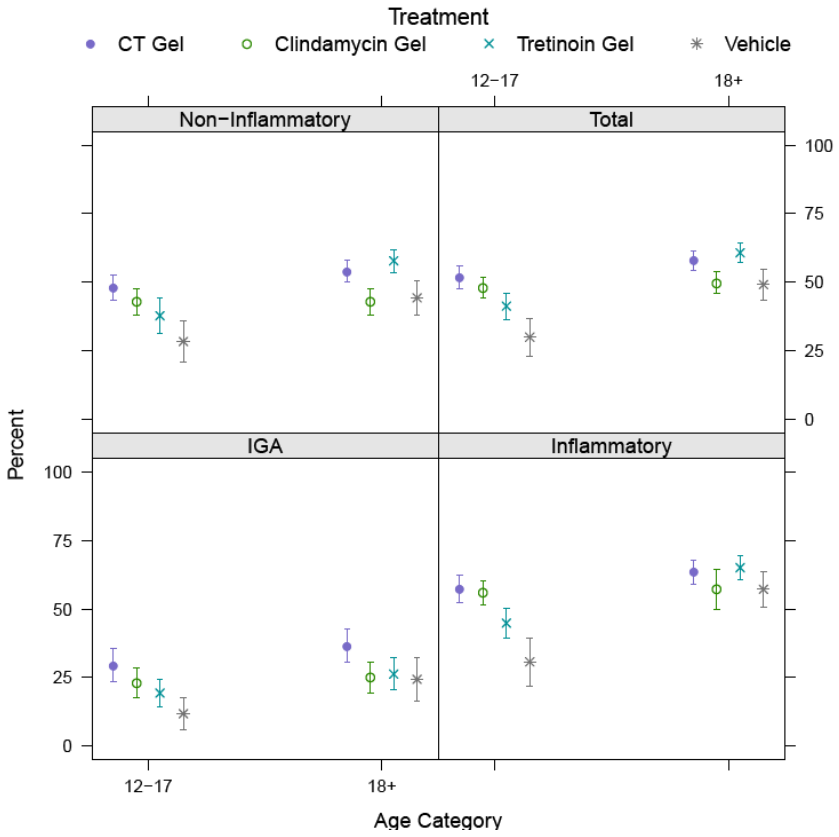
- The proportion of subjects who had a minimum 2-grade improvement in ISGA score at weeks 2, 4, and 8.
- The time to 50% reduction in total lesion counts.
- The absolute and percentages in lesion counts from baseline to weeks 2, 4, and 8.
- The proportions of subjects with SGA or ISGA scores of 0 or 1 at weeks 2, 4, and 8.

No tertiary endpoints will be included in the product labeling and therefore, no further analyses are conducted on these clinical endpoints.

6.1.7 Subpopulations

Analysis of the data subdivided by age, race, and gender was performed. The age of the subjects was dichotomized into two categories: 12 to 17 years old and 28 years and older (median age was 17 years old). In general, subjects who were 18 years and older tended to have slightly higher efficacy than subjects 12 to 17 years old. **Figure 9** presents efficacy results according to age category along with unadjusted 95% confidence intervals

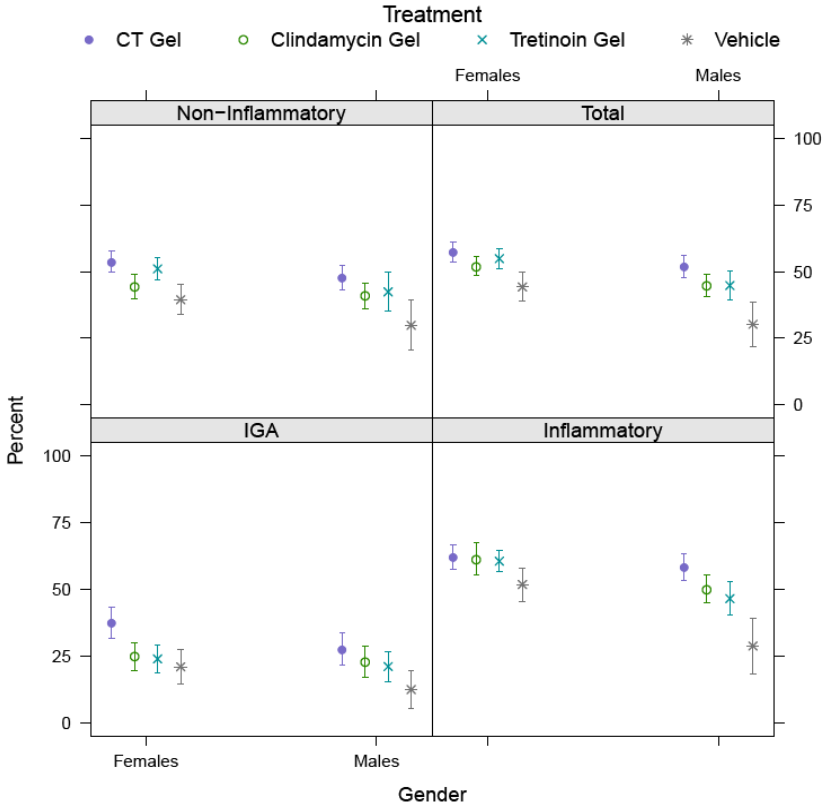
Figure 9: Efficacy Results According to Age



Source: Agency Statistical Review and Evaluation by Mat Soukup, Ph.D.

Figure 10 presents efficacy results according to gender along with unadjusted 95% confidence intervals. For IGA successes, there are larger treatment effects for females treated with Veltin Gel over its monads and vehicle gel compared to males. For inflammatory lesions, females had similar mean percentage changes when treated with Veltin Gel and the two actives, whereas males had a higher mean percent change when treated with Veltin Gel than when treated with the monads. Patterns are similar in males and females for both non-inflammatory and total lesion mean percentage changes.

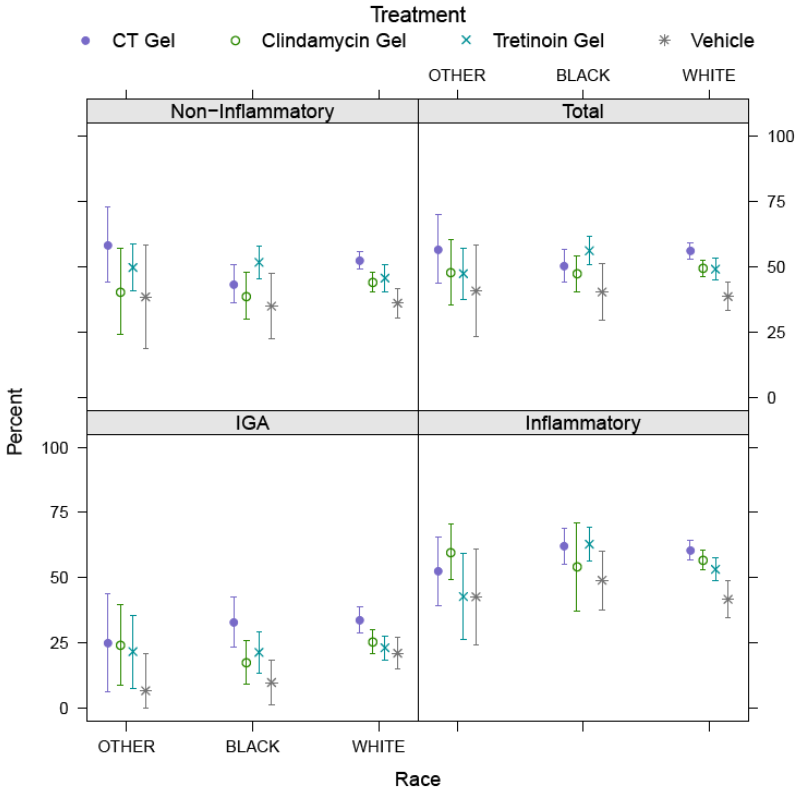
Figure 10: Efficacy Results According to Gender



Source: Agency Statistical Review and Evaluation by Mat Soukup, Ph.D.

Race was dichotomized into three categories: White, Black, and Other where Other consists of those with multiple races recorded, native American, or Native Hawaiian or Pacific Islander (**Table 9**). **Figure 11** depicts the mean for each endpoint along with unadjusted 95% confidence intervals by race for each of the co-primary endpoints. Overall, the efficacy results were consistent across subgroups which show the highest means in subjects treated with Veltin Gel.

Figure 11: Efficacy Results According to Race



Source: Agency Statistical Review and Evaluation by Mat Soukup, Ph.D.

Reviewer's comment: Race representation was considered sub-optimal in this study, since the majority of subjects were Caucasian. No specific dosing regimens based on age, race, or gender will be incorporated in labeling.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No dose-response evaluations were conducted with this combination product. Evaluation of the pharmacokinetics of Veltin Gel can be found in **section 4.4**, Clinical Pharmacology.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy and tolerance effects were not evaluated during the conduct of the phase 3 trial. Recurrence or recrudescence was not evaluated.

6.1.10 Additional Efficacy Issues/Analyses

The sponsor did not provide a formal statistical analysis plan for comparing efficacy data from all phase 3 trials nor was the efficacy data presented integrating data from all phase 3 trials.

The biostatistics reviewer, Dr. Mat Soukup, conducted an Agency review of efficacy results across the three phase 3 trials, using the current definition for success in IGA scores (the percent of subjects with a week 12 ISGA score of 0 or 1 with at least a two grade improvement) which was not used in the original Agency Velac Gel study analyses. The phase 3 trials are: VLC.C.304, VLC.C.305, and W0265-03. Results are presented for the ITT population with missing data imputed using LOCF.

Integrated efficacy results on the ISGA scale utilize a definition of success as the percent of subjects with a week 12 ISGA score of 0 or 1 with at least a two grade improvement. Note that this definition of success was not incorporated into the prior review of Studies VLC.C.304 and VLC.C.305. Utilizing this definition of ISGA success, the treatment effects comparing Veltin Gel to each of its monads and vehicle were similar for Study VLC.C.304 and W0265-03 (**Table 13**).

Table 13: Investigator Global Results (ITT/LOCF); ISE

	Combination Gel	Clindamycin Gel	Tretinoin Gel	Vehicle Gel
Study VLC.C.304				
X/N (%)	72/309 (23.3)	43/311 (13.8) 9.4	36/310 (11.6)	12/153 (7.8)
Trt. Effect (ˆδ)		(3.3, 15.5)	11.6	15.1
95% CI for ˆδ			(5.7, 17.5)	(8.7, 21.5)
Study VLC.C.305				
X/N (%)	95/325 (29.2)	81/324 (25.0)	79/325 (24.3)	18/162 (11.1)
Trt. Effect (ˆδ)		4.2	4.9	17.8
95% CI for ˆδ		(-2.6, 11)	(-1.9, 11.7)	(10.8, 24.7)
Study W0265-03				
X/N (%)	158/476 (33.2)	112/467 (24.0)	105/464 (22.6)	43/242 (17.8)
Trt. Effect (ˆδ)		9.2	10.5	15.2
95% CI for ˆδ		(3.4, 14.9)	(4.8, 16.2)	(8.8, 21.6)

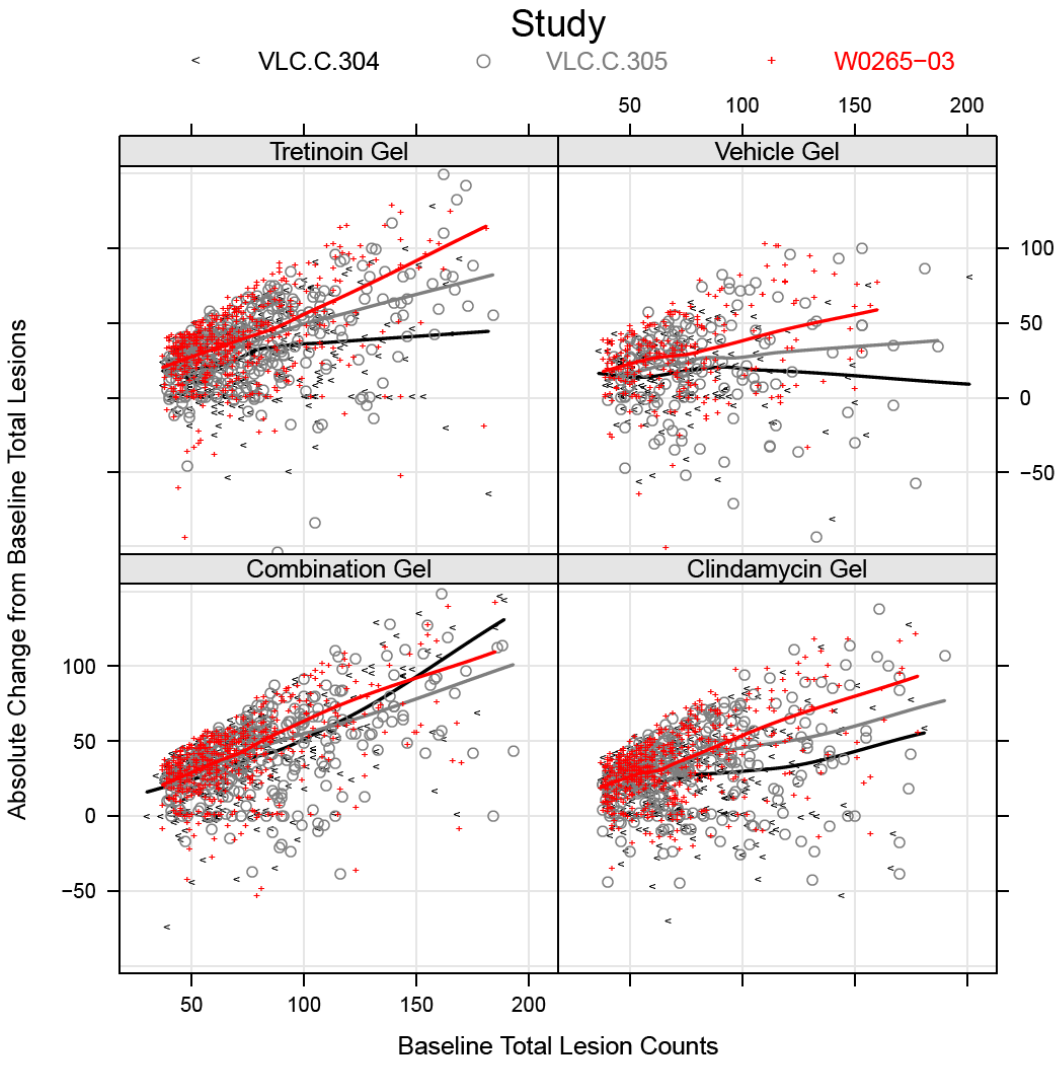
Source: Agency Biostatistics reviewer analysis: Statistical Review and Evaluation by Mat Soukup, Ph.D. Table 17
Note: Confidence intervals are unadjusted and based upon Wilson estimates of the percent of success.

Based upon the above definition of treatment success, the observed treatment effects were smaller in study VLC.C.305 than in the other Phase 3 studies. The highest rates of success were in Study W0265-03.

Figure 12 presents the total lesion count data across all studies. This figure was constructed with the baseline total lesion count plotted against the end of treatment absolute change in total lesion counts, where the data is paneled on the treatment and studies are shown as the grouping variable. In each panel, Loess non-parametric regression lines summarize the

relationships between baseline and absolute change for total lesion counts. Similar to the ISE efficacy results using the ISGA score, the absolute change for total lesion counts is greatest in Study W0265-03 for all treatment groups.

Figure 12: Total Lesion Counts (ISE)



Source: Agency Biostatistics reviewer analysis: Statistical Review and Evaluation by Mat Soukup, Ph.D.

Similar analyses for inflammatory and non-inflammatory lesion counts were conducted across the three studies. Consistent with results observed for total lesions, Study W0265-03 had the smallest estimated treatment effect for all comparisons in inflammatory and non-inflammatory lesions. Overall, the general trend for all phase 3 studies is that the treatment effect is greatest comparing the Veltin Gel to vehicle with the smallest treatment effect occurring when comparing Veltin Gel to clindamycin gel in inflammatory lesion counts and Veltin Gel to tretinoin gel in non-inflammatory lesion counts.

In conclusion, statistical superiority of the combination drug product Veltin Gel has been demonstrated over its monads, clindamycin phosphate in vehicle gel and tretinoin in vehicle gel, and its vehicle gel in one well-controlled, phase 3, multi-center, randomized, double-blind, vehicle-controlled, 12 week clinical trial (W0265-03). Efficacy was evaluated using Investigator Static Global Assessment (ISGA) and mean absolute change in inflammatory and non-inflammatory lesion counts at Week 12 as defined in the study protocol. In addition, superiority of the combination to its monads were demonstrated in two previously conducted phase 3 clinical trials with an earlier formulation (Velac Gel). The results of these three clinical trials indicate that Veltin Gel applied once daily for 12 weeks is effective in the treatment of lesions of facial acne vulgaris. No claims of efficacy should be made for non-facial areas, since they were not included in the efficacy analysis.

Reviewer's comment: The efficacy for ISGA endpoints and lesion counts were comparable across all three clinical trials. The results of these three clinical trials are consistent and support the conclusion that Veltin Gel applied once daily for 12 weeks is effective in the treatment of lesions of acne vulgaris. While the two supportive trials conducted with Velac Gel are not the precise, to-be-marketed-formulation, they will be descriptively contained in the Veltin Gel prescribing information.

7 Review of Safety

Safety Summary

The safety database for Veltin Gel clinical development program included 6 studies conducted with the newly reformulated drug product (CTG.103, W0265-103, W0265-104, W0265-02, W0265-306, and W0265-03). The pivotal phase 3 trial, W0265-03, enrolled 1,649 subjects. In total 476 subjects were exposed to Veltin Gel, 467 subjects to clindamycin gel, 464 subjects to tretinoin gel, and 242 subject to the vehicle gel. In this trial, no deaths occurred; however, 396 of 1,649 subjects (24%) experienced adverse events (AEs). Six subjects experienced serious AEs. Only one of these occurred on Veltin Gel treatment. None appear related to the use of the study product, and none resulted in discontinuation of the study product.

In trial W0265-03, the safety assessment of local skin reactions for irritability of Veltin Gel was similar to tretinoin gel. While the mean irritation was not severe in nature, the mean irritation peaked at week 2 with a gradual decrease towards baseline levels by week 12. Adverse events, other than local skin reactions, were not discordant in subjects treated with Veltin Gel versus the monads and vehicle.

In the special safety studies, 108 subjects with acne vulgaris were exposed to Veltin Gel, 11 (9.8%) subjects reported an AE related to the study product. No subjects were discontinued due to an AE. One subject experienced a serious AE (depression) in study CTG.103 (cutaneous irritation study) that was not study related.

Across the six studies conducted with Veltin Gel, the majority of study drug discontinuations were due to application site reactions. No serious adverse events were associated with the Veltin Gel and no deaths occurred.

7.1 Methods

The safety data of the pivotal phase 3 trial (W0265-03) with Veltin Gel will be the main focus of this safety review. The three dermal safety studies conducted with the reformulated Veltin Gel, one tolerability study, and one other special safety study will also be discussed as part of the Integrated Summary of Safety.

The original clinical review of Velac Gel from 2005 will be summarized and presented as contributing evidence of safety for Veltin Gel. Cross analysis of the safety data was appropriate since the safety outcomes in the Veltin Gel studies were similar to the safety outcomes in the Velac Gel studies and the three phase 3 clinical trials had comparable designs and enrolled similar subject populations. This will be evident in the final portion of the safety review when the summary of the pooled safety data, from the applicant's submission, will be presented to show consistency across the three clinical trials.

The safety of the product was evaluated by an assessment of vital signs, adverse events, changes in signs and symptoms of facial acne (local tolerability and subject global assessment). No clinical laboratories or ECGs were performed during the pivotal phase 3 trial (W0265-03).

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The following clinical studies were review for safety: phase-3 clinical trial (W0265-03), phase 3b tolerance study (W0265-306), phase 2 bioequivalence study (W0265-02), phase 1 cutaneous irritation (CT-103), phase 1 phototoxicity (W0265-103), and phase 1 photoallergenicity study (W0265-104).

Table 14: Clinical Studies that Contributed to the Safety Analysis of Veltin Gel

Study Identifier	Subject Population	Study Design	Exposed Number of Subjects	Application & Duration of Treatment
W0265-03	Subjects 12 years of age and older with acne vulgaris	Randomized, double-blind, parallel group, active- and vehicle-controlled, multicenter	Veltin Gel= 476	Once daily application to entire face/ 12 Weeks
W0265-02	Subjects 12 years of age and older with acne vulgaris	Randomized, open-label, parallel-group, active-controlled, single-center	Veltin Gel=17 Velac Gel= 17	Once daily of 3 g of study product to face neck, upper chest, and upper back/ 5 days
CTG.103	Subjects 16 years of age and older with acne vulgaris	Open-label, single-arm, multicenter	Veltin Gel= 30	Once daily application to entire face/ 8 Weeks
W0265-306	Subjects 12 to 45 years of age with mild to moderate acne vulgaris	Randomized evaluator-blinded, parallel-group, multicenter	Veltin Gel and benzoyl peroxide= 30 Veltin Gel and soap-free cleanser= 31	Once daily to entire face of Veltin Gel in the evening and either benzoyl peroxide wash or soap free cleanser in the AM/ 4 Weeks
W0265-103	Healthy subjects 18 to 65 years of age	Randomized, evaluator-blinded, negative- and vehicle-controlled, single center	Veltin Gel= 37	3 sets of 3 single patch applications/ 24 Hours
W0265-104	Healthy subjects 18 to 65 years of age	Randomized, evaluator-blinded, negative- and vehicle-controlled, single center	Veltin Gel= 64	3 patch applications applied at each of 6 induction phase visits and 1 challenge phase visit/ 7 x 24 Hours
Velac Gel Phase 3 Trials				
VLC.C.304[a]	Subjects 12 years of age and older with acne vulgaris	Randomized, double-blind, parallel group, active- and vehicle-controlled, multicenter	Velac Gel = 309	Once daily application to entire face/ 12 Weeks
VLC.C.305[a]	Subjects 12 years of age and older with acne vulgaris	Randomized, double-blind, parallel group, active- and vehicle-controlled, multicenter	Velac Gel = 325	Once daily application to entire face/ 12 Weeks

Source: Adapted from applicant's submission Table 1 section 2.7.4.1
[a] These studies were conducted as part of development plan for Velac Gel and is included in this table as reference to the Integrated Summary of Safety.

Special safety studies contributed 108 subjects that were exposed to Veltin Gel. **Table 14** presents a listing of all the studies that contributed to the safety evaluation of Veltin Gel. With the exceptions of W0265-103 and W0265-104, all studies enrolled subjects with mild to moderate acne vulgaris. Healthy subjects were enrolled for the phototoxicity and photoallergenicity testing of the drug product in studies W0265-103 and W0265-104.

7.1.2 Categorization of Adverse Events

Verbatim descriptions of adverse events (AEs) were assigned to system organ classes and preferred terms using the MedDRA (*version* 11.0) dictionary. Events that had unknown relationships or were considered possibly, probably, or definitely related to the use of the study product are described as being related; events that were considered not related, or unrelated to the use of the study product are described as being not related. A serious AE included, but was not limited to, an event that was fatal, was life threatening, required inpatient hospitalization or prolongation of an existing hospitalization, was a persistent or significant disability/incapacity, or was a congenital anomaly/birth defect. Significant AEs were considered only to be those events that resulted in subject discontinuation of the study and/or subject discontinuation of the study product.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety data from five supporting special studies conducted with Veltin was not pooled with the phase 3 clinical trial safety data due to differences in various trial designs. The safety data from the pivotal phase 3 clinical trial will be evaluated independently.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Pivotal Phase 3 trial (W0265-03)

A total of 1,649 subjects were included in the ITT analysis set. The formulation of the Veltin Gel study product differs from the two previously conducted phase 3 trials (VLC.C.304 and VLC.C.305) (b) (4) . The reformulated Veltin Gel contains the same concentration of active ingredients found in the previous formulation (clindamycin 1% and tretinoin 0.025%), with the exception of (b) (4) POE 4.

Please refer to **section 5.3** for a summary of the phase 3 protocol (W0265-03). All eligible subjects were randomized (2:2:2:1) to receive Veltin Gel, clindamycin gel, tretinoin gel, or vehicle gel. Subjects applied the study product every evening for the 12-week duration of the trial, even in the event that a subject's facial acne cleared prior to week 12 visit. **Table 15** summarizes the duration of drug exposure in this trial.

Overall, within the ITT analysis set, approximately 88% of the subjects applied Veltin Gel for at least 8 weeks. The percentage of subjects across the study groups had similar duration of use. The mean duration of use was approximately 80 days in each group, and the mean number of days of use was approximately 79 days in each group.

Reviewer's comment: Local and systemic safety was adequately assessed given the population exposure with the reformulated drug product.

The mean age of all subjects in the ITT analysis was 20.4 years; approximately half of the subjects (51%) were less than 18 years of age, while the remaining half (49%) were 18 up to 65 years of age. There were slightly more females (57%) than males (43%) and the majority of the subjects were White (75%), while only 20% were Black. Of the 476 subject exposed to Veltin (CT) Gel, 230 (48%) were under 18 years of age and 246 (52%) were between 18 and 65. The demographic characteristics of the ITT analysis set can be found on **Table 9** in **section 6.1.2**.

Reviewer's comment: Across the study groups, no significant differences were observed for any baseline characteristic. No significant geriatric population was studied and the trial did not included subjects younger than 12 years of age.

Table 15: Study Drug Exposure for W0265-03- ITT Population

	Veltin Gel (N=476)	Clindamycin Gel (N=467)	Tretinoin Gel (N=464)	Vehicle Gel (N=242)
Missing, n (%)	25 (5)	19 (4)	21 (5)	17 (7)
Duration, n (%)[a]				
≥ 1 day	451 (95)	448 (96)	443 (95)	225 (93)
≥ 2 weeks	442 (93)	445 (95)	433 (93)	224 (93)
≥ 4 weeks	431 (91)	439 (94)	420 (91)	219 (90)
≥ 8 weeks	421 (88)	427 (91)	411 (89)	217 (90)
≥ 12 weeks	271 (57)	257 (55)	271 (58)	141 (58)
Duration in days, mean (sd)[a]	79.4 (17.5)	81.1 (13.7)	79.4 (17.4)	81.6 (13.2)
Use in days, mean (sd)[b]	77.4 (17.4)	79.3 (13.6)	77.5 (17.4)	80 (13.4)
Total application in grams (mean [SD])				
Overall				
n	449	452	444	229
mean (SD)	44.1 (22.34)	48.2 (24.1)	43.6 (22.63)	51.2 (24.91)

Source: Adapted from applicant's submission Table 20 section 12.1
[a] Duration is inclusive of missed applications.
[b] Use is exclusive of missed applications.
sd= standard deviation

7.2.2 Explorations for Dose Response

There were no studies performed for dose-response relationships for Veltin Gel. The applicant is relying on the pharmacology, pharmacokinetics, and toxicology literature reports of both tretinoin and clindamycin. In addition, the applicant is also relying on the clinical use of both products over the years that have helped establish their safety profile. While clindamycin

and tretinoin have been used in conjunction in clinical practice, the specific safety issues that may arise for a fixed-combination product, such as Veltin Gel, were addressed by the applicant by conducting bridging non-clinical and clinical studies.

The non-clinical studies include single and repeat-dose toxicity studies, pharmacokinetic studies, dermal safety studies, and carcinogenicity studies. The applicant also conducted a bioavailability study comparing the previous formulation (Velac Gel) to Veltin Gel. Thus, dose exploration has been assessed by a combination of literature reports regarding the two individual components, as well as the drug development program.

7.2.3 Special Animal and/or In Vitro Testing

A 2-year dermal carcinogenicity study of the reformulated Veltin Gel vehicle, and Veltin vehicle gel containing 1% clindamycin was conducted in CD-1 mice. In addition, non-clinical studies to support approval included a 28-day dose dermal toxicity study in FVB/N mice (Study AA56ZZ.2D32.01BTL), a 35-day toxicity study of clindamycin administered by the dermal route to rats (Study NPB00013), a 90-day toxicity study of clindamycin administered by the dermal route to mice with a 21-day interim sacrifice (Study NPB00018), a 90-day toxicity study of clindamycin administered by the dermal route to rats with a 21-day interim sacrifice (Study NPB00019), and a 27-week dermal carcinogenicity study in mice (Study AA56ZZ.7D8T.BTL). Please see **section 4.3**, Pre-clinical Pharmacology, for details on the non-clinical development program.

7.2.4 Routine Clinical Testing

Urine pregnancy test for all females of childbearing potential was the only routine clinical testing performed. There was no other laboratory testing collected during the trial. Clinical lab evaluations were performed for study VLC.C.304 (original Velac Gel study) for 318 subjects at 4 selected investigative sites.[5] No clinically significant changes were noted in these labs form baseline to end of treatment and across all treatment groups.

Reviewers comment: This reviewer concurs that clinical laboratory testing was not necessary for safety evaluation of this topical drug product. The evaluations reported by the applicant are acceptable.

7.2.5 Metabolic, Clearance, and Interaction Workup

The individual components of Veltin Gel have been well characterized in clinical practice with a long history of clinical use. A single bioavailability study (W0265-02) was conducted with Veltin Gel. In this study, once daily topical application of either Veltin Gel or Velac Gel (original formulation) to face, neck, upper chest, and back was assessed with plasma sample collections. The study failed to show bioequivalence of Veltin Gel to that of Velac Gel. Please

5 Nikhar, Bindi. Clinical review of NDA 50-803 Velac® Gel (clindamycin 1% - tretinoin 0.025%). May 16, 2005.

refer to **section 4.4**, Clinical Pharmacology, for a discussion of the clinical pharmacology development plan.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no attempts to evaluate for unseen adverse events by the applicant.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred in any of the studies conducted with Veltin Gel. No deaths occurred in any of the supporting special studies conducted with Veltin Gel.

7.3.2 Nonfatal Serious Adverse Events

Within the ITT analysis set, six subjects experienced serious AEs, which included abdominal pain (moderate intensity, clindamycin gel group), bronchitis (mild intensity, vehicle gel group), concussion (moderate intensity, tretinoin group), infectious mononucleosis (severe intensity, Veltin Gel group), ovarian cyst (severe intensity, tretinoin gel group), and suicide attempt (severe intensity, tretinoin gel group). A listing of the Serious Adverse Events is presented in **Table 16**.

Table 16: Serious Adverse Events for Clinical Trail W0265-03 (ITT)

Subject Number	Study Product Assignment	Event	Severity	Subject disposition
010-1340	clindamycin gel	abdominal pain	moderate	Completed
026-1495	vehicle gel	bronchitis	mild	Completed
001-1003	tretinoin gel	concussion	moderate	Completed
005-2205	Veltin Gel	infectious mononucleosis	severe	Completed
002-1259	tretinoin gel	ovarian cyst	severe	Completed
004-1695	tretinoin gel	suicide attempt	severe	Completed

Source: Applicant's submission section 16.3

No subject discontinued the study product due to serious adverse events. Two additional serious AEs (induced abortion and spontaneous abortion) were reported for pregnant subjects after the end of the study participation and were not reported in the clinical data listing. These events were included in the applicant's pharmacovigilance safety database and will be discussed later in **section 7.6.2**.

A brief summary of narratives for the 6 subjects who experienced serious AEs in clinical trial W0265-03 are provided here.

Subject number 001-1003: Concussion

A serious AE of concussion was reported for this 15 year old male subject with acne vulgaris. The subject was hospitalized due to concussion following a wake boarding accident. The subject had a medical history that included a previous concussion from a football injury several years ago. No concomitant medications were reported. The subject started blinded study product (tretinoin gel) on June 9, 2008. The last application of study product applied before the concussion (b) (6). The subject was hospitalized overnight for observation following trauma to the head during the accident. He was discharged the following day. On follow-up in September 8, 2008, the concussion and it related symptoms were completely resolved and the subject completed the study per protocol.

Reviewer's comment: This event does not appear to be related to study treatment.

Subject number 002-1259: Right ovarian cyst

A 28 year old, white, female subject with acne vulgaris was started on blinded study product (tretinoin gel) on May 13, 2008. (b) (6), she was diagnosed with a right ovarian cyst and scheduled for surgery (b) (6). The study product was interrupted as the subject underwent a laparoscopic right ovarian cystectomy with lysis of bowel adhesions under general anesthesia. The subject improved and the right ovarian cyst was resolved (b) (6). Study product application was resumed on July 19, 2008. Subject completed the trial.

Reviewer's comment: This event does not appear to be related to study treatment.

Subject number 010-1340: Abdominal Pain

A 29 year old female subject with history of cholelithiasis (2008) with cholecystectomy and tubal ligation (2004), started blinded study product (clindamycin gel) on April 30, 2008. (b) (6) she experienced moderate epigastric abdominal pain and was admitted to the hospital for observation. The subject described the pain as similar to the pain she experienced with her gallbladder problem. Serum laboratories showed a significant elevation in WBC with a left shift and she was started on IV hydration. (b) (6) (the next day), her serum laboratories normalized and she was discharged on clear liquids with instruction to schedule and outpatient ultrasound. The ultrasound was inconclusive and no definitive diagnosis was every made.

Reviewer's comment: This event does not appear to be related to study treatment.

Subject number 026-1495: Acute bronchitis

A 20 year old, black, female subject with acne vulgaris and history of asthma (1990) started blinded study product (vehicle gel) on July 17, 2008 and ended application of study product on October 3, 2008. On (b) (6), the subject reported that she was congested,

sneezing, and had developed a cough. She was seen by a physician and was treated with over-the-counter cold medications and doxycycline. The subject's condition continued to worsen during the week. (b) (6), she presented to the ER with trouble breathing. Chest X-ray in the ER showed no acute disease and she was treated conservatively. She was diagnosed as having acute bronchitis and her antibiotic regimen was changed for doxycycline to azithromycin. On October 10, 2008, the subject completed the study and reported that her symptoms had subsided.

Reviewer's comment: This event does not appear to be related to study treatment.

Subject number 004-1695: Suicide attempt

A 16 year old, white, male subject with a medical history of depression (2008) and previous suicide attempt (2008) started blinded study product (tretinoin gel) on August 12, 2008. Concomitant medications included Celexa 20mg daily for depression from April 2008 to September 2008, which was increased to twice daily in September 2008 for worsening depression. The subject was reported noncompliant with his medications. (b) (6) (b) (6) days after the first study product application, the subject had a fight with his girlfriend and immediately went home an overdose on Tylenol PM. On (b) (6), the subject was hospitalized due to the suicide attempt. Acetaminophen level was found to be 10.4 mg/dL and a drug screen was positive for nortriptyline, citalopram, and diphenhydramine. The subject was also reported to have a seizure. The subject was treated in intensive care (b) (6) the subject was transferred to an inpatient psychiatric unit at another medical facility. On (b) (6), the subject was started on Abilify for his depression. During his psychiatric hospitalization, an EKG showed wide QRS complexes but no active cardiac disease was found. On (b) (6), the subject was discharged home on Abilify. The study product was temporarily interrupted on October 15, 2008 and restarted on October 29, 2008.

Reviewer's comment: This event does not appear to be related to study treatment.

Subject number 005-2205: Mononucleosis

A 16 year old, white, male subject with a history of seasonal allergies (1993) started blinded study product (Veltin Gel) on December 15, 2008. (b) (6) subject experienced severe mononucleosis for which Z-Pak was prescribed. The subject presented to the ER with sore throat, difficulty swallowing, and fever. He was subsequently hospitalized and found to have a positive Mono Spot test. Subject received aggressive hydration and treatment and was discharged from the hospital (b) (6). On February 9, 2009, at the week-4 study visit, the subject's condition was improving.

Reviewer's comment: None of the six described serious adverse events were considered related to the application of the drug product, only one occurred on Veltin Gel, and none are plausibly

related to the products' mechanisms of action.. Based on the review of serious adverse events, no serious safety signals or trends were observed with clinical trial W0265-03.

7.3.3 Dropouts and/or Discontinuations

In this clinical trial (W0265-03), 14 subjects (7 in the Veltin Gel group and 7 in the tretinoin gel group) discontinued study product because of AEs. A summary list of all subjects who discontinued study product due to AEs is presented in **Table 17**. All subjects were accounted for in this table with the exception of subjects 006-1910, 027-1971, and 015-1483. Two of these 3 subjects (006-1910 and 027-1971) were discontinued due to consent withdrawal, and the third subject (015-1483) was discontinued due to use of prohibited medications. This subject (015-1483),in the tretinoin gel group, discontinued study product due to an event of poison ivy and concomitant use of prohibited medications.

Table 17: Subjects Discontinued Study Product Due to Adverse Events (W0265-03)

Subject Number	Study Product Assignment	Event	Severity	Relationship to Study Product
001-1010	Veltin Gel	sunburn	mild	possibly related
		application site dermatitis	moderate	definitely related
005-1705	tretinoin gel	application site exfoliation	moderate	probably related
005-1718	Veltin Gel	viral skin infection	moderate	not related
006-1043	tretinoin gel	application site dryness	moderate	definitely related
		application site erythema	severe	definitely related
006-1910	Veltin Gel	application site pruritis	mild	definitely related
		application site dryness	mild	definitely related
		application site irritation	severe	definitely related
010-2366	Veltin Gel	application site erythema	moderate	definitely related
		application site irritation	severe	definitely related
011-1098	tretinoin gel	application site erythema	moderate	definitely related
		application site irritation	moderate	definitely related
		application site dryness	moderate	definitely related
		application site exfoliation	moderate	definitely related
011-1105	Veltin Gel	lip swelling	severe	possibly related
013-2296	Veltin Gel	application site dermatitis	moderate	definitely related
015-1483	tretinoin gel	contact dermatitis	mild	note related
019-2260	tretinoin gel	application site dryness	moderate	probably related
027-1960	Veltin Gel	application site dermatitis	severe	possibly related
027-1971	tretinoin gel	application site irritation	moderate	possibly related
029-2609	tretinoin gel	application site pain	moderate	definitely related

Source: Applicant's submission section 16.3
Note: Subjects 006-1910 and 027-1971 withdrew their consent
Note: Subject 015-1483 was discontinued due to prohibited medications

The majority of subjects that discontinued the study product due to adverse events were related to application site reactions. The most frequent events were generally due to dermatitis, dryness, erythema, exfoliation, and irritation. Events that resulted in study product discontinuation are similar between the Veltin Gel and tretinoin group. There were no adverse

events that caused discontinuation of study product in the clindamycin gel or vehicle gel groups. A severe adverse reaction of lip swelling occurred in subject 011-1105; however, the investigator graded this reaction as "possibly related" due to multiple concomitant medications and the timing of the adverse event.

Reviewer's comments: After CRF review of subject 011-1105, this reviewer deemed the adverse event as not related to the study product. The subject was on multiple concomitant medications and was likely not compliant with study protocols.

7.3.4 Significant Adverse Events

No other significant adverse events occurred. Pregnancies and births will be discussed in **section 7.6.2**.

7.3.5 Submission Specific Primary Safety Concerns

The most serious and frequent safety concern was due to application site reactions, a common cause of study drug discontinuation. These events are likely associated with the tretinoin component of the combination drug product. No serious adverse events were associated with application site reactions.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Of the 396 subjects who reported AEs in this clinical trial, 59 (15%) subjects reported events that were considered related to the study product. **Table 18** represents a summary incidence of AEs by system organ class and preferred terms. Combining "Abdominal pain", "Abdominal pain upper", and "stomach discomfort", the adverse events profile for clindamycin for any abdominal pain was 5.7%. When any abdominal pain was combined for Veltin Gel, the adverse events were comparable to placebo at <1%. Only nasopharyngitis was reported by 5% or more of the subjects in any study product group. Most of the reported AE were mild or moderate in severity. Application site reactions, as reported in the general disorders and administration site conditions, was highest in the tretinoin gel group (7%) followed by the Veltin Gel group (5%), the clindamycin gel (<1%), and the vehicle gel (<1%) groups.

Table 18: Summary of Study Total Adverse Events (ITT) W0265-03

SYSTEM ORGAN CLASS Preferred Term	**Veltin Gel (N=476)**	**Clindamycin Gel (N=467)**	**Tretinoin Gel (N=464)**	**Vehicle Gel (N=242)**
Subjects with Adverse Events, N (%)	108 (23)	123 (26)	116 (25)	49 (20)
GASTROINTESTINAL DISORDERS	5 (1)	12 (3)	9 (2)	5 (2)
Abdominal Pain	0	2 (<1)	0	0
Abdominal Pain upper	1 (<1)	3 (1)	0	0
Diarrhea	1 (<1)	3 (1)	0	0
Nausea	1 (<1)	3 (1)	4 (1)	2 (1)
Stomach discomfort	0	2 (<1)	0	1 (<1)
Vomiting	1 (<1)	2 (<1)	4 (1)	1 (<1)
COMBINED (Abdominal pain, Abd pain upper, and Stomach discomfort)	**1 (<1)**	**7 (5.7)**	**0 (0)**	**1 (<1)**
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	22 (5)	2 (<1)	31 (7)	1 (<1)
Application site dermatitis	6 (1.3)	0	6 (1.3)	1 (<1)
Application site dryness	9 (2)	0	13 (2.8)	0
Application site erythema	5 (1)	0	6 (1.3)	0
Application site exfoliation	0	0	9 (2)	0
Application site irritation	5 (1)	0	13 (3)	0
Application site pain	0	0	4 (1)	0
Application site pruritis	2 (<1)	0	2 (<1)	0
Application site rash	1 (<1)	0	0	0
Thirst	0	1 (<1)	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	14 (3)	13 (3)	11 (2)	7 (3)
Sunburn	6 (1)	1 (<1)	1 (<1)	2 (1)
INFECTIONS AND INFESTATIONS	51 (11)	53 (11)	51 (11)	27 (11)
Gastroenteritis	1 (<1)	4 (1)	2 (<1)	0
Gastroenteritis viral	2 (<1)	1 (<1)	0	1 (<1)
Nasopharyngitis	27 (6)	35 (7.5)	27 (5.8)	19 (7.9)
NERVOUS SYSTEM DISORDERS	16 (3)	19 (4)	15 (3)	6 (2)
Headache	16 (3)	18 (4)	14 (3)	5 (2)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS				
Dysmenorrhea	9 (0.2)	6 (1.3)	5 (1.1)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (<1)	1 (<1)	0	0
Hyperhidrosis	0	1 (<1)	0	0
Skin hyperpigmentation	1 (<1)	0	0	0

Source: Applicant's submission section 15.3 and Biostatistics reviewer's analysis using AE.XPT
This table is abbreviated and does not contain all the adverse events data available
Note: Subjects reporting a particular AE more than once are counted only once for that event. Application-related events are those determined by the investigator to have a possible, probable, definite or unknown relationship to the study product.

Within the Veltin Gel group, the most commonly reported events were application site dermatitis (1%), application site dryness (2%), application site erythema (1%), and application site irritation (1%). Within the tretinoin gel group, the most commonly reported events included application site dermatitis (1%), application dryness (3%), application site erythema (1%), application site exfoliation (2%), application site irritation (3%), and application site pain (1%). There were no commonly reported events in either the clindamycin gel or vehicle gel groups.

Reviewer's comment: There was no specific safety signals were observed when comparing Veltin Gel to clindamycin gel in systemic adverse events analysis. Similar or less occurrences of gastrointestinal disorders such as abdominal pain, nausea, and diarrhea were seen across the Veltin Gel and clindamycin gel arms. Adverse events commonly associated with application site reactions were similar when compared to the tretinoin gel group. The adverse events analysis is consistent with the know combination drug product adverse events.

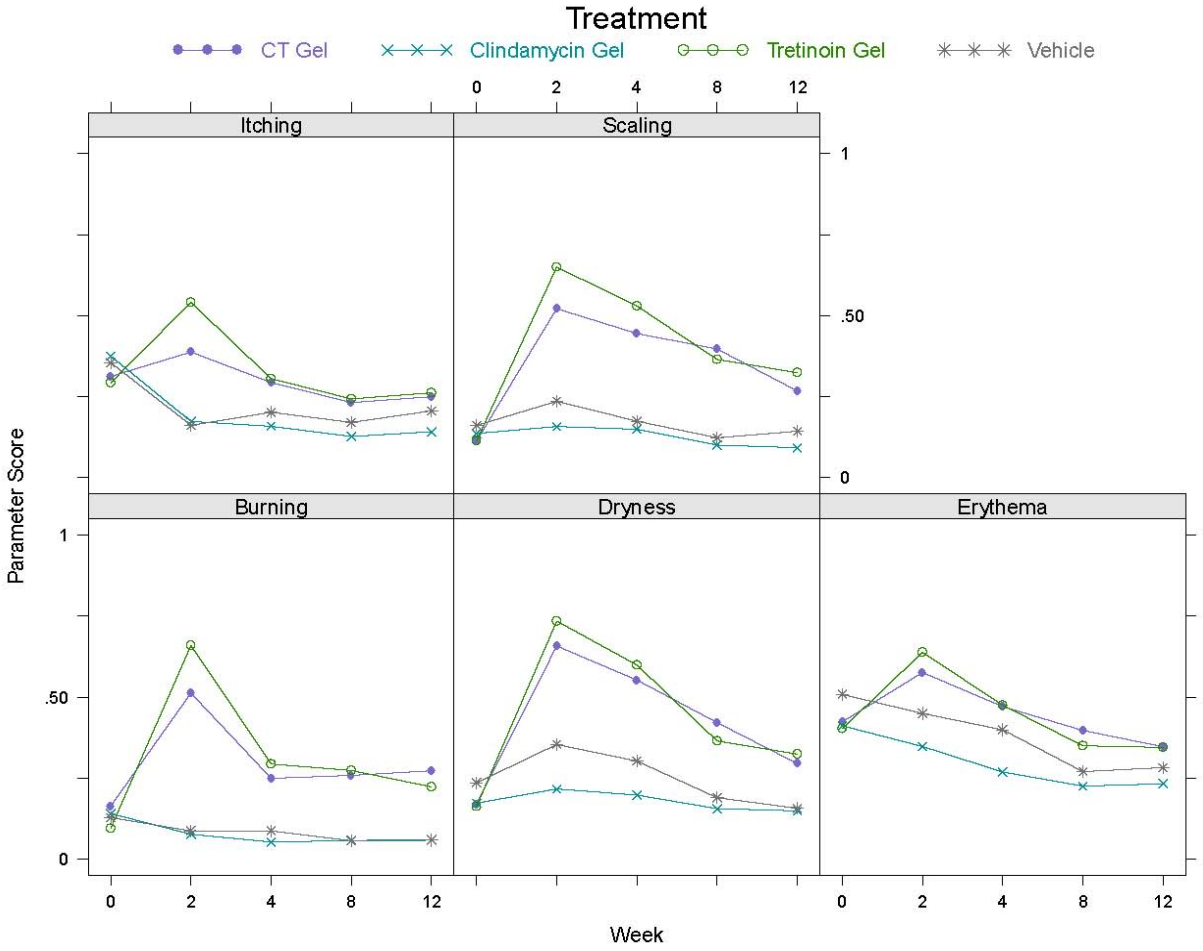
Five local skin reactions: erythema, dryness, scaling, burning, and itching were actively assessed at each visit with scores of 0 to 5 with no descriptors for each level. Changes from baseline were minimal for the local tolerability assessments in the clindamycin gel and vehicle gel groups (**Figure 13**). For the Veltin Gel and tretinoin gel groups, the peak local tolerability assessments were most notable at week 2 and then decrease during weeks 4, 8, and 12. Veltin Gel was associated with less burning and itching at week 2 than tretinoin.

Table 19: Veltin Gel Treated patients with Local Skin Reaction for W0265-03

Local Reaction	Baseline N= 476 N (%)	End of Treatment N= 409 N (%)
Erythema	114 (24%)	87 (21%)
Scaling	39 (8%)	77 (19%)
Dryness	52 (11%)	89 (22%)
Burning	39 (8%)	55 (13%)
Itching	79 (17%)	60 (15%)

Source: Applicant's submission section 15.3

Figure 13: Local Skin Reaction (W0265-03)



Source: Agency Biostatistics Reviewer Analysis using AE.XPT

Reviewer's comments: Local skin reactions to Veltin Gel were assessed in clinical trial W0265-03 with the new formulation, but not in the clinical trials with the previous formulation. Product labeling will present data on the localized skin reactions of erythema, scaling, dryness, burning, and itching.

7.4.2 Laboratory Findings

No serum laboratory testing was included in clinical trial W0265-03.

7.4.3 Vital Signs

Vital signs including temperature, pulse, systolic and diastolic blood pressure were measured for subjects at baseline and at the end of study (week 12). **Table 20** presents the mean change, calculated based upon the mean difference of baseline measurements to exit

measurement (week 12). Across the study groups, the average systolic blood pressure was 114 mmHg and diastolic was 71.8 mmHg. No significant outliers were found in the four main vital sign measurements. The changes in vital signs are negligible across the study groups.

Table 20: Vital Signs (W-0265-03) - Change from Baseline to Week 12 (exit)

Change from Baseline		Veltin Gel/ Velac Gel (n=476)	Clindamycin Gel (n=467)	Tretinoin Gel (n=464)	Vehicle Gel (n=242)
Measurement					
Systolic blood pressure (mmHg)	n	428	431	429	220
	mean (SD)	0.1 (10.07)	-0.9 (10.14)	0.8 (10.34)	-0.4 (10.58)
	min, max	-50, 28	-52, 40	-32, 53	-43, 47
Diastolic blood pressure (mmHg)	n	428	431	429	220
	mean (SD)	-0.5 (7.99)	-0.4 (7.97)	0.1 (7.79)	-0.7 (7.96)
	min, max	-32, 31	-26, 33	-36, 34	-28, 19
Pulse (bpm)	n	427	431	428	220
	mean (SD)	0.3 (9.91)	0.9 (10)	0.6 (9.37)	0.5 (9.05)
	min, max	-37, 44	-50, 47	-38, 33	-36, 28
Temperature (C°)	n	429	432	428	220
	mean (SD)	0.0 (0.43)	0.0 (0.39)	0.0 (0.40)	0.0 (0.4)
	min, max	-1.6, 2.3	-1.5, 1.5	-1.8, 1.2	-1.7, 1.1

Source: Applicant's submission Table 25, section 15.3

Reviewer's comment: No safety signals were identified in the vital sign measurements.

7.4.4 Electrocardiograms (ECGs)

Electrocardiogram testing was not recommended nor performed as part of the drug development program.

7.4.5 Special Safety Studies/Clinical Trials

The combined demographics of the special safety studies conducted with Veltin Gel are presented on **Table 21**. A total of 226 subjects were enrolled in the five special safety studies. The average age across these studies is 31 years old. There was no predominant sex or race enrolled in these studies.

A waiver was granted for the contact sensitization study.

Reviewer's comment: A clinical contact sensitization study was not conducted with the reformulated Veltin Gel product. The applicant requested a waiver with the assertion that the new formulation does not include any new excipients that will have clinically meaningful effect

on a sensitization reaction. This reviewer agrees with this rationale; repeating the sensitization study on Veltin Gel will not provide new safety data or improve labeling for Veltin Gel.

Table 21: Demographics of Special Safety Studies with Veltin Gel

Phase 1, 2, and 3b Study Demographics					
	W0265-02	**CTG.103**	**W0265-306**	**W0265-103**	**W0265-104**
Subjects (n)	34	30	61	37	64
Study Type	Bioavailability study	Cutaneous irritation study	Tolerability with BPO study	Phototoxicity study	Photoallergy study
Mean age (sd)	21.45 (4.2)	23.7 (9.18)	18.55 (5.1)	43.3 (10.7)	48 (11.4)
Male (%)	16 (47)	9 (30)	23 (38)	20 (54)	23 (36)
Female (%)	18 (53)	21 (70)	38 (62)	17 (46)	41 (64)

Source: Applicant's submission, pooled source
BPO= Benzoyl peroxide

CTG.103 (cutaneous irritation study)

This was a phase 1, multicenter, open-label study of the irritation potential of Veltin Gel. The study enrolled 30 subjects aged 16 years or older with mild to moderate facial acne vulgaris. All subjects received Veltin Gel once daily (in the evening), applying a sufficient amount of product to cover the entire face, for 8 weeks. Each subject was required to have an Investigator's Static Global Assessment (ISGA) of 2 or 3 at baseline, without any nodulo-cystic lesions.

The results of the study showed improvement in facial acne vulgaris by ISGA scores. At weeks 8 (end of study), 3 subjects (10%) had an ISGA score of 0, 12 subjects (40%) had an ISGA score of 1, 12 subjects (40%) had an ISGA score of 2 , and 2 subjects (7%) had an ISGA score of 3. Adverse events were reported in 9 subjects (30%), study related AEs were application site pain, sunburn, and chelitis.

Within this study, nine subjects (30%) experienced 1 or more AEs, 3 of which were related to Veltin Gel (application site pain, sunburn, and chelitis). All 3 related events resolved and no subject discontinuations were due to an AE. One subject experienced a serious AE (depression) that was also severe; this event resolved and the subject completed the study.

W0265-103 (phototoxicity study)

This was a phase 1 single-center, evaluator-blinded, randomized, vehicle-controlled study to evaluate the phototoxic potential of Veltin Gel using 24-hour single applications of 3 sets of 3 study patches. Each set of study patches consists of a Veltin Gel patch, a vehicle gel patch, and a blank patch. Thirty-seven healthy subjects, between the ages 18 to 65 and possessing Fitzpatrick skin types I, II, or III, were enrolled. After concurrent 24-hour single application of all 9 patches, 1 set of patches was removed, and those sites were irradiated with 16 joules/cm^2 of ultraviolet A light (UVA) and 0.75 minimal erythema dose (MED) with UVA/UVB. The second set of patches was then removed, and those site were irradiated with 16 joules/cm^2 of ultraviolet A light (UVA), 0.75 MED with UVA/UVB, followed by 15 joules/cm^2 of visible light (VIS). The third set of patches was then removed, and those sites served as non-irradiated control. Inflammatory responses and other cutaneous effects were scored 1 hour after patch removal and during follow-up visits at 24, 48, 72 hours after patch removal.

The proportion of subjects given an erythema grade of 0 at non-irradiated blank patch sites was high (>91%) and consistent over time. The proportion of subjects given an erythema grade of 0 at UVA, UVB/UVA irradiated or UVA, UVB/UVA, VIS irradiated blank patch sites was >72% at 1 hour, 50% at 24 hours, and increase at subsequent time points. Overall, Veltin Gel had a low phototoxic potential after 24 hours of dermal application with or without irradiation.

No AEs were reported for this study.

W0265-104 (photoallergy study)

This was a phase 1 single-center, randomized, vehicle-controlled study evaluating the photoallergic potential of Veltin Gel. Sixty-four subjects were enrolled. Each subject had the test articles (Veltin Gel, vehicle and blank patches) and controls applied on his/her back with occlusive patches fro 24 hours. After patch removal, the sites were irradiated with ultraviolet B light (UVB) and visible light (VIS) during the induction period (consisting of 6 consecutive induction phases), and ultraviolet A light (UVA)/UVB and VIS during the challenge and rechallenge periods. Each application site was observed approximately 1, 24, 48, and 72 hours later for sign of inflammation.

The results showed that most subjects had no visible reaction to Veltin Gel whether the patch site was non-irradiated, UVA, UVB/UVA irradiated, or UVA, UVB/UVA, VIS irradiated. Under the conditions of this study, Veltin Gel did not appear to induce photoallergic dermatitis and has a low potential for photoallergic reactions.

In this study, 10 subjects (17.2%) experienced 1 or more AEs, 4 of which were related to the patch applications (pruritis, reported separately by 2 subjects; application site irritation and erythema, both reported by the same individual subject). All 4 related events resolved without use of concomitant medications, but study product was withdrawn from one subject who reported the events of application site irritation (mild) and erythema (mild). There were no serious AEs, but 2 subjects discontinued because of AEs. Both AEs were reported by the same subject due to reports of respiratory tract infection (severe) and vomiting (mild). The other AE was the aforementioned withdrawal due to application site reaction.

Reviewer's comment: The three dermal safety studies (CTG.103, W0265-103, and W0265-104) conducted with Veltin Gel were appropriately done with sufficient amount of evaluable subjects. Veltin Gel proved to be well tolerated in the irritation study (CTG.103) and no significant potential for phototoxicity or photoallergy was found.

W0265-02 (bioavailability study)

Please see **section 4.4.3**, Clinical Pharmacology, for a summary description of this study.

W0265-306 (tolerability with benzoyl peroxide study)

This was a multicentered, phase 3b study of tolerability of Veltin Gel when used in conjunction with benzoyl peroxide 4% wash in subjects with mild to moderate acne vulgaris. The study enrolled 61 male and female subjects' ages 12 to 45 years with a Investigator's Static Global Assessment of 2 or greater at baseline and with facial acne lesion counts within the prespecified range. Subjects were instructed to use either Veltin Gel with benzoyl peroxide wash or Veltin Gel with soap free wash (SFW) twice a day (morning and evening). Subjects were evaluated for safety and tolerability by the investigators assessments of dryness, scaling, and erythema.

In this study, 9 subjects (14.8%) experienced at least 1 AE. This included 1 subject in the Veltin Gel + benzoyl peroxide (BPO) wash group and 8 subjects in the Veltin Gel + soap free wash (SFC) group. The single event in the Veltin Gel+BPO wash group (nasopharyngitis) is not related to the study product. In the Veltin Gel+SFC group however, the events of application site dryness, application site irritation, application site erythema, and sunburn were related to the study product. All were determined to be mild and resolved without the need for concomitant medication. Two AEs (influenza and sinusitis), both moderate in severity and not related to the study product, were ongoing at the end of the study.

Reviewer's comment: Although the results of this study did not indicate an increase irritation potential or safety concern when Veltin Gel was used in combination with benzoyl peroxide, the study results has limited regulatory utility in labeling or marketing of the drug product. No marketing claims are supportable from this limited study, and the data do not support co-packaging with a benzoyl peroxide product.

7.4.6 Immunogenicity

Not applicable, as the drug products are small molecule drugs, and not therapeutic proteins.

7.5 Other Safety Explorations

Additional exploration of systemic safety data was conducted in response to the finding of higher clindamycin exposure in the reformulated Veltin Gel. A comparison of the adverse

events for the pivotal phase 3 trial (W0265-03) to the two previously conducted phase 3 trials (old formulation) was performed to evaluate systemic safety. **Table 22** represents adverse events data from clinical trial W0265-03 in which the subjects exposed to the reformulated vehicle of Veltin Gel and clindamycin gel are extrapolated for analysis. This table included all the adverse events by system organ class associated with the new formulation.

The adverse events from trial W0265-03 was compared to the two previously conducted clinical trials done with Velac Gel (VLC.C.304 and VLC.C.305) in an attempt to elucidate any increase in AEs due to the change in vehicle formulation. Specific and detailed evaluation of systemic adverse events related gastrointestinal disorders are reviewed across the three clinical trials.

Table 22: All Adverse Events by System Organ class for Veltin Gel (n=476) and Clindamycin (n=467) in W0265-03

System Organ Class (SOC)	Site-Subject	Study Group	Preferred Term/ Verbatim	Severity	Causality
Blood and Lymphatic system disorders					
	010-1340*[a]	Clindamycin	Anaemia/ANEMIA	Mild	NR
	010-1340*[a]	Clindamycin	Leukocytosis/LEUKOCYTOSIS	Mild	NR
Gastrointestinal Disorders					
	010-1340*[a]	Clindamycin	Abdominal pain/ABDOMINAL PAIN	Mod	NR
	017-2223	Clindamycin	Abdominal pain/ABDOMINAL PAIN	Mild	NR
	007-2154	Veltin Gel	Abdominal pain/STOMACH ACHES	Mod	NR
	001-1097	Clindamycin	Abdominal pain/STOMACH ACHES	Mod	NR
	019-1795	Clindamycin	Abdominal pain/STOMACH ACHES	Mild	NR
	028-2648	Clindamycin	Abdominal pain/STOMACH ACHES	Mild	NR
	013-2006	Clindamycin	Diarrhoea/DIARRHEA	Mod	NR
	027-2447	Veltin Gel	Diarrhoea/DIARRHEA	Mild	NR
	028-2656*	Clindamycin	Diarrhoea/DIARRHEA	Mild	NR
	032-2916	Clindamycin	Diarrhoea/DIARRHEA	Mild	NR
	028-2656*	Clindamycin	Dyspepsia/HEART BURN	Mild	NR
	002-1882	Clindamycin	Nausea/NAUSEA	Mild	NR
	003-1663*	Veltin Gel	Nausea/NAUSEA	Mild	NR
	010-1340*[a]	Clindamycin	Nausea/NAUSEA	Mild	NR
	027-1631	Clindamycin	Nausea/NAUSEA	Mild	NR
	024-1237	Clindamycin	Stomach Discomfort/UPSET STOMACH	Mild	NR
	024-1427	Clindamycin	Stomach Discomfort/UPSET STOMACH	Mild	NR
	003-1663*	Veltin Gel	Vomiting/VOMITING	Mild	NR
	010-1340*[a]	Clindamycin	Vomiting/VOMITING	Mild	NR
	027-1631*	Clindamycin	Vomiting/VOMITING	Mild	NR
Infections and Infestations					
	013-2011	Clindamycin	Gastroenteritis/GASTROENTERITIS	Mod	NR
	027-1636	Veltin Gel	Gastroenteritis/GASTROENTERITIS	Mod	NR
	027-1965	Clindamycin	Gastroenteritis/GASTROENTERITIS	Mod	NR
	027-1967	Clindamycin	Gastroenteritis/GASTROENTERITIS	Mod	NR
	027-2250	Clindamycin	Gastroenteritis/GASTROENTERITIS	Mild	NR
	019-1803	Veltin Gel	Gastroenteritis Viral/STOMACH FLU	Mild	NR
	022-1916	Veltin Gel	Gastroenteritis Viral/STOMACH FLU	Mod	NR
	022-2493	Clindamycin	Gastroenteritis Viral/GASTRIC INFLUENZA	Mod	NR

* Subjects with multiple AEs recurring in the table.
[a] Subject 010-1340 (clindamycin) experienced a Severe Adverse Event but is not related to study drug.
Mod= Moderate; NR= Not Related to Study Drug

According to the 2005 Clinical Review of Velac Gel by Dr Bindi Nikhar, one specific severe adverse event in trial VLC.C.304 (subject number 105-3034 - clindamycin arm) warranted examination. A 25 year old female hospitalized for severe gastroenteritis 40 days after initiating treatment with clindamycin gel with nausea, vomiting, and diarrhea. No action was taken with study drug. No cultures for *C. difficile* were obtained. Ova and parasites were negative and stool cultures were unremarkable. The subject recovered and completed the study on clindamycin.

A review of the applicant submitted adverse events analysis across all three phase 3 clinical trials revealed no specific systemic safety signal within the Veltin Gel and the clindamycin gel groups. Across all treatment groups, the percentage of adverse events (as described by system organ class) was consistent (**Table 23**).

Table 23: Incidence of Adverse Events in the System Organ Class Gastrointestinal Disorders, Classified by Preferred Term, in Studies W0265-03, VLC.C.304, and VLC.C.305 (ITT Analysis Set)

	W0265-03		VLC.C.304 and VLC.C.305	
SYSTEM ORGAN CLASS Preferred Term	**Veltin Gel (N=476)**	**Clindamycin in Veltin Gel Vehicle (N=467)**	**Velac Gel (N=634)**	**Clindamycin in Velac Vehicle Gel (N=635)**
Subjects reporting any Adverse Events, n (%)	**108 (23)**	123 (26)	**232 (37)**	172 (27)
Gastrointestinal disorders	**5 (1)**	14 (3)	**19 (3)**	13 (2)
Abdominal discomfort	**0**	0	**1 (<1)**	0
Abdominal pain	**0**	2 (<1)	**2 (<1)**	0
Abdominal pain upper	**1 (<1)**	3 (1)	**1 (<1)**	1 (<1)
Aphthous stomatitis	**0**	0	**1 (<1)**	0
Constipation	**0**	0	**1 (<1)**	0
Diarrhoea	**1 (<1)**	3 (1)	**0**	2 (<1)
Dysgeusia	**0**	0	**0**	1 (<1)
Dyspepsia	**0**	1 (<1)	**0**	1 (<1)
Food poisoning	**0**	0	**1 (<1)**	1 (<1)
Gastric ulcer	**0**	0	**2 (<1)**	0
Gastritis	**0**	0	**1 (<1)**	0
Gastro esophageal reflux disease	**0**	0	**0**	1 (<1)
Lip dry	**1 (<1)**	0	**1 (<1)**	0
Lip swelling	**1 (<1)**	0	**0**	0
Nausea	**1 (<1)**	3 (1)	**2 (<1)**	4 (1)
Stomach discomfort	**0**	2 (<1)	**0**	0
Toothache	**0**	0	**4 (1)**	1 (<1)
Vomiting	**0**	2 (<1)	2 (<1)	5 (1)

Source: Applicant's submission- Safety Amendment (SN 0030: March 9, 2010)

Reviewer's comment: Six adverse events were recorded from clinical trial W0265-03 with the possibility of systemic safety concerns due to the higher bioavailability revealed by the BA study (W0265-02). A close examination of each event concludes that they are not related to the study drug and no specific safety signals were found across the trials to suggest that the higher BA of Veltin Gel is a concern at this time. There were no increased safety signals from the previous (Velac Gel) formulation to the new formulation (Veltin Gel).

A literature review of topical clindamycin causing antibiotic associated colitis revealed limited reported occurrences, however; cases do occur.[6,7] The potential for higher absorption of the clindamycin in the Veltin Gel combination suggest that the labeling should include

6 Parry MF, Rha CK. Pseudomembranous colitis casued by topical clindamycin phosphate. Arch Dermatol 1986; 122 (5): 583-4.
7 Milstone EB, McDonald AJ, Scholhamer Jr CF. Pseudomembranous colitis after topical application of clindamycin. Arch Dermatol 1981; 117 (3): 154-5.

contraindications for patients with a history of regional enteritis, ulcerative colitis, or antibacterial-associated colitis.

Reviewer's comment: Labeling for antibiotic associated colitis should mirror that of Cleosin T® Gel product, including contraindications and warning and precautions.

In regards to the non-clinical studies of clindamycin gel, the applicant has obtained the right of reference to a 27-week Dermal Carcinogenicity study of clindamycin phosphate gel (0, 0.5, 1, and 2%) in Tg.AC mice (b) (4) which provides evidence that clindamycin does not exhibit activity indicative human carcinogenic potential across a range of concentrations. The applicant has also conducted a 2-year dermal carcinogenicity study of Veltin Gel vehicle, and Veltin gel containing 1% clindamycin in CD-1 mice. A summary discussion of non-clinical data to support this NDA can be found in **section 4.3**.

7.5.1 Dose Dependency for Adverse Events

During the conduct of the phase 3 study, safety and efficacy of Veltin Gel was evaluated, no additional dose-dependency safety explorations were conducted.

7.5.2 Time Dependency for Adverse Events

Adverse events were reported during the dosing and follow-up periods. No additional time-dependent safety explorations were conducted.

7.5.3 Drug-Demographic Interactions

Acne vulgaris is most prevalent in adolescents, appearing earlier in females than males; possibly reflecting the earlier onset of puberty.[8] A significant number of patients either continue to experience acne or develops new-onset acne after the teenaged years. Post-adolescent acne predominately affects women, in contrast to adolescent acne which has a male predominance.[9]

Due to the experience with the combination of clindamycin and tretinoin in the original formulation (Velac Gel), the applicant's early phase trials with Veltin Gel included subjects with mild to moderate acne vulgaris (except in dermal safety studies which enrolled healthy subjects). The mean ages were approximately 20 years old and a balance of males and females were achieved in these studies.

SUBSET ANALYSIS

8 Stathakis B; Kilkenny M; Marks R. Descriptive epidemiology of acne vulgaris in the community. Australas J Dermatol 1997 Aug;38(3): 115-23.
9 Collier CN; Harper JC; Cantrell WC; Wang W; Foster KW; Elewski BE. The prevalence of acne in adults 20 years and older. J Am Acad Dermatol. 2008 Jan;58(1):56-9.

In general, there were no clinically meaningful differences between subgroups identified in the incidences of AEs (subgroup analysis by age, race and gender). The proportions of subjects in the Veltin Gel group reporting any AE were 25% of males and 21% females, 23% subjects 12 to 16 years and 22% of subjects older than 16 years; and 26% of White subjects, 9% of Black subjects, and 25% of subjects who were other than Black or White.

Within the system organ class of general disorders and administrative site conditions (i.e., application site reactions), the proportions of subjects in the Veltin Gel group reporting an AE were 3% of males and 6% of females; 5% of subjects 12 to 16 years and 4% of subjects older than 16 years; and 5% of White subjects, 1% of Black subjects, and 13% of subjects who were other than Black or White.

Reviewer's comment: No specific safety signals were discovered with the subgroup analysis. It should be noted that 73% of the subject ITT population was White.

Other subset analysis performed by this reviewer included an examination of women on hormone contraception or hormone acne treatment within clinical trial W0265-03. Thirty-three subjects were on some hormone contraception in this study with 269 females representing the Veltin Gel study arm. This was approximately 13% of the female population in the Veltin Gel arm concomitantly receiving hormone treatment. Of those 33 subjects, seven were on YAZ®/YASMIN® (drospirenone & ethinyl estradiol), an FDA approved treatment for acne vulgaris. There were other single hormone agents that are not FDA approved for acne control, and there were a few hormone contraceptives that are marketed outside of the United States.

Reviewer's comment: The numbers of subjects on hormonal contraceptives were too small to influence the efficacy of the Veltin Gel, no specific statistical analysis is required. No other proposed labeling is needed to address risks in women on contraception..

7.5.4 Drug-Disease Interactions

For the ITT analysis, local tolerability assessments (erythema, dryness, scaling, burning, and itching) were stratified for age, race, and gender. Overall, there were no major differences across the stratified subgroups for each of the local tolerability assessments.

7.5.5 Drug-Drug Interactions

Per trial exclusion criteria, the following subjects were excluded:

1) Patients with concurrent use of photo sensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

2) Patients with concomitant use of neuromuscular blocking agents, since clindamycin has neuromuscular blocking activities which may have enhanced the action of other neuromuscular blocking agents.

3) Concomitant topical acne therapy should be used with caution because cumulative irritancy effect may occur.

As such, no drug-drug interaction studies were conducted. In the proposed label, the drug interactions section advises caution in the use of astringents and other topical drying products and also includes caution regarding concurrent use of neuromuscular blocking agents and photo sensitizers. These warnings are carried over from similar products already with approved labeling.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No malignancies were reported to have developed during the 12 week clinical trial conducted for this NDA.

7.6.2 Human Reproduction and Pregnancy Data

Eleven pregnancies were reported during the clinical trial: four were normal infants, 1 spontaneous abortion, 1 elective termination, 3 were ongoing (as of the study report), and 2 were lost to follow-up. The single spontaneous abortion pregnancy was reported for a 20 year old, black, female subject who was taking Ortho-Novum and Alavert concomitantly. The subject started blinded study product (clindamycin gel) on August 28, 2008 and last application was applied on November 19, 2008. (b) (6), at the (b) (6) end of study visit, the subject's urine pregnancy test was positive. The subject reported missing a couple doses of her birth control pills on unknown dates. (b) (6), the subject experienced cramping and went to the hospital where she experienced a miscarriage. The subject had completed the dosing of treatment portion of the study at the time.

Reviewer's comment: The events as described do not seem to be related to the study product. Labeling recommendations including: Pregnancy Category C, lack of data regarding use in pregnancy, and caution in breastfeeding mothers should be adequate for this product. The class labeling from similar topical tretinoin products should be adequate for this product as well.

Per inclusion criteria, subjects must have a negative pregnancy test prior to enrollment and be actively using combinations of contraception or abstinence. Therefore, the study drug effects are unknown in pregnant women and should carry a Pregnancy Category C (Tretinoin carries a Category C rating, Clindamycin carries a category B rating). There are known congenital malformations associated temporally with administration of tretinoin. Dermal tretinoin has been shown to be fetotoxic in rabbits when administered in doses 40 times the recommended human clinical dose based on a body surface area comparison. Clindamycin has no known teratogenicity.

7.6.3 Pediatrics and Assessment of Effects on Growth

No studies or evaluations were conducted on pediatrics or effects on growth. The applicant requested a waiver for pediatric patients younger than 11 years old. However, based on Veltin Gel being pharmacoequivalent to a marketed product (Ziana™ Gel), the PeRC meeting was not officially held and Veltin Gel did not trigger PREA.

Reviewer's comment: No further assessments for pediatric subjects are recommended as a condition of approval or post-approval.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No instances of drug abuse were reported in subjects treated with and of the study drugs or its vehicle. There are no known potential for drug abuse from the topical drugs used in this study. There are no instances of withdrawal or rebound from this drug product.

7.7 Additional Submissions / Safety Issues

In the original submission, Velac Gel safety was determined from a combined review of the two pivotal phase 3 clinical trials and from six European clinical safety and efficacy studies. In addition, one dermal irritation and sensitization safety study was reviewed for approval. A summary of the Agency's clinical safety findings for Velac Gel will be presented as part of this safety review. In addition, pooled safety data (Safety Analysis Set) from the applicant's submission will be summarized to substantiate a complete safety profile and to show consistency across trials.

Original NDA 50-803, Velac Gel

The safety profile was determined from a combined review of the two pivotal studies VLC.C.304 and VLC.C.305, and from the six European clinical safety and efficacy studies. In addition, one dermal irritation and sensitization safety study, VLC.C.101 was performed and this was supported by dermal safety studies conducted in Europe.

These studies have been previously reviewed by Dr Bindi Nikhar in 2005. A summary of that data is presented for completeness in this review, as the original application is deemed supportive of the single clinical trial conducted with the Veltin formulation.

The safety analysis proved no unexpected findings; the most frequently reported AEs were in the class of Infections and Infestations (14%), followed by General Disorders and Administration Site Conditions (12%). Adverse events reported by ≥ 2% of subjects in the first group included nasopharyngitis, influenza and upper respiratory tract infections; these are common respiratory infections and were not considered treatment-related. In the second group, AEs reported by ≥ 2% of subjects included application site dryness, desquamation, burning and erythema. These local AEs were considered treatment-related and were felt to be in keeping with the known AE profile of tretinoin. The majority of these application site AEs were mild,

were seen most frequently in the Velac and Tretinoin groups and resolved after the first 2-3 weeks of treatment.

Similar to the current submission, these results pertain only to facial lesions; the applicant chose not to assess safety on non-facial areas. There were 7 serious AEs in the US studies and 1 in the European studies; none were considered related to study treatment No deaths were reported in either the US or European studies.

Table 24: Serious Adverse Events – ISS ITT Population

Preferred Term	Velac Gel (N= 1003)	Clindamycin Gel (N= 836)	Tretinoin Gel (N= 804)	Vehicle Gel (N= 315)	Total (N=2958)
Subjects with a SAE	**3(0)**	**1(0)**	**3(0)**	0(0)	**7(0)**
Abdominal pain upper	0(0)	0(0)	**1(0)**	0(0)	**1(0)**
Gastroenteritis NOS	0(0)	**1(0)**	0(0)	0(0)	**1(0)**
Ankle fracture	0(0)	0(0)	**1(0)**	0(0)	**1(0)**
Diabetic ketoacidosis	**1(0)**	0(0)	0(0)	0(0)	**1(0)**
Convulsions NOS	**1(0)**	0(0)	0(0)	0(0)	**1(0)**
Depression aggravated	**1(0)**	0(0)	0(0)	0(0)	**1(0)**
Menometrorrhagia	0(0)	0(0)	**1(0)**	0(0)	**1(0)**
Pelvic pain NOS	0(0)	0(0)	**1(0)**	0(0)	**1(0)**
Respiratory failure (Excl Neonate)	**1(0)**	0(0)	0(0)	0(0)	**1(0)**

Source: Table adopted from original NDA Clinical Review by Bindi Nikhar, MD. 2005

Pregnant and breastfeeding females were excluded from the study because Velac gel appropriately carries a Pregnancy Category C rating (Tretinoin carries a Category C rating, Clindamycin carries a category B rating). Nine subjects became pregnant during the conduct of the studies; 5 in VLC.C.304 and 4 in VLC.C.305. Four subjects had healthy babies, 1 subject had a spontaneous abortion and 1 had an elective abortion, and the outcomes of 3 subjects were unknown.

Generally, the overall incidence of treatment-related AEs for the combined ITT population of the US studies was similar to the ISS ITT population. A significantly greater proportion of patients reported treatment-related AEs in the Velac gel group compared to the Clindamycin and Vehicle gel groups, while patients in the Tretinoin gel groups had a comparable incidence of AEs to the Velac group. The majority of these AEs were local and included dryness, desquamation, burning, erythema and pruritis; these AEs fit in with the known AE profile of Tretinoin (**Table 25**).

Table 25: Incidence of Significant Treatment Related Adverse Events – ISS-ITT Population

Preferred term	Velac Gel (N= 1003)	Clindamycin Gel (N= 836)	Tretinoin Gel (N= 804)	Vehicle Gel (N= 315)	Total (N=2958)	*P*-value
Subjects with treatment-related adverse experience	160(16)	45(5)	121(15)	16(5)	342(12)	<0.0001 0.5989 <0.0001
Eye swelling	0(0)	0(0)	1(0)	0(0)	1(0)	
Eyelid pruritis	1(0)	0(0)	0(0)	0(0)	1(0)	
Abdominal pain upper	1(0)	0(0)	0(0)	0(0)	1(0)	
Chapped lips	1(0)	0(0)	1(0)	0(0)	2(0)	
Desquamation mouth	1(0)	0(0)	0(0)	0(0)	1(0)	
Application site bleeding	0(0)	0(0)	1(0)	0(0)	1(0)	<0.0001 0.9659 <0.0001
Application site burning	44(4)	3(0)	44(5)	5(2)	96(3)	<0.0001 0.2866 0.0220
Application site desquamation	51(5)	2(0)	47(6)	2(1)	102(3)	<0.0001 0.4778 0.0005
Application site dryness	67(7)	12(1)	52(6)	3(1)	134(5)	<0.0001 0.8565 <0.0001
Application site erythema	36(4)	6(1)	37(5)	3(1)	82(3)	<0.0001 0.2772 0.0160
Application site irritation	29(3)	7(1)	7(1)	1(0)	44(1)	
Application site edema	1(0)	0(0)	1(0)	0(0)	2(0)	
Application site pain	4(0)	0(0)	0(0)	0(0)	4(0)	
Application site pigmentation changes	1(0)	1(0)	6(1)	0(0)	8(0)	
Application site pruritis	26(3)	7(1)	23(3)	6(2)	62(2)	
Application site rash	5(0)	0(0)	7(1)	0(0)	12(0)	
Application site reaction NOS	4(0)	0(0)	5(1)	0(0)	9(0)	
Application site swelling	2(0)	0(0)	0(0)	0(0)	2(0)	
Sunburn	10(1)	5(1)	5(1)	3(1)	23(1)	
Dermatitis NOS	1(0)	0(0)	1(0)	0(0)	2(0)	

Source: Table adopted from original NDA Clinical Review by Bindi Nikhar, MD. 2005
P-values based on comparing Velac gel versus Clindamycin gel (top), Tretinoin gel (middle) and Vehicle gel (bottom). Based on the Chi-square test ($\alpha = 0.10$) and are calculated when the incidence is at least 5% in any one treatment group.

Reviewer's comments: The common adverse events reported were similar in frequency to the pivotal phase 3 trial (W0265-03). The most frequently reported AE was application site dryness 6%, application site desquamation 5%, nasopharyngitis 4%, application site burning 4%, application site erythema 4%, application site pruritis 3% and upper respiratory site infection 2%. These findings are similar to clinical trail W0265-03 with application site disorders as the most common adverse events observed. The change in vehicle has not substantially altered the adverse event profile for this reformulated product.

The applicant appropriately performed a subgroup safety analyses for age, race and gender; however, Caucasian subjects were in the majority and as such, only Caucasian patients were included in the European studies. In general, there were no significant safety differences among the treatment groups based on baseline and demographic characteristics.

The conclusion of the safety analysis from the original NDA review:

> "Velac gel was shown to be safe in the 12 week clinical studies as conducted for this NDA, the adverse effects seen in patients were predominantly local and limited to application site and appeared to be in keeping with the known adverse effect profile of Tretinoin. However, the results of the non-clinical carcinogenicity results that showed the vehicle of Velac gel to be a carcinogen are concerning. These safety concerns stem from the fact that there will be chronic use of an acne medication that has the potential of causing cutaneous cancers in a young population that is also vulnerable to UV induced skin damage over a course of time. Besides, there are multiple other treatment options available to treat acne vulgaris and therefore, upon weighing the risk-benefit profile of Velac gel, it is deemed non-approvable."

Applicant's Pooled Safety Data (VLC.C.304, VLC.C.305, and W0265-03)

The Safety Analysis Set describes all three phase 3 trial conducted with the reformulated Veltin Gel and Velac Gel. Overall, the combined Safety Analysis Set included 3,831 subjects that used 1 of 4 study products: the combination (Veltin Gel or Velac Gel), clindamycin gel, tretinoin gel, or vehicle. Overall, 1,104 subjects (28.8%) used Veltin Gel or Velac Gel, 1,091 subjects used clindamycin gel, 1,084 subjects (28.3%) used tretinoin gel, and 552 subjects (14.4%) used vehicle gel. Across all trials, subjects applied the study medication over the entire face (including forehead, nose, cheeks, and chin). Safety of Velac and Veltin Gel over non-facial areas was not assessed in these studies. Duration of treatment was 12 weeks in all phase 3 trials.

Table 26 shows the disposition of all subjects across the phase 3 trials. Overall, 3,348 subjects (87%) completed the three phase 3 trials. Of the subjects receiving either Veltin Gel or Velac Gel, 88% completed the phase 3 trials, 2% experienced an AE, and 6% were lost to follow-up.

Table 26: Disposition of Safety Analysis Set - ITT

Disposition, n (%)	Veltin Gel/Velac Gel (N=1104)	Clindamycin Gel (N=1091)	Tretinoin Gel (N=1084)	Vehicle Gel (N=552)	All Combined (N=3831)
Completed	966 (88)	974 (89)	938 (87)	470 (85)	3348 (87)
Discontinued	138 (13)	117 (11)	146 (13)	82 (15)	483 (13)
Reasons for Discontinuation					
Adverse event	17 (2)	0	22 (2)	0	39 (1)
Lost to follow-up	61 (6)	58 (5)	59 (5)	40 (7)	218 (6)
Lack of efficacy [a]	2 (<1)	5 (<1)	4 (<1)	7 (1)	18 (<1)
Subject non-compliance [b]	9 (1)	8 (1)	7 (1)	6 (1)	30 (1)
Withdrawal by subject [c]	40 (4)	31 (3)	43 (4)	24 (4)	138 (4)
Other [d]	9 (1)	15 (1)	11 (1)	5 (1)	40 (1)

Source: applicant's submission
[a] Reported as „progressive disease" in studies VLC.C.304 and VLC.C.305
[b] Reported as "non-compliance with study treatment" in study W0265-03 and "subject non-compliance" in studies VLC.C.304 and VLC.C.305
[c] Reported as "withdrawal of consent" in study W0265-03 and "subject request to withdraw" in studies VLC.C.304 and VLC.C.305
[d] "Lost to follow-up" was reported as "other" in studies VLC.C.304 and VLC.C.305

Across the three phase 3 studies (W0265-03, VLC.C.304, and VLC.C.305), the mean age of all subjects was 19.9 years; approximately half the subjects (54%) were less than 18 years of age, while the remaining subjects (46%) were 18 years of age and older. No subjects older than 65 years were exposed to the Veltin Gel or Velac Gel products. The subjects were primarily female (55%) and White (69%). Demographic of the pooled safety data showed no significant differences observed for any demographic variable across the Safety Analysis Set as demonstrated by the calculated *P* values (**Table 27**).

Reviewer's comment: The combined demographics of the three phase 3 trials show consistency of subject characteristics across the trials. The pooled safety data is appropriate given the similarities of the demographics and the adverse events profile of the subjects.

Table 27: Demographics of Pooled Clinical Trials (Safety Analysis Set)

	Veltin Gel/Velac Gel (N=1104)	Clindamycin Gel (N=1091)	Tretinoin Gel (N=1084)	Vehicle Gel (N=552)	All Combined (N=3831)
Age					
n	1104	1091	1084	552	3831
mean (SD)	19.9 (7.9)	19.8 (7.7)	20.1 (8.0)	19.7 (7.8)	19.9 (7.9)
P value [a]	0.517				
Age Category, n (%)					
< 18	595 (54)	601 (55)	576 (53)	314 (57)	2086 (54)
18-65	509 (46)	490 (45)	507 (47)	238 (43)	1744 (46)
≥ 65	0	0	1 (<1)	0	1 (<1)
P value [b]	0.558				
Sex, n (%)					
Male	500 (45)	494 (45)	461 (43)	252 (46)	1707 (45)
Female	604 (55)	597 (55)	623 (57)	300 (54)	2124 (55)
P value [b]	0.558				
Race, n (%)					
American Indian or Alaska Native	4 (<1)	4 (<1)	4 (<1)	3 (1)	15 (<1)
Asian	19 (2)	26 (2)	26 (2)	14 (3)	85 (2)
Black	212 (19)	202 (19)	226 (21)	115 (21)	755 (20)
Multiracial	12 (1)	16 (1)	19 (2)	5 (1)	52 (1)
Native Hawaiian/Other Pacific Islander	0	4 (<1)	2 (<1)	1 (<1)	7 (<1)
White	780 (71)	752 (69)	727 (67)	374 (68)	2633 (69)
Other	13 (1)	24 (2)	22 (2)	8 (1)	67 (2)
Missing	64 (6)	63 (6)	58 (5)	32 (6)	217 (6)
P value [b]	0.575				
Ethnicity, n (%)					
Hispanic or Latino	174 (16)	167 (15)	157 (14)	91 (16)	589 (15)
Not Hispanic or Latino	930 (84)	924 (85)	927 (86)	461 (84)	3242 (85)
P value [b]	0.751				

Source: Data from applicant's submission section 2.7.4.7
The data is pooled ITT demographics from VLC.C.304, VLC.C.305, and W0265-03
a The *P* value was based on an ANOVA with factors of treatment, center, and interaction of treatment-center. If the treatment-center interaction was not significant at the 0.1 level, this interaction was excluded from the ANOVA model.
b The *P* value was derived from a Cochran-Mantel-Hansel test stratified by pooled center.

The combined the safety data of the three phase 3 trials to form an adverse events table (**Table 28**) classified by system organ class (SOC). In total, 340 (31) of subjects in the Veltin/Velac Gel group reported any adverse event, the most common recorded events were in general disorders and administration site conditions (12%) and infections and infestations (13%). The adverse events were consistent across the study groups. In addition, a breakdown of the more common study related adverse events are presented in **Table 29**.

Table 28: Adverse Events ≥2% Classified by System Organ Class for Safety Analysis Set

SYSTEM ORGAN CLASS	Veltin Gel/Velac Gel (N=1104)	Clindamycin Gel (N=1091)	Tretinoin Gel (N=1084)	Vehicle Gel (N=552)
Subjects reporting any Adverse Events, n (%)	340 (31)	295 (27)	348 (32)	139 (25)
Gastrointestinal disorders	23 (2)	24 (2)	26 (2)	14 (3)
General disorders and administration site conditions	132 (12)	34 (3)	142 (13)	20 (4)
Infections and infestations	139 (13)	139 (13)	138 (13)	76 (14)
Injury, poisoning, and procedural complications	46 (4)	30 (3)	41 (4)	16 (3)
Nervous system disorders	30 (3)	35 (3)	30 (3)	9 (2)
Respiratory, thoracic and mediastinal disorders	24 (2)	33 93)	28 (3)	11 (2)

Source: Applicant's submission section 2.7.4.7
Note: Subjects reporting a particular event more than once are counted only once for that event.

The overall proportion of subjects with AEs in each study product group was similar to one another (Veltin/Velac Gel= 31%, clindamycin gel= 27%, tretinoin gel= 32%, and vehicle gel= 25%). Incidence of study product related AEs was highest in the tretinoin gel (13%) and Veltin/Velac Gel (13%) groups.

Adverse reactions resulting in study product discontinuation were generally associated with application site reaction. Forty-five of the 3,831 subjects (2%) had their study product withdrawn because of an AE (25 in the tretinoin gel group and 20 in the Veltin Gel group).

There were no deaths in any of the 3 studies; however, 13 subjects (<1%) experienced 15 serious AEs; no single event was reported by more than 1 subject. This reviewer evaluated and determined that none of the serious AEs were related to the use of the study product.

Table 29: Common Study Product Related Adverse Events (Studies W0265-03, VLC.C.304, and VLC.C.305, Combined)

SYSTEM ORGAN CLASS Preferred Term, n (%)	Veltin Gel/Velac Gel (N=1104)	Clindamycin Gel (N=1091)	Tretinoin Gel (N=1084)	Vehicle Gel (N=552)
Subjects reporting any adverse event	140 (13)	38 (3)	141 (13)	17 (3)
GASTROENTESTINAL DISORDERS	2 (<2)	0	2 (<2)	0
Abdominal pain upper	1 (<1)	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	127 (12)	28 (3)	136 (13)	15 (3)
Application site bleeding	0	0	1 (<1)	0
Application site dermatitis	6 (1)	0	8 (1)	1 (<1)
Application site discoloration	1 (<1)	1 (<1)	6 (1)	0
Application site dryness	64 (6)	12 (1)	62 (6)	3 (1)
Application site erythema	40 (4)	6 (1)	39 (4)	3 (1)
Application site exfoliation	50 (5)	2 (<1)	56 (5)	2 (<1)
Application site hyperesthesia	1 (<1)	0	0	0
Application site inflammation	1 (<1)	0	0	0
Application site irritation	50 (5)	4 (<1)	57 (5)	5 (1)
Application site edema	0	0	1 (<1)	0
Application site pain	4 (<1)	0	4 (<1)	0
Application site perspiration	0	1 (<1)	0	0
Application site pruritis	26 (2)	7 (1)	23 (2)	6 (1)
Application site rash	4 (<1)	0	5 (<1)	0
Application site reaction	1 (<1)	0	5 (<1)	0
Application site swelling	2 (<1)	0	0	0
Application site vesicles	1 (<1)	0	0	0
INFECTIONS AND INFESTATIONS	1 (<1)	0	0	0
Cellulitis	1 (<1)	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	11 (1)	6 (1)	7 (1)	3 (1)
Sunburn	11 (1)	6 (1)	7 (1)	3 (1)

Source: Applicant's submission Summary Table 5 in section 2.7.4.2.1
Note: Not all of the preferred term is represented under the SOC.

Reviewer's comment: The severe adverse events analysis in the Safety Analysis Set is consistent with the severe adverse events profile of the newly conducted phase 3 clinical trial, W0265-03. Across the trials, application site severe adverse events are the most common drug product limitations and will be reflected in the products labeling.

Market Experience

The previous formulation of Velac Gel was evaluated in Europe and approved for marketing in France; however, it was never marketed due to corporate business reasons of the original sponsor (Yamanouchi). There is no post-marketing data available for Velac or Veltin

Gel from US or foreign experience and ODS has not conducted any safety assessments for Velac or Veltin Gel.

9 Appendices

9.1 Literature Review/References

1. Akhavan A, Bershad S. Topical acne drugs: review of clinical properties, systemic exposure, and safety. Am J Clin Dermatol. 2003;4:473-92.

2. Berson DS, Shalita AR. The treatment of acne: the role of combination therapies. J Am Acad Dermatol. 1995;32:S31-41.

3. Collier CN; Harper JC; Cantrell WC; Wang W; Foster KW; Elewski BE. The prevalence of acne in adults 20 years and older. J Am Acad Dermatol. 2008 Jan;58(1):56-9.

4. Feldman S, Careccia RE, Barham KL, Hancox J. Diagnosis and treatment of acne. Am Fam Physician. 2004;69(9):2123-30

5. Gollnick HP, Zouboulis CC, Akamatsu H, Kurokawa I, Schulte A. Pathogenesis and pathogenesis related treatment of acne. J Dermatol 1991;18:489-99.

6. Katsambas A, Dessinioti C. New and emerging treatments in dermatology: acne. Dermatol Ther. 2008;21(2):86-95.

7. Milstone EB, McDonald AJ, Scholhamer Jr CF. Pseudomembranous colitis after topical application of clindamycin. Arch Dermatol 1981; 117 (3): 154-5.

8. Parry MF, Rha CK. Pseudomembranous colitis casued by topical clindamycin phosphate. Arch Dermatol 1986; 122 (5): 583-4.

9. Stathakis B; Kilkenny M; Marks R. Descriptive epidemiology of acne vulgaris in the community. Australas J Dermatol 1997 Aug;38(3): 115-23.

9.2 Labeling Recommendations

Review of the proposed label submitted by the applicant was based on evaluations of the clinical study for the NDA as well as DMEPA, DRISK, and DDMAC consultative reviews. The proposed name, Veltin Gel, has been accepted by DMEPA. Carton and container labeling has been accepted by the CMC reviewer and the clinical team. DRISK has provided comments for the patient information section of the label which has been incorporated into the proposed labeling. The principle area of disagreement with this section relates to DMEPA suggestion (b) (4)

(b) (4) which was not accepted by the review team, judged to be "promotional" in nature.

Veltin Gel was studied in patients 12 years and older, since acne vulgaris is more prevalent in that age group and was suggested by the applicant to occur with insufficient frequency to study in younger age groups. The applicant requested a partial waiver for pediatric patients younger than 11 years old. The PeRC met on February 24, 2010 to discuss the waiver for Veltin Gel. Due to its pharmacoequivalence to Ziana™ Gel, Veltin Gel did not trigger PREA and no further pediatric studies will be recommended.

Efficacy and safety data for Veltin Gel was subgrouped by age, race, and gender, and based on those findings, there are no special dosing considerations for different demographic populations. The adverse event profile of Veltin Gel is similar to the individual monads in the combination product. There are no safety data to suggest that the increase in the clindamycin exposure due to the change in vehicle causes any further systemic safety concerns. The label should reflect the application site reactions that are prevalent in this class of topical products.

Pregnant and breast-feeding subjects were excluded from the clinical trials (based on the teratogenic effects of tretinoin) and if approved, the labeling should reflect this with a Pregnancy Category C and cautioned use in nursing mothers.

No drug-drug interaction studies were conducted for this drug product. Given the exclusion criteria of the clinical trials, the label should include caution regarding concurrent use of neuromuscular blocking agents and photo sensitizers.

The significant area of disagreement regarding the prescribing information relates to the information descibing inducible-clindamycin resistance in section 12.4. The proposed Microbiology labeling is somewhat different from that recommended by the Clinical Microbiology review, but the clinical team feels this is adequate given the expected clinical use of this product in an essentially healthy population, in conjunction with the post marketing experience of other clindamycin products.

The recommended labeling for Section 12.4 is listed below:

12.4 Microbiology

No microbiology studies were conducted in the clinical trials with this product.

Mechanism of Action

Clindamycin binds to the 50S ribosomal subunit of susceptible bacteria and prevents elongation of peptide chains by interfering with peptidyl transfer, thereby suppressing protein synthesis. Clindamycin has been shown to have *in vitro* activity against *Propionibacterium acnes (P. acnes)*, an organism that has been associated with acne vulgaris; however, the clinical significance of this activity against *P. acnes* was not examined in clinical studies with VELTIN Gel. *P. acnes* resistance to clindamycin has been documented.

Inducible Clindamycin Resistance

The treatment of acne with antimicrobials is associated with the development of antimicrobial resistance in *P. acnes* as well as other bacteria (e.g. *Staphylococcus aureus, Streptococcus pyogenes*). The use of clindamycin may result in developing inducible resistance in these organisms. This resistance is not detected by routine susceptibility testing.

Cross Resistance

Resistance to clindamycin is often associated with resistance to erythromycin.

Reviewer's comment: Final labeling negotiations are in process with the applicant as of the date of this review.

9.3 Advisory Committee Meeting

No advisory committee meetings were recommended, nor held to discuss the current Veltin Gel application.

2 Pages Draft Labeling have been Removed Immediately Following this Page as B4 (CCI/TS)

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/

GARY T CHIANG
06/25/2010

DAVID L KETTL
06/25/2010
Concur with approval recommendation. See full CDTL review.

Veltin (clindamycin 1% - tretinoin 0.025%) Gel
NDA 50-803
Mid-Cycle Review
Clinical Outline
February 17, 2010

505(b)(2): Combination product
Other similar marketed product: Ziana™ (clindamycin 1.2% - tretinoin 0.025%) Gel (approved 11/06) ? implications for generic application ?
Indication: Acne Vulgaris

Brief Regulatory History:
8/26/02: Pre-IND meeting
5/27/04: Pre-NDA meeting
8/23/04: NDA submitted
3/29/05: ECAC meeting
6/10/05: NA letter
10/3/05: SPA
12/18/07: SPA guidance meeting
10/15/09: Type-2 complete response

Reason for NA letter: The non-clinical carcinogenicity study, conducted on Velac (old formulation) Gel, showed the vehicle, [redacted] (b) (4), to be a carcinogen (cutaneous cancers) with clindamycin augmenting its carcinogenic effects.
Reformulation: Veltin (reformulated) Gel has the same active ingredients (clindamycin 1% and tretinoin 0.025%) [redacted] (b) (4) and [redacted] (b) (4) excipient POE 4.

Efficacy:

Table 1: Phase 3 Clinical Trial W0265-03

Type of Study	Study Identifier	Objectives of Study	Study Design and Type of control	Test Products	Number of Subjects	Diagnosis of subjects	Duration of Treatment	Efficacy Endpoints
Safety and Efficacy	W0265-03	**Efficacy:** Demonstrate superiority of VELTIN Gel versus clindamycin gel, tretinoin gel, and vehicle gel based on co-primary endpoints **Safety:** All adverse events occuring in the study	3 armed, multicentered, randomized, double-blind, parallel-group, active and vehicle-controlled	VELTIN (CT) Gel (clindamycin 1% and tretinoin 0.025%)	**1,565 total** In ITT: VELTIN GEL-476 Clindamycin gel-467 tretinoin gel-467 vehicle gel-242	mild to moderate acne with an ISGA score of 2 or greater	12 weeks	**Co-primary:** The proportion of subjects who had a minimum 2-grade improvement in ISGA score from baseline to week 12 & The absolute change in lesion counts (total, inflammatory, non-inflammatory) from baseline to week 12

This phase 3 clinical trial was conducted to demonstrate the superiority of the combination product (Veltin Gel) is superior to its individual components and vehicle in the treatment mild to moderate acne vulgaris.

Sponsor analysis: Overall, Veltin Gel was superior to clindamycin gel (P=0.002), tretinoin gel (P<0.001), and vehicle gel (P<0.001) in regards to the 2-grade improvement in ISGA from baseline to week 12 (end of treatment). The mean absolute reduction in inflammatory lesions observed was superior for Veltin Gel compared to clindamycin gel (P=0.022), tretinoin gel (P=0.002), and vehicle gel (P<0.001) from baseline to week 12. The mean absolute reduction in non-inflammatory lesions observed was superior for Veltin Gel compared to clindamycin gel (P=0.001), vehicle gel (P<0.001), but not to the tretinoin gel group (P=0.524). The mean absolute reduction in total lesions observed was superior for Veltin Gel compared to clindamycin gel (P=<0.001), tretinoin gel (P=0.025), and vehicle gel (P<0.001) from baseline to week 12. This clinical trial confirmed that the combination product, Veltin Gel, was superior to its components and vehicle, in all three lesion counts (except tretinoin in non-inflammatory lesions) and ISGA scores.

Safety:

1. Demal Safety: The applicant conducted 3 dermal safety studies with the final formulation of Veltin Gel, a cutaneous irritation study (30 subjects), a photoxicity study (37 subjects), and a photoallergy study (64 subjects). There is a request to waive contact sensitization studies with Veltin Gel. The sponsor asserts that the new formulation includes no new excipients and will not have any clinically meaningful effect in a sensitization reaction. *Clinical prelimary assessment is to recommend waiver of the sensitization study.*

2. Adverse event data was collected for 6 studies; three phase 1 (dermal safety), one phase 2 (BA) study, one phase 3 (safety and efficacy) clinical trial, and one phase 3b (tolerability) study with BPO.

W0265-103 (phototoxicity)----------37 healthy subjects
W0265-104 (photoallergy)----------64 healthy subjects
CTG.103 (cutaneous irritation)----------30 healthy subjects

W0265-02 (Bioavailability)----------34 subjects with mild to moderate acne
W0265-306 (tolerability with BPO)-------61 subjects with mild to moderate acne

W2065-03 (efficacy & safety)----------1,656 subjects with mild to moderate acne

No deaths occurred in any study.

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 sponsor or this reviewer.

Discontinuations: 2 subjects in the photoallergy study discontinued the study product, the first reported respiratory tract infection (severe) and the second subject withdrew from the photoallergy study due to application site reactions (irritation and erythema). In clinical trial W0265-03, 14 (of 1566) subjects discontinued the study product due to AEs. 7 of these used the Veltin drug product

Table 2: Subjects Discontinued Study Product Due to Adverse Events (W0265-03)

Subject Number	Study Product Assignment	Event	Severity	Relationship to Study Product
001-1010	Veltin (CT) Gel	sunburn	mild	possibly related
		application site dermatitis	moderate	definitely related
005-1705	tretinoin gel	application site exfoliation	moderate	probably related
005-1718	Veltin (CT) Gel	viral skin infection	moderate	not related
006-1043	tretinoin gel	application site dryness	moderate	definitely related
		application site erythema	severe	definitely related
		application site pruritis	mild	definitely related
006-1910	Veltin (CT) Gel	application site dryness	mild	definitely related
		application site irritation	severe	definitely related
010-2366	Veltin (CT) Gel	application site erythema	moderate	definitely related
		application site irritation	severe	definitely related
011-1098	tretinoin gel	application site erythema	moderate	definitely related
		application site irritation	moderate	definitely related
		application site dryness	moderate	definitely related
		application site exfoliation	moderate	definitely related
011-1105	Veltin (CT) Gel	lip swelling	severe	possibly related
013-2296	Veltin (CT) Gel	application site dermatitis	moderate	definitely related
015-1483	tretinoin gel	contact dermatitis	mild	note related
019-2260	tretinoin gel	application site dryness	moderate	probably related
027-1960	Veltin (CT) Gel	application site dermatitis	severe	possibly related
027-1971	tretinoin gel	application site irritation	moderate	possibly related
029-2609	tretinoin gel	application site pain	moderate	definitely related

The most common AEs were classified in: GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS (SOC). The reported AEs by subject in this SOC is described in **table 2**.

No laboratories studies were performed.

Eleven pregnancies were reported during the clinical trial: four were normal infants, 1 spontaneous abortion, 1 elective termination, 3 were ongoing (as of the study report), and 2 were lost to follow-up. The single spontaneous abortion pregnancy was reported for a 20 year old, black, female subject who was taking Ortho-Novum and Alavert concomitantly. The subject started blinded study product (clindamycin gel) on August 28, 2008 and last application was applied on November 19, 2008. On (b) (6) end of study visit, the subject's urine pregnancy test was positive. The subject reported missing a couple doses of her birth control pills on unknown dates. On (b) (6), the subject experienced cramping and went to the hospital where she experienced a miscarriage. The subject had completed the dosing of treatment portion of the study at the time.

Summary

No new safety concerns were evident in the phase 3 clinical trial conducted with the combination Veltin Gel (clindamycin 1% - tretinoin 0.025%). The previously conducted dermal sensitization safety studies with the original Velac formulation, may be sufficient granting a waiver for Veltin Gel sensitization study.

Labeling will be adequate to address the safety issues for this product.

The implications of the lack of BA/BE will need to be discussed with Clinical Pharmacology.

CLINICAL REVIEW

Application Type: NDA 505 (b)(2)
Submission Number: 50-803
Submission Code: N - 000

Letter Date: 08/23/2004
Stamp Date: 08/25/2004
PDUFA Goal Date: 06/25/05

Reviewer Name: Bindi Nikhar, MD
Review Completion Date: 04/15/05
Revised Completion Date: 05/16/05

Established Names: Clindamycin phosphate and Tretinoin
(Proposed) Trade Name: (Velac® Gel) Trade Name
Therapeutic Class: Antimicrobial and Retinoid
Applicant: Connetics Corporation

Priority Designation: S

Formulation: Hydro-gel
Dosing Regimen: Once a day
Indication: Treatment of acne vulgaris
Intended Population: Patients 12 years and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The sponsor, Connetics Corporation has submitted a marketing application for Velac® gel, which is a fixed-combination product containing clindamycin phosphate 1% and tretinoin 0.025%. The indication sought by the sponsor is the once a day treatment of acne vulgaris in patients 12 years of age and older.

The two active pharmaceutical ingredients in Velac gel, clindamycin and tretinoin, are thought to target two different pathways in the multi-factorial etiology of acne vulgaris. Both ingredients have been previously approved and marketed individually in various topical formulations for the treatment of acne vulgaris and, in clinical practice, physicians often prescribe clindamycin to be used in the morning and tretinoin in the evening. The sponsor's dual action product would provide synergistic efficacy with a once daily dosing regime.

Efficacy analysis for Velac gel has been derived from two pivotal safety and efficacy studies conducted by the sponsor in the US, while the integrated safety analysis has been derived from these two studies as well as six European studies conducted with the older formulation of Velac gel. The results of the 12 week clinical studies as conducted for this NDA, showed Velac gel to be safe and effective in the treatment of acne vulgaris. However, as part of the drug development program, the non-clinical carcinogenicity study conducted by the sponsor showed the vehicle of Velac gel to be a carcinogen and the addition of clindamycin to the vehicle augmented its effect.

The risk-benefit profile of a topical acne drug that has the potential to cause cutaneous cancers does not lend itself to product approval.

To summarize, a Non-Approvable action is recommended for Velac gel in the treatment of acne vulgaris because of the following:

- As per discussion with the Pharmtox reviewer, and the Executive Carcinogenicity Assessment Committee report dated 3/29/05, the primary concern is the presence of a component of the vehicle that may be a carcinogen as demonstrated by the positive Tg.AC mouse carcinogenicity study.

Additional concerns for clinical practice are:

1) Acne vulgaris can be a chronic condition and a drug product approved for acne would be used in younger age groups over facial skin that would be prone to sun damage over a course of time. Since most skin cancers occur in the presence of UV induced skin DNA damage, the use of a topical product that has a carcinogenic potential would add to the risk burden in such patients.
2) Acne vulgaris is not a life-threatening condition and since there are multiple, alternative treatments available for its treatment, the approval of a drug product that has a negative risk-benefit ratio is not justifiable.

The sponsor is not aware of withdrawal or approval of Velac gel in other countries besides France, where it was approved for marketing, but never marketed due to corporate decisions.

1.2 Recommendation on Post-marketing Actions

1.2.1 Risk Management Activity

There are no recommendations for risk management activities.

1.2.2 Required Phase 4 Commitments

There are no recommendations for Phase 4 commitments due to the Non-Approvable (NA) action. Regardless of the NA action, consideration needs to be given by the sponsor to conduct phototoxicity and photoallergenicity studies in sufficient numbers of patients. However, due to carcinogenicity concerns of the current formulation of Velac gel, this recommendation will entail a *de novo* clinical development program.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Velac gel was originally studied and developed in Europe, where six pivotal safety and efficacy studies were conducted by Yamanouchi Pharmaceutical Company. Although approval was granted for Velac gel to be marketed in France, it was never marketed due to Yamanouchi's corporate decisions. Subsequently, on 14th May, 2002, Connetics Corporation purchased the rights for developing and marketing Velac gel in the US. The European and the US formulations of Velac gel are identical, except for the concentration of methylparaben (b) (4) in the European formulation and (b) (4) in the US formulation. A bioequivalence program was conducted by Connetics to bridge results obtained from the US and European studies.

Clindamycin phosphate (an antimicrobial) was first approved in the US as a topical formulation (Cleocin® T) in 1987, while Tretinoin (a retinoid) was approved in a topical formulation prior to 1982 (Retin-A®).

Efficacy for NDA 50,803 has been derived from two pivotal safety and efficacy studies VLC.C.304 (n = 1043) and VLC.C.305 (n = 1136), conducted by the sponsor in the US, while safety information has been derived from these two US studies and a bioavailability study (VLC.C.201) also conducted by Connetics in the US and the six clinical studies previously

conducted by Yamanouchi in Europe. For the safety analysis, the combined Connetics and Yamanouchi studies enrolled 2988 subjects with acne vulgaris; of these, 2958 received at least one dose of study drug and are included in the overall safety population. Since Velac gel has never been marketed, there is no post-marketing data available.

1.3.2 Efficacy

Both studies VLC.C.304 and VLC.C.305 were nearly identical, Phase 3, multi-center, randomized, double-blind, active and vehicle-controlled studies to evaluate the safety and efficacy of Velac gel, Clindamycin gel, Tretinoin gel and Vehicle gel in subjects with mild to moderate acne vulgaris. Demonstration of efficacy of Velac gel was to require statistical superiority of Velac gel to its individual active components (clindamycin and tretinoin) and the vehicle for the following two primary efficacy endpoints:
1) Percent reduction in two out of three lesion counts (total, inflammatory and non-inflammatory) from baseline to week 12 (end-of-treatment).
2) Proportion of subjects who have an Investigator's Static Global Assessment (ISGA) score of 0 or 1 at week 12.

An <u>interim analysis</u> was conducted only in Study VLC.C.304 after ~ 424 subjects had completed study treatment for 12 weeks. The purpose of this study was to estimate sample size needed to ensure robustness of study results.

<u>Study VLC.C.304 results</u>
1) Percent reduction in lesion counts at week 12.
Superiority of Velac gel to Tretinoin and Vehicle gel was demonstrated for the mean percent reduction in all three lesion counts: Velac versus Tretinoin gel (total, $p < 0.0001$; inflammatory, $p < 0.0001$; and non-inflammatory, $p = 0.0065$), and Velac versus Vehicle gel (total, $p < 0.0001$; inflammatory, $p < 0.0001$; and non-inflammatory, $p < 0.0001$). Superiority of Velac gel to Clindamycin gel was demonstrated for two of the three lesion counts (total, $p < 0.0001$ and non-inflammatory, $p < 0.0001$). For inflammatory lesions, the mean percent reduction for Velac gel was greater than Clindamycin gel, but had a borderline statistical significance ($p = 0.0503$). However, Velac gel showed statistical superiority in percent reduction in two out of three lesions and thus achieved success for this primary efficacy endpoint.
2) ISGA score at week 12.
At week 12, the proportion of subjects who attained treatment success was 35% (107/309) for Velac gel; 21% (66/311) for Clindamycin gel; 19% (60/310) for Tretinoin; and 12% (19/153) for Vehicle gel. Pair wise comparisons performed between the Velac gel group and the Clindamycin group ($p = 0.0002$), the Tretinoin gel group ($p < 0.0001$) and the Vehicle gel group ($p < 0.0001$) were statistically significant for all comparisons. Velac gel was shown to be superior to its comparators for the endpoint of ISGA score of 0 (clear skin) or 1 (almost clear).

After reviewing the results of the <u>interim analysis</u> in Study VLC.C.304, although the sample size was increased by 196 subjects for both studies, it was felt that this decision did not inflate the likelihood of success and did not yield favorably biased results for the sponsor.

Study VLC.C.305- results

1) Percent reduction in lesion counts at week 12.

Statistical superiority of Velac gel to Clindamycin gel, Tretinoin gel and Vehicle gel was demonstrated in all three lesion counts: Velac gel versus Clindamycin gel (total, $p = 0.0001$, inflammatory, $p = 0.0306$, non-inflammatory, $p < 0.0001$); Velac versus Tretinoin gel (total, $p = 0.0034$, inflammatory, $p = 0.0041$, non-inflammatory $p = 0.0121$); Velac versus Vehicle gel (total, $p < 0.0001$, inflammatory, $p < 0.0001$; non-inflammatory, $p < 0.0001$). Velac gel showed success for this primary efficacy endpoint.

2) ISGA score at week 12.

At week 12, the proportion of subjects who attained treatment success was 39% (128/325) for Velac gel; 32% (105/324) for Clindamycin gel; 31% (100/325) for Tretinoin gel; 15% (24/162) for Vehicle gel. Pair wise comparisons performed between the Velac gel group and the Clindamycin group ($p = 0.0441$), the Tretinoin gel group ($p = 0.0108$) and the Vehicle gel group ($p < 0.0001$) were statistically significant for all comparisons. Velac gel was shown to be superior to its comparators for the endpoint of ISGA score of 0 (clear skin) or 1 (almost clear).

Efficacy analysis conclusion: In both studies VLC.C.304 and VLC.C.305, Velac gel was able to show statistical superiority to the individual components (Clindamycin gel and Tretinoin gel) and Vehicle gel for both primary efficacy endpoints. In general, subgroup analyses appropriately performed by the sponsor for race, age and gender were in keeping with the above results.

1.3.3 Safety

Safety was determined from a combined review of the two pivotal studies VLC.C.304 and VLC.C.305, and from the six European clinical safety and efficacy studies. In addition, one dermal irritation and sensitization safety study, VLC.C.101 was performed with the new formulation and this was supported by dermal safety studies conducted in Europe. Results from the dermal irritation and contact sensitization study VLC.C.101 indicate that Velac gel induces a low level of irritation and rarely induces contact sensitization.

Spectrophotometric analysis of the European formulation of Velac gel had shown absorption in the 290-700 nm. range, with the peak being at ~ 359 nm; an analysis performed on the US formulation showed similar results. However, the phototoxicity ($n = 10$) and photoallergenicity ($n = 26$) studies were not performed using the to-be-marketed formulation of Velac gel and the number of patients in the European studies was considered inadequate. The Agency generally requires 30 patients for the phototoxicity studies and 50 for the photoallergenicity studies.

The safety analysis did not reveal any new or unexpected findings; the most frequently reported adverse events (AEs) were in the class of Infections and Infestations (14%), followed by General Disorders and Administration Site Conditions (12%). Adverse events reported by $\geq$ 2% of subjects in the first group included nasopharyngitis, influenza and upper respiratory tract infections; these are common respiratory infections and were not considered treatment-related. In the second group, AEs reported by $\geq$ 2% of subjects included application site dryness,

desquamation, burning and erythema. These local AEs were considered treatment-related and were felt to be in keeping with the known AE profile of tretinoin. The majority of these application site AEs were mild, were seen most frequently in the Velac and Tretinoin groups and resolved after the first 2-3 weeks of treatment. However, these results pertain only to facial lesions; the sponsor chose to not assess safety on non-facial areas, although this had been recommended by the Agency. There were 7 serious AEs in the US studies and 1 in the European studies; none were considered related to study treatment

Pregnant and breastfeeding females were excluded from the study because Velac gel appropriately carries a Pregnancy Category C rating (Tretinoin carries a Category C rating, Clindamycin carries a category B rating). Nine subjects became pregnant during the conduct of the studies; 5 in VLC.C.304 and 4 in VLC.C.305. 4 patients had healthy babies, 1 patient had a spontaneous abortion and 1 had an elective abortion, and the outcome of 3 patients is unknown. Patients 12 years and older were included in these studies and since acne vulgaris is not significantly seen in younger children, the sponsor has appropriately received a partial pediatric waiver.

Although the sponsor appropriately performed subgroup safety analyses for age, race and gender, the drawback was that Caucasian patients were in the majority and as such, only Caucasian patients were included in the European studies. In general, there were no significant safety differences among the treatment groups based on baseline and demographic characteristics.

No instances of overdose, drug abuse or withdrawal or rebound were reported; the topical drugs used in these studies are not known to have an abuse potential. Although Velac was approved for marketing in France, it has never been marketed; hence there is no post-marketing data available.

Non-clinical Carcinogenicity Study:
The sponsor conducted a previously agreed upon 26 week Tg.AC mouse dermal carcinogenicity study, the results of which were reviewed by the Executive Carcinogenicity Assessment Committee. Results form this study indicated a positive, statistically significant response in the incidence of papillomas in all treatment groups, including the vehicle control. The Committee concluded that the study was adequate and that the vehicle of Velac gel alone caused a statistically significant increase of skin papillomas compared to the untreated controls and that Clindamcyin in Velac gel caused further significant dose-related increases in papillomas relative to the vehicle controls and untreated animals. These findings indicate that the vehicle is a complete carcinogen or at the very least a promoter.

Safety analysis conclusion:
Velac gel was shown to be safe in the 12 week clinical studies as conducted for this NDA, the adverse effects seen in patients were predominantly local and limited to application site and appeared to be in keeping with the known adverse effect profile of Tretinoin. However, the results of the non-clinical carcinogenicity results that showed the vehicle of Velac gel to be a carcinogen are concerning. These safety concerns stem from the fact that there will be chronic use of an acne medication that has the potential of causing cutaneous cancers in a young population that is also vulnerable to UV induced skin damage over a course of time. Besides,

there are multiple other treatment options available to treat acne vulgaris and therefore, upon weighing the risk-benefit profile of Velac gel, it is deemed non-approvable (Please see Pharmacotoxicology review).

Given the chronic nature of the indication, the need for long-term safety studies per ICH E1A criteria had been discussed at the 5/27/2004 pre-NDA meting; proposals for such studies have not been submitted for review. (Please see Section 2.5)

Safety update:
The 4 month safety update submitted on 1/7/2005 showed no new safety information obtained for Velac gel/Clindamycin/Tretinoin.

1.3.4 Dosing Regimen and Administration

Velac gel is intended for use once daily in the evening; this is appropriate since it will help to minimize exposure to sunlight and therefore local adverse effects associated with tretinoin. The duration of the two pivotal clinical studies was 12 weeks; (b) (4) [redacted]. Based on the division's statistical analysis, this claim does not appear to be true and will have to be reassessed.

1.3.5 Drug-Drug Interactions

Per exclusion criteria, the following patients were excluded:

- Patients with concurrent use of photo sensitizers (eg., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented photoxicity.
- Patients with concomitant use of neuromuscular blocking agents, since Clindamycin has neuromuscular blocking activities which may have enhanced the action of other neuromuscular blocking agents.

As such, no drug-drug interaction studies were conducted. In the proposed label, the drug interactions section advises caution in the use of astringents and other topical drying products. However, the label should include caution regarding concurrent use of neuromuscular blocking agents and photo sensitizers.

1.3.6 Special Populations

Velac gel was appropriately studied in patients more than 12 years of age since acne vulgaris is not commonly seen in the younger age groups. Efficacy and safety of Velac gel was tested in the subgroups - age, race and gender, and based on those findings, there are no special dosing considerations for different demographic populations. However, this is limited by the fact that

Caucasian patients were in the majority in the US studies and the European studies enrolled only Caucasian patients.

Pregnant and breast-feeding subjects were excluded form the study (this was based on the teratogenic adverse effects of Tretinoin) and if approved, Velac gel would have a Pregnancy Category C.

Although the sponsor had been advised at previous Agency meetings to assess safety over non-facial areas, the safety of Velac gel has not been assessed in subjects with non-facial acne.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Velac is a topical combination product consisting of Clindamycin 1% (topical antibacterial) and Tretinoin 0.025% (topical retinoid) in a gel-based formulation, developed to treat lesions of acne vulgaris. Both clindamycin and tretinoin already exist on the market to treat lesions of acne vulgaris; in clinical practice, topical clindamycin 1% in the morning coupled with topical tretinoin 0.025% at nighttime has been thought to be efficacious in treating lesions of acne vulgaris for a number of years. Acne vulgaris (AV) is a chronic disease of the pilosebaceous glands that is multi-factorial in etiology and is characterized by the formation of two major types of acne lesions: non-inflammatory (open and closed comedones) and inflammatory (papules, pustules and in severe cases, nodules/nodulo-cystic lesions). AV has its onset in puberty, but may persist past the third decade of life; severity is greater in male patients and it affects all races.

The sponsor's rationale for choosing a combination of Clindamycin 1% and Tretinoin 0.025% in a gel base is as follows: Tretinoin is known to have comedolytic activity which is exerted by increasing epithelial cell turnover, resulting in the expulsion of existing comedones and decreasing horny cell adherence of follicular ducts, thereby preventing formation of micro-comedones. Inflammation surrounding such lesions may be produced in part by colonization with bacteria such as *Propionibacterium acnes* and *Staphylococcus epidermidis.* Clindamycin is a bactericidal antibiotic with anti-inflammatory activity that has been used in the past to treat inflammatory lesions of acne. Thus, the sponsor hopes to adopt a multi-point approach in treating AV and also hopes that penetration of the antibiotic into the sebaceous glands will be enhanced by the thinning effect of tretinoin on the stratum corneum and that the gel vehicle would be useful in oily skin.

As such, Velac gel would be the first fixed-combination product in its class for the treatment of AV; currently, there is no similar product on the market. The proposed indication for Velac gel is all lesions of acne vulgaris as a once a day at bedtime treatment (qhs) in patients 12 years of age and older. The duration of treatment in the pivotal clinical studies was 12 weeks.

2.2 Currently Available Treatment for Indications

As mentioned above, clindamycin and tretinoin have been approved as topical agents for the treatment of acne vulgaris for a number of years; topical clindamycin phosphate 1% was first introduced in 1987 and topical tretinoin 0.025% in 1975. Depending upon the severity of lesions, there are a number of other topical and systemic drugs available for the treatment of AV; these include the antibacterial agents such as erythromycin, and the tetracyclines (doxycycline, minocycline) as well as the retinoids in various strengths. The oral formulation of Isotretinoin is well described as being useful for severe, nodulo-cystic acne.

2.3 Availability of Proposed Active Ingredient in the United States

Clindamycin phosphate was approved as a topical formulation under the trademark of Cleocin® T in 1987 at a strength of 1% (base equivalent), while tretinoin was approved in a topical formulation prior to 1982 (Retin-A®); both were approved for the topical treatment of acne vulgaris. Tretinoin has since been marketed for a variety of dermatoses at strengths ranging from 0.025% to 0.1% topical formulations. Both clindamycin and tretinoin are also available for systemic use.

Clindamycin is indicated systemically for the treatment of serious infections caused by anaerobic bacteria and for susceptible strains of streptococci, staphylococci and pneumococci, while topical clindamycin is indicated only for acne vulgaris. The main concern associated with the use of clindamycin is the development of diarrhea and pseudomembranous colitis. The label for the Clindamycin Phosphate 1% gel states that orally and parentally administered Clindamycin has been associated with severe colitis, which may result in patient death and the label for oral clindamycin has a boxed warning for pseudomembranous colitis. Absorption of clindamycin can take place from topical application and diarrhea, bloody diarrhea and colitis (including pseudomembranous colitis) have also been reported with the use of topical clindamycin. Studies indicate that a toxin(s) produced by Clostridia is a primary cause of this antibiotic-associated colitis.

Oral Isotretinoin is indicated for the treatment of severe, recalcitrant, nodular acne, but the main concern associated with its use is teratogenicity; it has a pregnancy Category X and the label has a boxed warning for teratogenicity. The boxed warning mentions that major human fetal abnormalities related to Accutane administration in females, increased risk of spontaneous absorption and premature births have been reported. The label for topical Tretinoin has a Pregnancy Category C and it mentions that animal teratogenicity tests have generated equivocal results. It also mentions the following: ‘Thirty human cases of temporally associated congenital malformations have been reported during the two decades of clinical use of Retin-A. Although no definite pattern of teratogenicity and no causal association have been established from these cases, five of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known’.

In addition, topical Tretinoin is known to have local adverse effects that include dryness, desquamation, erythema and burning which are usually more intense in the first few weeks of initiating therapy.

2.4 Important Issues with Pharmacologically Related Products

Safety concerns for products related to topical retinoids are as described above.

2.5 Presubmission Regulatory Activity

Pre-IND meeting on 8/26/2002.
The sponsor was requesting guidance for their Phase 3 clinical development program and also wished to reference data generated by Yamanouchi (previous sponsor for Velac gel) for their European studies. The following was conveyed.
1. Two adequate and well-controlled trials that have the sponsor's combination product vs. tretinoin in the sponsor's gel vehicle vs. clindamycin in the sponsor's gel vehicle vs. vehicle (4 armed studies) would be required for NDA filing.
2. For a 505 (b)(2) application, the sponsor would, in addition to the Phase 3 trials, need to conduct two three-armed studies to demonstrate bioequivalence to the reference drugs: a reference clindamycin gel (Clindagel) vs. clindamycin in the sponsor's gel vs. the sponsor's vehicle and a reference tretinoin gel (Retin-A) vs. tretinoin in the sponsor's gel vs. the sponsor's vehicle.
3. The Agency agreed with the sponsor's primary efficacy endpoints, but suggested that an 'almost clear' category (few lesions requiring no further treatment) be added to the ISGA scale. It was also specified that superiority of the sponsor's product should be demonstrated over clindamycin in the sponsor's vehicle, tretinoin in the sponsor's vehicle and vehicle alone, in two of the three lesion counts and in the ISGA.
3. The sponsor was to enroll as many pediatric subjects as possible from the ages of 12-16 years in the studies and studies were to reflect the racial and geographical diversity of the US population.
4. The design of an open-label safety study was considered acceptable.
5. The safety database was discussed as follows: The extent to which the sponsor could reference the safety data from the Yamanouchi studies would be limited since the formulation in those studies was different from the US studies. Twelve hundred subjects would approach the number needed for fileability, but approvability of an application would be based on review data. Bridging through physical and chemical testing would not speak to patient tolerance of the new formulation; topical safety studies would need to be conducted with the to-be-marketed formulation. Safety studies recommended were – cumulative irritancy, contact sensitization, phototoxicity and photocontact allergenicity. If irritancy was noted and the sponsor agreed to label the product as an irritant, provocative cumulative irritancy testing would not be required. If spectrophotometric analysis of the drug product revealed no absorption in UVB, UVA or visible range, phototoxicity and photoallergenicity studies would not be required.
6. The Agency agreed with the sponsor's proposal not to conduct pediatric studies in subjects less than twelve year of age for product approval and asked the sponsor to request a waiver.
7. The sponsor was to provide information on how the dosing regimen was determined.
8. Safety assessments of non-facial sites were to be conducted if those areas were treated with study drug. No labeling claims could be made regarding efficacy of the product on those sites.
9. It was noted that labeling of approved tretinoin products advises that astringents should be used with caution.
10. The type of 505 (b) application was discussed – The Agency noted that although the type of 505 (b) application was not mentioned, the sponsor had indicated that they planned to adopt appropriate labeling related to the safety of Clindamycin and Tretinoin from the product prescribing information for the approved products containing these ingredients. The sponsor was

informed that if they wanted to rely upon the Agency's finding of safety and efficacy of a listed drug(s), they must submit an application as described under Section 505(b)(2) of the act. This would enable them to adopt portions of the labeling of the approved drug products but they would have to do a comparative bioavailability or bridging study to the listed drug(s).

IND submission 10/10/2002:
The salient points were as follows:
1). Restriction of concurrent use of photosensitizing dugs and neuromuscular blocking agents may be noted in labeling.
2). It was recommended that tolerance of the sponsor's product on non-facial sites be included in the safety assessments.
3). The Agency would like to be party to the selection of any photographs that would be intended for marketing purposes. It was suggested that any photographs selected for such purposes represent typical results and not best cases.

Pre-NDA meeting 5/27/2004:
1). The Agency agreed that the clinical development program as described by the sponsor would appear to support the filing of a marketing application.
2). The Agency agreed that the pivotal trials were of appropriate design for a fixed combination product for purposes of demonstrating 'proof of effectiveness' and that the data presented from the two Phase 3 trials appeared to support the filing of a marketing application.
3). The sponsor was told that a waiver request for subjects younger than 12 years along with the appropriate rationale should be included in the marketing application.
4). The Agency agreed that the safety database of 1200 subjects would approach the requirements of fileability. The sponsor intended to meet this requirement by including subjects from the pivotal US studies and supportive studies in Europe.
5). The sponsor mentioned that the Yamanouchi data would be included in the Integrated Summary of Safety, but not in the Integrated Summary of Efficacy, since the Yamanouchi data is only intended to support safety and not efficacy.
6). The sponsor was advised that the application could be submitted as a 505 (b) (1) application if it satisfied full reports requirement of the Act and the drug was shown to be safe and effective in use. However, if the sponsor did not have a right of reference to one of the essential studies, then it would be a 505 (b) (2) application even though it would be considered a "full NDA". It appeared that the NDA would be supported by referring to published literature for fertility and peri/postnatal development and possibly other non-clinical information for which the sponsor did not have the rights to the underlying data. Since this information was considered required for approval, a NDA relying on this published data would be a 505 (b) (2) NDA.
7). The sponsor was asked to include the complete absorption spectra for the to-be-marketed product (280-700 nm range). The sponsor was also told that there may be additional informational needs for phototoxicity and photoallergenicity testing, since generally 30 evaluable subjects are recommended for phototoxicity and 50 evaluable subjects for photoallergenicity.
8). Given the chronic nature of the indication, long-term safety data would be needed. The sponsor was referred to the ICHE1A guidelines. Ideally, the long-term data should be submitted at the time of NDA filing. However, if Phase 3 trials did not reveal safety signals, it may be

acceptable for the sponsor to submit a proposal for addressing long-term safety early in the NDA.
9). The Division would like to participate in the selection of photographs intended for marketing purposes. The sponsor was asked to submit all photographs in the NDA and not select ones.

2.6 Other Relevant Background Information

Velac gel was approved for marketing in France, but was never marketed due to Yamanouchi's (previous sponsor) corporate business decisions. (b) (4) No new information was contained in the French label submitted by the sponsor.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Description and Composition of Velac Gel:

Velac gel is an aqueous based hydro-gel manufactured as a fixed-combination drug product. Velac gel has (b) (4) non-compendial excipients, Polyoxyethylene 4 Monolauryl Ether (POE 4) (b) (4) is not on the FDA Inactive Ingredient List (b) (4).

When Connetics acquired Velac gel from Yamanouchi in 2002, the drug formulation was modified (b) (4) methylparaben (b) (4) There were no other differences in the formulations besides this change and a comparability bridging program was undertaken to assess the original formulation to the to-be-marketed (TBM) formulation.

A spectroscopic analysis of the TBM formulation of Velac gel showed absorption in the UVA/UVB and visible light range. (Please see Section 7.1.12)

No microbiology studies were conducted in the clinical trials for Velac gel with the to-be - marketed formulation.

3.2 Animal Pharmacology/Toxicology

Please see Pharmtox review by Dr. Jill Merrill

3.3 Carcinogenicity Studies:

The sponsor conducted a 26 week Tg.AC mouse dermal carcinogenicity study, the results of which were reviewed by the Executive Carcinogenicity Assessment Committee (eCAC) on 3/29/05. The protocol for this study was reviewed and concurred with by the eCAC on 12/16/03. The test groups are as indicted in Table No. 1.

Results form this study (Table No. 2) indicated a positive, statistically significant response in the incidence of papillomas in all treatment groups, including the vehicle control. The Committee concluded that the study was adequate and that the vehicle of Velac gel alone caused a statistically significant increase of skin papillomas compared to the untreated controls and that Clindamcyin in Velac gel caused further significant dose-related increases in papillomas relative to the vehicle controls and untreated animals. These findings indicate that the vehicle is either a promoter or a complete carcinogen. The Pharmtox reviewer has determined Velac gel non-approvable based on the results of this study.

Table No. 1
26 week Tg.AC Mouse Carcinogenicity Study Groups (Source eCAC report)

Group	Test Article	Volume (ml/day)	Dose of clindamycin phosphate (mg/kg)
1	Velac gel vehicle control	0.1	0
2	Shaved, untreated control	0	0
3	50 µg TPA in Velac gel vehicle	0.1 ml, 3 x/week	0
4	1% clindamycin phosphate in Velac gel vehicle	0.1	40
5	3% clindamycin phosphate in Velac gel vehicle	0.1	120
6	5% clindamycin phosphate in Velac gel vehicle	0.1	200

Table No. 2
Results form the 26 week Tg AC Mouse Carcinogenicity Study (Source eCAC report)

		Incidence	Burden (all papillomas)	
Group #	Sex (M or F)	Animals bearing at least one latent or actual papilloma per effective # of animals (% incidence)	All papillomas per papilloma bearing animal	All papillomas per effective animal
		SOA	SOA only	SOA only
1	M	9/20 ** (45)	1.8	0.8
1	F	5/20 ** (25)	2.0	0.5
2	M	0/18 (0)	0.0	0.0
2	F	0/16 (0)	0.0	0.0
3	M	NA	NA	NA
3	F	NA	NA	NA
4	M	12/20 ** (60)	2.2	1.3
4	F	6/20 ** (30)	1.7	0.5
5	M	15/20** (75)	2.7	2.0****
5	F	12/20 * ** (60)	1.8	1.1****
6	M	16/20 * ** (80)	3.4	2.8 *** ****
6	F	16/20 * ** (80)	2.2	1.8 *** ****

* $p \leq 0.05$, Fisher's exact Test, when compared to vehicle (Group 1)
** $p \leq 0.05$, Fisher's exact Test, when compared to untreated (Group 2)
*** $p \leq 0.05$, ANOVA and Dunnett's t-test, when compared to vehicle (Group 1)
**** $p \leq 0.05$, ANOVA and Dunnett's t-test, when compared to untreated (Group 2)

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Efficacy of Velac gel was derived from the conduct of two pivotal safety and efficacy studies VLC.C.304 and VLC.C.305 conducted in the US, while safety for Velac gel is based on results from three Connetics studies of Velac gel in patients with acne vulgaris in the US and six clinical studies of Velac gel in patients with acne vulgaris conducted in Europe by Yamanouchi. The Connetics studies consisted of one bioavailability study VLC.C.201 and the two Phase 3 studies VLC.C.304 and VLC.C.305.

Overall, the combined studies enrolled 2988 subjects. 15 subjects were enrolled in VLC.C.201, 1083 subjects in VLC.C.304 and 1136 subjects in VLC.C.305. Yamanouchi enrolled 769 subjects in the European studies.

4.2 Tables of Clinical Studies

Following is a tabular listing of all studies. The studies are grouped by purpose.

Table No. 3
Listing of all PK/PD studies in the US and European population

Type of study	Study Identifier	Study Objective	Study Design	Study Drugs	N & disposition of subjects	Duration of treatment
BA	VLC.C.201 (US study)	Evaluate bioavailability of clindamycin & tretinoin	Open-label	Velac gel, qd, topical	15 subjects with mild-moderate acne vulgaris (AV)	28 days
BA	91-CTC-06 (European study)	Compare percutaneous absorption of clindamycin from two investigative gels and from a commercially available lotion	Open-label, cross-over	Velac gel, clindamycin HCl/tretinoin gel, Dalacin T® lotion, to chin, cheeks & forehead	12 healthy subjects	5 days
BA	92-CTC-01 (European study)	Evaluate plasma levels of tretinoin	Randomized, double-blind	Velac gel, qd, topical	20 patients with moderate-severe AV	12 weeks

Table No. 4
Listing of Safety and Efficacy studies in the US & European population

Type of study	Study Identifier	Study Objective	Study Design	Study Drugs	N & disposition of subjects	Duration of treatment
Efficacy	VLC.C.304 (US study)	Evaluate safety & efficacy	Randomized, double-blind, active & vehicle controlled	Velac gel, clindamycin in vehicle gel, tretinoin in vehicle gel, vehicle gel; qd, topically to entire face	1083 subjects (309 Velac gel, 311 clindamycin gel, 310 tretinoin gel, 153 vehicle gel) with mild-moderate AV	12 weeks
Efficacy	VLC.C.305 (US study)	Evaluate safety & efficacy	Randomized, double-blind, active & vehicle controlled	Velac gel, clindamycin in vehicle gel, tretinoin in vehicle gel, vehicle gel; qd, topically to entire face	1136 subjects (325 Velac gel, 324 clindamycin gel, 325 tretinoin gel, 162 vehicle gel) with mild-moderate AV	12 weeks
Efficacy	91-CTC-01 (European study)	Safety & efficacy (only safety assessed for this review)	Randomized, investigator-blind, active-controlled	Velac gel, clindamycin in vehicle gel; qd	162 subjects with moderate –severe AV	12 weeks
Efficacy	91-CTC-02 (European study)	Safety & efficacy (only safety assessed for this review)	Randomized, double-blind, active-controlled	Velac gel, tretinoin in vehicle gel; qd	157 subjects with moderate-severe AV	12 weeks
Efficacy	91-CTC-04 (European study)	Safety & efficacy (only safety assessed for this review)	Randomized, double-blind, active-controlled	Velac gel, Aberela (tretinoin 0.025%) qd	161 subjects with moderate-severe AV	12 weeks
Efficacy	92-CTC-01 (European study)	Safety & efficacy (only safety assessed for this review)	Randomized, double-blind, active-controlled	Velac gel, Aberela (tretinoin 0.025%) qd	40 subjects with moderate-severe AV	12 weeks
Efficacy	95-CTC-01 (European study)	Safety & efficacy (only safety assessed for this review)	Randomized, open-label, active-controlled	Velac gel qd, Dalacin® T lotion bid (clindamycin 1%)	40 subjects with moderate-severe AV	12 weeks
Efficacy	96-CTC-01 (European study)	Safety & efficacy (only safety assessed for this review)	Randomized, investigator-blind, active-controlled	Velac gel qd, Dalacin® T lotion bid (clindamycin 1%)	209 subjects with moderate-severe AV	12 weeks

Table No. 5
Listing of Dermal Safety Studies in the US & European population

Type of study	Study Identifier	Study Objective	Study Design	Study Drugs	N & disposition of subjects	Duration of treatment
Initial tolerability	VLC.C.101 (US study)	Cutaneous irritation & allergic contact sensitization	Treatment-site randomized, vehicle-controlled	Velac gel, vehicle gel, sodium lauryl sulfate, distilled water under occlusion	243 healthy subjects	21 days for irritation, 48-72 hr for sensitization
Initial tolerability	91-CTC-05 (European study)	Compare irritation between test articles	Treatment-site randomized, active and vehicle - controlled	Velac gel, vehicle gel, Acid-a-Vit cream (tretinoin 0.05%), 3 times a week on forearm	20 healthy subjects	18 days
Initial tolerability	94-CTC-01 (European study)	Determination of photo-irritation & photo-toxicity potential of test articles	Treatment-site randomized, active and vehicle - controlled	Velac gel, tretinoin in vehicle gel, vehicle gel to cellophane stripped skin on upper arm or back followed by 45 minute irradiation	10 healthy subjects	24 hours
Initial tolerability	94-CTC-02 (European study)	Evaluate irritation & sensitization in a repeat insult patch test	Treatment-site randomized; active and vehicle controlled	Velac gel, tretinoin in vehicle gel, clindamycin in vehicle gel, vehicle gel under occlusion	196 healthy subjects	21 days for irritation,72 hours for sensitization
Initial tolerability	94-CTC-03 (European study)	Evaluate irritation & photo-sensitization in a repeat insult patch test	Treatment-site randomized; active and vehicle controlled	Velac gel, tretinoin in vehicle gel, vehicle gel, 3 times per week under occlusion with irradiation	26 healthy subjects	21 days for irritation, 24 hours for sensitization
Initial tolerability	94-CTC-04 (European study)	Relative irritancy potential of test articles	Treatment-site randomized; active and vehicle controlled	Velac gel, tretinoin in vehicle gel, clindamycin in vehicle gel, Aberela gel, Antibio-Aberela gel (tretinoin, erythromycin), vehicle gel 5 days per week under occlusion	27 healthy subjects	21 days
Initial tolerability	94-CTC-05 (European study)	Relative contact irritancy potential of test articles	Treatment-site randomized; active and vehicle controlled	Velac gel, tretinoin in vehicle gel, clindamycin in vehicle gel, vehicle gel.	10 healthy subjects	15-30 minutes

4.3 Review Strategy

The efficacy review for Velac gel is based on the two pivotal studies conducted by Connetics in the US, VLC.C.304 and VLC.C.305. The safety review is based on these two studies as well as the reports of the six safety and efficacy European studies conducted by the previous sponsor (Yamanouchi) in Europe. Connetics conducted one dermal irritation and sensitization safety study in the US and submitted reports of six European dermal safety studies. Thus, the efficacy review is based solely on the two pivotal studies, while the safety review is an integrated analysis of the US and European studies.

The sponsor has submitted non-clinical and clinical literature references in support of the use of Clindamycin and Tretinoin in acne vulgaris. These are literature reports that discuss safety, efficacy, pharmacokinetics of both products, and compare the use of these products to other products used to treat acne vulgaris.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) was consulted to review the conduct of the two pivotal studies VLC.C.304 and VLC.C.305. Both these multi-center studies were conducted by Connetics in the US; two sites (one from each study) were chosen for DSI audit. These sites, # 103 and # 124 were selected for inspection because they yielded robust efficacy results for Velac over its comparators, Clindamycin and Tretinoin, which had a significant impact on the overall pooled efficacy analysis. When site # 124 (VLC.C.304) was deleted from the statistical analysis, Velac was no longer significantly greater than Clindamycin with respect to inflammatory lesion counts. Similarly, when site # 103 (VLC.C.305) was deleted from the statistical analysis, Velac was no longer significantly greater than Clindamycin with respect to inflammatory lesion counts and IGA scores.

At site 103, for study VLC.C.305, Bonnie Elewski, MD from Birmingham, Alabama was investigated. The investigator reviewed all of the 31 subjects' records randomized to this site. 3 protocol deviations were observed, however, this action was classified by DSI as Voluntary Action Indicated (VAI) with no response required.

At site 124, for study VLC.C.304, Diane Thiboutot, MD from Hershey, Pennsylvania was investigated. In this routine, data audit inspection, the field investigator reviewed the records of 21 out of the 33 subjects randomized at this site. The investigator compared the source documents to the Case Report Forms (CRFs) and indicated that there was adequate documentation to support that all subjects existed. One protocol deviation was observed that was not listed in the data-listing submitted to the Agency. This was as follows:
Subject # 3668 did not meet inclusion criteria. The subject was enrolled in the study despite having 44 inflammatory lesions and the protocol deviation was not discovered until after Visit # 3. The sponsor was notified of the deviation and granted a protocol exception on August 4, 2003 to continue enrollment of this subject in the study. This subject was randomized to the Clindamycin gel arm and completed the study. It was concluded that data from this clinical site appeared acceptable for use and a Form FDA 483 was not issued.

DSI conclusion: There were two subjects who did not meet one of the inclusion/exclusion criteria (lesion count). Overall, the data submitted in support of this NDA were found to be acceptable.

4.5 Compliance with Good Clinical Practices

The studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and the International Conference on Harmonization (ICH) harmonized tripartite guidelines for Good Clinical Practice and in compliance with local and FDA regulatory requirements. Written informed consents were obtained from subjects at the first (baseline) visit. The Intent-to-Treat (ITT) population included all subjects randomized and dispensed study drug. The Per-Protocol (PP) population excluded subjects who missed more than a total of 16 applications of study medication during the treatment period, and/or subjects who did not have efficacy evaluations at the baseline and week 12 visits, and/or subjects who used prohibited medications at anytime during the study period. Subjects with the following significant protocol deviations were excluded from the PP population:

- failure to meet entry criteria without obtaining exemption to participate
- unblinding of treatment assignment
- use of wrong study treatment

Table No. 6
Analysis Populations for Study VLC.C.304

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel	Total
ITT Population	309 (100%)	311 (100%)	310 (100%)	153 (100%)	1083 (1000%)
PP Population	257 (83%)	260 (84%)	227 (73%)	115 (75%)	859 (79%)

In Study VLC.C.304, 202 subjects (Velac gel 47; Clindamycin gel 46; Tretinoin gel 78; Vehicle gel 31) reported missing more than 16 applications and were excluded from the PP analyses. 4 subjects did not have efficacy evaluations at the baseline and week 12 visits and 6 subjects failed to meet an entry criterion and did not obtain an exemption to participate in the study.

Table No. 7
Analysis Populations for Study VLC.C.305

	Velac	Clindamaycin gel	Tretionoin gel	Vehicle gel	Total
ITT Population	325 (100%)	324 (100%)	325 (100%)	162 (100%)	1136 (100%)
PP Population	258 (79%)	274 (85%)	272 (84%)	134 (83%)	938 (83%)

In Study VLC.C.305, 180 subjects (Velac gel 60; Clindamycin gel 46; Tretinoin gel 48; Vehicle gel 26) reported missing more than 16 applications and were excluded from the PP analyses. 3 subjects did not have efficacy evaluations at baseline and week 12 visits and 8 subjects failed to meet an entry criterion and did not obtain an exemption to participate in the study.

Per protocol, smaller sites (enrolling fewer than 70 subjects) were to be combined based on geographical location and climate similarities. Therefore, prior to unblinding the data, for VLC.C.304, 9 of the 18 investigative sites were combined, resulting in a total of 13 combined

sites and for VLC.C.305, 10 of the 19 investigative sites were combined, resulting in a total of 13 combined sites for the analyses.

4.6 Financial Disclosures

During the conduct of the (b) (6) studies (b) (6) three principal investigators (b) (6) all of whom were from (b) (6) had been paid (b) (6) each. Upon request of information by the Agency, the sponsor clarified that the payment should have been listed as Grant Support and that these payments were unrelated to the Velac gel program and studies. No other investigators had any financial disclosure information.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Velac gel is a combination of Clindamycin 1% and Tretinoin 0.025% in a hydrogel base. Clindamycin, a synthetic derivative of the antibiotic lincomycin, is a broad-spectrum antibiotic that functions by irreversibly binding to the 50S subunit of the bacterial ribosome, inhibiting bacterial protein synthesis and producing bactericidal or bacteriostatic effects in susceptible bacteria. Clindamycin phosphate is biologically inactive and is rapidly hydrolyzed to active clindamycin in the blood or in the skin. In the blood, ~ 90% of Clindamycin is bound to plasma proteins and the serum half-life is approximately 3 hours in adults and 2.5 hours in children. Clindamycin is reported to be distributed in many fluids and tissues, crosses the placental barrier, and according to the sponsor, its activity has been shown in the comedones of acne subjects following topical application of 1% Clindamycin phosphate solution.

Tretinoin, the all-trans-retinoic acid is a Vitamin A derivative. Current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells and decreases microcomedone formation. It is also thought to stimulate mitotic activity and increase turnover of follicular epithelial cells causing the stratum corneum to become thinner and extrude the comedones. The all-trans-retinoic acid is transported in the general circulation almost entirely bound to plasma albumin and biliary excretion is the major route of elimination for metabolites of tretinoin.

Biopharmaceutical Program for Velac Gel

Since clindamycin and tretinoin are approved drugs with evaluated pharmacokinetic profiles, the biopharmaceutical program for Velac gel was designed to evaluate if the individual active ingredients affected the systemic bioavailability of each other when combined in a single drug product. The three bioavailability studies of Velac gel are as follows:

1. VLC.C.201 – US study conducted by Connetics.
2. 91-CTC-06 – European study conducted by Yamanouchi – A crossover comparison of the absorption of clindamycin from three topically applied formulations in healthy volunteers.

3. 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.

Study VLC.C.201 has been discussed in brief. Please see Biopharm review for a detailed review of the above studies.

Study VLC.C.201:

The objective of this open-label study was to evaluate the bioavailability (absorption) of clindamycin and tretinoin (including the metabolite 4-oxo-tretinoin), individually in subjects with acne vulgaris following 28 days of once daily application of 3 gm of Velac gel.
15 Caucasian subjects, 6 females and 9 males were enrolled; the age range was 12-20 years, the mean age was 15 years. Blood samples for evaluation of absorption were taken at screening, day 1, 5, 6 and 28 and all samples were analyzed for clindamycin, tretinoin and 4-oxo-tetinoin. Urine was collected on day 5 and day 6 (24 hour collection period).

Results of this study showed that low levels of clindamycin were detected (LLOQ 0.5 ng/ml) in plasma of all 15 subjects on day 5. Peak concentrations ranged from 0.597 to 6.520 ng/ml and occurred between 4 and 12 hours post-dose. Less than 0.1% of the daily clindamycin dose was excreted in the urine. On day 28, detectable clindamycin concentrations were seen in 3 of the 15 subjects. However, these levels did not exceed the mean Cmax on day 5.

Both tretinoin and 4-oxo-tretinoin were present only in 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. On day 28, detectable levels of tretinoin and 4-oxo-tretinoin were observed in 5 out of 11 and 4 out of 12 evaluable subjects, respectively. These levels were consistent with endogenous levels seen at baseline.

The conclusion of study VLC.C.201 was that Velac gel was safe in healthy patients with acne vulgaris and the individual active ingredients did not affect the bioavailability of each other when combined into a single drug product.

Overall, the PK studies for Velac gel showed that the concentrations of clindamycin and tretinoin in plasma and urine were generally low and that (b) (4) methylparaben did not affect systemic absorption.

Drug interactions:

As such, no drug interaction studies were conducted for this NDA. However, since Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents, such patients were excluded from the protocols. In addition, because of the known phototoxicity associated with tretinoin use, those patients who had a concurrent history of use of photosensitizers (eg. thiazides, tetracyclines, fluoroquinolones, phenothiazides, sulfonamides) were excluded because of the risk of augmented phototoxic reactions.

Since there is a risk of possible interaction with tretinoin of topical astringent products and abrasive soaps and cleansers, such products should be used with caution when using Velac gel.

*Restriction of concurrent use of photosensitizing dugs and neuromuscular blocking agents may be noted in labeling***.**

5.2 Pharmacodynamics

No pharmacodynamic studies were conducted for Velac gel.

5.3 Exposure-Response Relationships

No dose-duration studies were conducted for this NDA; Velac gel has been evaluated in six clinical trials in Europe by Yamanouchi (previous sponsor) and Connetics conducted their clinical studies as part of a bridging program. The sponsor is also relying on the extensive clinical experience with both topical clindamycin and tretinoin in the treatment of acne vulgaris. The duration of 12 weeks was chosen since it is the standard dosing regimen for the treatment of acne vulgaris in clinical studies.

6 INTEGRATED REVIEW OF EFFICACY

The efficacy of Velac gel was determined from two pivotal Phase 3, safety and efficacy trials (VLC.C.304 and VLC.C.305) conducted by Connetics in the US with the to-be-marketed formulation (methylparaben (b) (4) of Velac gel. Both these studies are discussed in detail in the following sections. The six European studies for Velac gel (original formulation, methylparaben (b) (4) were not included in the efficacy review, but only in the safety review.

6.1 Indication

Velac gel is a combination product developed for the treatment of acne vulgaris. It contains clindamycin 1% as clindamycin phosphate and tretinoin 0.025%, formulated in an aqueous hydro-gel base. It has been developed to treat the multi-factorial origin of acne, i.e. both comedones (keratolytic activity of a retinoid - tretinoin) and inflamed lesions (antibiotic - clindamycin). Both active ingredients have been marketed in the US for years in the treatment of acne vulgaris and in clinical practice, they are often used together, for eg. clindamycin in the morning and tretinoin at nighttime. Clindamycin phosphate was approved as a topical formulation (Cleocin T®) in 1980 and Tretinoin was approved in a topical formulation prior to 1982 (Retin–A®).

6.1.1 Methods

The two studies, VLC.C.304 and VLC.C.305 were nearly identical Phase 3, multi-center, randomized, double-blind, active and vehicle-controlled studies to evaluate the safety and efficacy of Velac gel, Clindamycin gel, Tretinoin gel and Vehicle gel in subjects with acne vulgaris.
The differences between the two studies were as follows:

- the protocol for VLC.C.304 included labs (complete blood count and serum chemistry panel) and clinical photography which were not included in VLC.C.305

- An interim analysis was prospectively planned to estimate the sample size needed to detect treatment differences based on the percent reduction in lesion counts in Study VLC.C.304 to increase probability of success and ensure robustness of study results.

Subjects in both studies were randomized to one of four parallel treatment groups in a 2:2:2:1 ratio; ~ 298 subjects in the Velac, Clindamycin, Tretinoin groups each and 149 subjects in the Vehicle group. Investigators, subjects and nurses/coordinators were blinded to the study medication assignment. The duration of treatment was 12 weeks for both studies, which is the standard dosing regimen for the treatment of acne vulgaris in both studies. Study visits were conducted at baseline (week 0/day 1), week 2, week 4, week 8 and week 12 (end of treatment). All treatments were administered once daily in the evening for 12 weeks.

6.1.2 General Discussion of Endpoints

It was discussed at the End-of-Phase 2 meeting that the demonstration of efficacy of Velac gel would require statistical superiority of Velac gel to its individual active components (clindamycin and tretinoin) for the following:
Primary efficacy endpoints (similar for both studies)
(1) Percent reduction in two out of three lesion counts (total, inflammatory and non-inflammatory) from baseline to week 12 (end of treatment).
(2) Proportion of subjects who have an Investigator's Static Global Assessment (ISGA) score of 0 or 1 at week 12 (end of treatment).
ISGA is a standard measure in acne studies. Vehicle gel was included in the studies to demonstrate that Velac gel was an effective treatment compared to the gel without the active ingredient (vehicle). Thus, vehicle gel was included as an inactive comparator (placebo) to Velac gel and to provide additional support that the study was appropriately planned.

Secondary efficacy endpoints for (similar for both studies)
(1) Absolute reduction in lesion counts (total, inflammatory and non-inflammatory) from baseline to week 12 (end of treatment).
(2) Absolute reduction in lesion counts (total, inflammatory and non-inflammatory) from baseline to week 12 (end of treatment).
(3) Time to a 50% reduction in lesion counts.

A number of tertiary endpoints were also analyzed descriptively for the Intent-to-Treat population. These have not been discussed as part of this review. Demographic and baseline values for primary and secondary endpoints were compared across treatment groups to ensure comparability of the results. All primary efficacy analyses were performed for the Intent-to-Treat (ITT) and Per-Protocol (PP) populations, but the ITT analysis was the primary analysis while the PP analysis was used to provide supportive evidence.

Target number of patients per site was at least 70 (10 in the vehicle group and 20 per each active drug group). Smaller sites were combined based on the geographical location and climate similarities to achieve the targeted number of subjects.

6.1.3 Study Design

The two studies discussed here are VLC.C.304 and VLC.C.305. Both studies were nearly identical, although there were some differences between the two. The differences in the two studies were the provisions in VLC.C.304 for clinical labs (complete blood count and a serum chemistry panel) and clinical photography which were not included in VLC.C.305. Also, an interim analysis was prospectively planned to verify assumptions used for sample size calculations only in the protocol for VLC.C.304. The study design for VLC.C.304 is discussed in detail and in brief for VLC.C.305.

STUDY VLC.C.304

Study title: A Phase III, multi-center, randomized, double-blind, active and vehicle-controlled study of the safety and efficacy of Velac gel for the treatment of acne vulgaris.
Investigators and Study Centers: 18 investigators and study centers. (Table No.8)
Study Period: 16th December, 2002 – 20th January, 2004.
Study Sponsor: Connetics Corporation, 3290 West Bayshore Rd., Palo Alto, CA 94303.
Study Objectives:

- To demonstrate the superiority of Velac gel versus Clindamycin gel and Tretinoin gel for 2 of the 3 lesion counts (total, inflammatory and non-inflammatory)
- To demonstrate overall greater improvement, or superiority in the Investigator's Static Global Assessment (ISGA) for Velac gel versus Clindamycin gel and Tretinoin gel
- To demonstrate the superiority of Velac gel versus Vehicle gel for 2 of the 3 lesion counts (total, inflammatory and non-inflammatory) and the ISGA
- To evaluate the safety of Velac gel in subjects aged 12 years of age and older with acne vulgaris

Table No. 8

List of Investigators for Study VLC.C.304 Source: Sponsor briefing document: Module 5, Volume1.8

Investigator	Site Number
Sunil Dhawan, MD	106
Joseph Fowler, MD	145
David Freid, MD	146
Michael Gold, MD	126
Jo Lynn Herzog, MD	104
Sewon Kang, MD	117
William Ko, MD	105
Jim Leyden, MD	123
Anne Lucky, MD	148
Steven Mings, MD	112
Amy Paller, MD	113
John Profitt, MD	116
Toivo Rist, MD	127
Joel Shavin, MD	111
Linda Stein, MD	118
Diane Thiboutot, MD	124
Guy Webster, MD	125
Hector Wiltz, MD	109

Table No. 9
List of IECs or IRBs for Study VLC.C.304

Name of IRB	Location
Children's Memorial Institute for Education and Research IRB	Chicago, IL
Henry Ford Health System IRB	Detroit, MI
Human Subjects Protection Office IRB	Hershey, PA
Jefferson Medical College IRB	Philadelphia, PA
University of Michigan Medical School IRB	Ann Arbor, MI
Western IRB	Olympia, WA

Source: Sponsor briefing document: Module 5, Volume 1.8

Data Monitoring:
This was performed by independent contractors and Connetics Clinical Research Associates. Connetics Corporation personnel performed co-monitoring at various sites during the conduct of the study. There was no Data Safety Monitoring Board.
Study Population: Male and female subjects, 18 years of age and older with facial acne vulgaris (subjects could also have had acne on other parts of the body, but non-facial areas were not included in safety and efficacy assessments).
Duration of study: 12 weeks.
Inclusion criteria:
1. Male or female subjects 12 years of age and older in good general health.
2. An ISGA score of 2 or greater at baseline.
3. Subjects must have both of the following:
   a. A minimum of 17, but not more than 40 facial inflammatory lesions (papules plus pustules) including nasal lesions.
   b. A minimum of 20, but not more than 150 facial non-inflammatory lesions (open and closed comedones), excluding nasal lesions.
4. Female participants (if of childbearing potential and sexually active) must use medically acceptable methods of birth control throughout their participation in the study.
5. The ability and willingness to follow all study procedures, attend all scheduled visits and successfully complete the study.
6. The ability to understand and sign a written informed consent form, which must be obtained prior to treatment. Subjects under the legal age of consent in the state where the study is conducted must provide assent and have the written informed consent of a parent or a guardian.

Exclusion Criteria:
1. Any nodulo-cystic lesions at baseline.
2. Pregnant or breast-feeding.
3. History or presence of regional enteritis or inflammatory bowel disease (eg., ulcerative colitis, pseudomembranous colitis, chronic diarrhea, or a history of antibiotic-associated colitis) or similar symptoms.
4. Use of topical antibiotics on the face within the past 4 weeks or during the conduct of the study and use of systemic antibiotics within the past 4 weeks.
5. Use of topical corticosteroids on the face or systemic corticosteroids within the past 4 weeks.

Use of inhaled, intra-articular, or intra-lesional (other than for facial acne lesions) steroids was acceptable.

6. Use of systemic retinoids within the past 3 months.
7. Concurrent use of drugs known to be photosensitizers (eg. thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.
8. Concomitant use of neuromuscular blocking agents. Clindamycin has neuromuscular blocking activities, which may have enhanced the action of other neuromuscular blocking agents.
9. Treatment with estrogens, including oral, implanted and topical contraceptives, androgens or anti-androgenic agents for 12 weeks or less immediately prior to starting study medication. Subjects who had been treated with estrogens, as described above, androgens or anti-androgenic agents for more than 12 consecutive weeks prior to start of study treatment were allowed to enroll as long as they did not expect to change dose, drug, or discontinue use during the study.
10. Use of topical anti-acne medications (eg. benzoyl peroxide, retinoids, azelaic acid, resorcinol, salicylates, etc.) within the past 4 weeks.
11. Concomitant use of the following types of facial products: abradents, facials, peels containing glycolic or other acids, masks, washes or soaps containing benzoyl peroxide or salicylic acid, non-mild facial acne cleansers, or moisturizers that contain retinol, salicylic, or alpha or beta hydroxy acids. Astringents and toners could be used as long as the subjects had been using the same regimen for at least 4 weeks and continued the regimen during the conduct of the study. The use of oil-free sunscreen was allowed as needed.
12. Concomitant use of medications that are reported to exacerbate acne (eg. mega-doses of certain vitamins, such as vitamin D, vitamin B 12, haloperidol, halogens such as iodide and bromide, lithium, hydantoin and phenobarbital) as these may have impacted efficacy assessments. Multivitamins, iron supplements and folate were acceptable.
13. Facial procedure (chemical or laser peel, microdermabrasion, etc.) performed by an esthetician, beautician, physician, nurse or other practioner, within the past 2 weeks or during the conduct of the study.
14. Concomitant use of tanning booths or sunbathing.
15. Known hypersensitivity or previous allergic reaction to any of the active components, lincomycin, retinoids or excipients of the study medication.
16. Use of any investigational therapy within the past 4 weeks.
17. Current drug or alcohol abuse.
18. Any other condition that, in the judgment of the investigator, would have put the subject at unacceptable risk for participation in the study.

Ethical Conduct of the Study:

This study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and the International Conference on Harmonization (ICH) harmonized tripartite guidelines for Good Clinical Practice and in compliance with local regulatory requirements.

Study design:

In this multi-center, randomized, double-blind, active and vehicle-controlled study to evaluate the safety and efficacy of Velac gel, Clindamycin gel, Tretinoin gel and Vehicle gel in subjects with acne vulgaris, 1043 subjects were enrolled in a 2:2:2:1 ratio to each of the four groups. 298 subjects were randomized to the Velac, Clindamycin and Tretinoin gel groups and 149 subjects to the Vehicle gel group. Investigators, subjects and nurses/coordinators were blinded to the study medication treatment assignment.

Study duration was 12 weeks with visits at baseline (week 0/day 1), week 2, week 4, week 8 and week 12 (end of treatment). (See Table No. 10 for Study Schedule)

Table No. 10
Schedule of Procedures for Study VLC.C.304

Parameter	**Visit 1 (Baseline) Week 0/Day 1**	**Visit 2 Week 2/Day 15 ± 3 days**	**Visit 3 Week 4/Day 29 ± 5 days**	**Visit 4 Week 8/Day 57 ± 5 days**	**Visit 5 (early term) Week 12/Day 85 ± 5 days**
Written informed consent	X				
Medical history/review of systems/physical exam	X				
Height & weight	X				
Vital signs	X				X
Concomitant medications query	X	X	X	X	X
AE query		X	X	X	X
Lesion count	X	X	X	X	X
Score signs & symptoms	X	X	X	X	X
ISGA	X	X	X	X	X
SGA	X	X	X	X	X
Urine pregnancy test (all female subjects)	X				X
Weigh & dispense study drug containers	X		X	X	
Collect & weigh study drug containers			X	X	X
Lab assessments (selected study centers)	X				X
Clinical photos (selected study centers)	X	X	X	X	X
DLQI or CDLQI	X				X

Source: Sponsor briefing document: Module 5, Volume 1.8

The baseline visit included a history and physical, labs (hematology & chemistry panels) and a urine pregnancy test on all females of childbearing potential. Lesion counts of papules, pustules, open and closed comedones were performed and an ISGA confined to the face was also performed. Signs (scaling, dryness, erythema) and symptoms (burning, itching) associated with facial acne vulgaris were also scored. Subjects completed a Subject's Global Assessment (SGA) and a Dermatology Life Quality Index (DLQI) or a Children's Dermatology Life Quality Index (CDLQI). Clinical photographs were performed at certain sites.

At week 2 (day 15), week 4 (day 29), week 8 (day 57) and week 12 (end of treatment), subjects were queried for concomitant medication use, adverse experiences (AEs) and study

compliance. Efficacy evaluations (lesion counts, ISGA, SGA) and signs and symptoms of acne were evaluated at all visits. Study medications were collected and weighed at weeks 8 and 12 and new study medication containers were weighed and dispensed at weeks 4 and 8. At week 12, vital signs were measured and the DLQI or CDLQI were administered. Selective sites performed labs at week 12 and other selected sites performed clinical photography at weeks 2, 4, 8 and 12.

Subjects applied a sufficient amount of study medication to cover the entire face (including forehead, nose, cheeks and chin). Other areas of the body (neck, chest and/or back) could be treated but were not included in the efficacy assessments. All treatments were applied once daily in the evenings for 12 weeks. Subjects washed their face with a mild soap and allowed the areas to dry fully for 20-30 minutes before applying the study drug. Other habitually used skin products were applied after the study drug.

Subjects did not disclose or discuss the color or appearance of their treatment with the study personnel or other subjects. Upon entry into the study, each subject was assigned a subject number, which defined the study drug assignment the subject was to receive and study treatments were designed to protect the blinding of the study.

Efficacy assessments:
Efficacy measurements included:
- Facial lesion counts (total, inflammatory and non-inflammatory)
- Investigator's Standard Global Assessment (ISGA)
- Subject's Global Assessment (SGA)

Primary efficacy variables assessed included lesion counts (total, inflammatory and non-inflammatory) and the ISGA, which were conducted at baseline (week 0) and at weeks 2, 4, 8 and 12. The entire face was included (hairline edge to mandibular line) in the assessments, but the non-inflammatory lesions (comedones) on the nose were not included.

Table No. 11
Investigator's Static Global Assessment

Score	Definition
Grade 0	Normal, clear skin with no evidence of acne vulgaris
Grade 1	Skin almost clear; rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red) requiring no further treatment in the investigator's opinion
Grade 2	Some non-inflammatory lesions present, with few inflammatory lesions (papules/pustules only, no nodulo-cystic lesions)
Grade 3	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident; several to many comedones and papules/pustules, there may or may not be 1 small nodulo-cystic lesion
Grade 4	Inflammatory lesions more apparent; many comedones and papules/pustules, there may or may not be a few nodulo-cystic lesions
Grade 5	Highly inflammatory lesions predominate; variable number of comedones, many papules/pustules and nodulo-cystic lesions

Source: Sponsor briefing document: Module 5, Volume 1.8

At each study visit, each subject also completed a Subject's Global Assessment. Clinical photography of the face was performed at selected sites. Neither the subject nor the investigator

was permitted to refer to the photographs at any subsequent study visit for the purposes of grading.

Table No. 12
Subject's Global Assessment

Score	Definition
0	My face is basically free of acne, with only an occasional blackhead and/or whitehead
1	My face has several blackheads and/or whiteheads and small pimples, but there are no tended deep-seated bumps or cysts
2	My face has several to many blackheads and/or whiteheads and small-to-medium sized pimples, and may have one deep-seated bump or cyst
3	My face has many blackheads and/or whiteheads, many medium-to-large sized pimples, and perhaps a few deep-seated bumps or cysts
4	My face has blackheads and/or whiteheads, and several to many medium-to-large sized pimples and deep-seated bumps or cysts dominate

Source: Sponsor briefing document: Module 5, Volume 1.8

Statistical Analysis:

Primary efficacy endpoints:

1) Percent reduction in two out of three lesion counts (total, inflammatory and non-inflammatory) from baseline to week 12 (end of treatment).
2) Proportion of subjects who have an Investigator's Static Global Assessment (ISGA) score of 0 or 1 at week 12 (end of treatment).

Secondary efficacy endpoints:

1) Absolute reduction in lesion counts (total, inflammatory and non-inflammatory) from baseline to week 12 (end of treatment).
2) Proportion of subjects who had an SGA of 0 or 1 at week 12.
3) Time to a 50% reduction in total lesion counts.

Tertiary efficacy endpoints (descriptive analysis only):

1) Proportion of subjects who had an ISGA score of 0 or 1 at weeks 2, 4 and 8.
2) Percent reduction in lesion counts (total, inflammatory and non-inflammatory) from baseline to weeks 2, 4 and 8.
3) Absolute reduction in lesion counts (total, inflammatory and non-inflammatory) from baseline to weeks 2, 4 and 8.
4) Proportion of subjects who had an SGA score of 0 or 1 at weeks 2, 4 and 8.
5) Change in quality of life as measured by the Dermatology Life quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI) from baseline to week 12.

Endpoints for subgroup analyses (gender, age, group and race):

1) Percent reduction in lesion counts (total, inflammatory and non-inflammatory) from baseline to week 12 (end of treatment).
2) Proportion of subjects who had an ISGA score of 0 or 1 at week 12.
3) Absolute reduction in lesion counts (total, inflammatory and non-inflammatory) from baseline to week 12.

Statistical Methods:
The comparisons between Velac, Clindamycin, and Tretinoin and Vehicle groups were performed at a 0.04806 two-sided significance level (adjusted for interim analysis) with at least 80% power. The null hypotheses were that the efficacy estimate for Velac gel is equal to that of Clindamycin, Tretinoin and Vehicle gels respectively, versus the alternative hypotheses that these efficacy estimates are different. Demographics and baseline values for primary and secondary endpoints were compared across treatment groups to assure comparability of results.

Primary Efficacy Analyses:

- Superiority based on percent reduction in lesion counts – The percent reduction from baseline to week 12 in each of the three lesion counts was analyzed using an ANOVA model with terms for treatment, center, and treatment-by-center interaction.
- Superiority based on ISGA – The proportion of subjects with an ISGA score of 0 or 1 were compared across the 4 treatment groups using the Cochran-Mantel-Haenszel test stratified by center. The pair wise comparisons between the Velac group and each of the other 3 groups were performed at the 0.04806 level.

Secondary Efficacy Analyses:

- Absolute reduction in lesion counts from baseline to week 12 was analyzed using the ANOVA model with terms for treatment, center and treatment-by-center interaction.
- Time to a 50% reduction in lesion counts was analyzed using Kaplan-Meier methodology. Median time to 50% reduction in total lesion counts was calculated by treatment group, when possible.

Tertiary Efficacy Analyses:
These were analyzed descriptively.

Additional Analyses:
Subgroup analyses were performed for the ITT population for all primary endpoints and the principal secondary endpoint. Each of these endpoints was grouped into the following demographic categories, but no statistical inferences were made within the subgroup analyses:

- Gender – male/female
- Age (years) – 12 to 16, 17 to 65, > 65 (if applicable)
- Race – Caucasian, African-American, Hispanic, 'Other'.

Combined Analysis of Results from the two Phase 3 studies, VLC.C.304 and VLC.C.305.
A combined analysis was performed on results from the ITT population of both studies. The results of the combined analysis, performed on the ITT population were noted to be similar to results of the individual studies; however, they have not been reviewed in detail.

Interim Analysis:
An interim analysis was conducted only in Study VLC.C.304. The purpose of this analysis was to estimate the sample size needed to detect treatment differences based on the percent reduction

in lesion counts. An independent Interim Analysis Committee was formed to evaluate the results of the interim analysis, the results of which according to the sponsor were not available to study investigators or Connetics personnel directly involved in the conduct of the study. The Interim Analysis Plan was finalized before the interim analysis was conducted.

Interim Analysis Objectives:

- Verify sample size to determine whether adjustment was needed based on the comparison of the percent change in lesion counts between Velac gel, Clindamycin gel, Tretinoin gel and Vehicle gel. Sample size was also to be verified for Velac vs. Vehicle gel comparison based on the ISGA.
- Determine whether the study can be stopped early based on meeting all primary endpoints at the 0.005 significance level.

Interim Analysis design:

The interim analysis was to be performed after approximately 424 subjects were enrolled and treated for 12 weeks. Only primary efficacy variables (percent reduction in all three lesion counts and the ISGA) were analyzed at the time of the interim analysis.

The analysis was to estimate the required sample size possibly needed to continue the study under at least 80% power at the 0.04806 significance level. This estimation was based on the following primary endpoints:

- Percent change in lesion counts (total, inflammatory and non-inflammatory) from baseline to week 12 for Velac versus Clindamycin, Tretinoin and Vehicle gels.
- Proportion of subjects with an ISGA score of 0 or 1 at week 12 for Velac vs. Vehicle gel.

If the new sample size estimate was higher than the original sample size (847 subjects), additional subjects were to be enrolled.

<u>Changes in the conduct of the study:</u>

As such, the interim analysis demonstrated that the proposed sample size was sufficient to achieve the study objectives. According to the sponsor, the independent Interim Analysis Committee reported the conclusion to Connetics' Executive Committee (EC) without breaking the study blind or disclosing any results of the interim analysis. Nonetheless, the EC increased the sample size by 196 subjects per study to ensure robust study results and increase the probability of success. On 6/27/03, the protocol was amended to adjust sample size and to change the medical monitor. After the results of the interim analysis were obtained, the sample size was increased to 1043 subjects (298 in each active group and 149 in the vehicle gel group) to ensure robust study results.

Details of the combined analysis of the efficacy data from studies VLC.C.304 and VLC.C.305 were clarified in the analysis plan prior to study completion and before study results were unblinded.

<u>Disposition of Subjects in Study VLC.C.304 (Table no. 13):</u>

1083 subjects were randomly assigned to one of the four treatment arms at 18 investigative sites. A total of 84% of subjects completed the study; the Velac group (88%) had the highest percentage of patients completing the study, while the Vehicle group (79%) had the lowest percentage. Overall, 16% of subjects discontinued the study prior to completion; the highest

frequency was in the Vehicle group (21%), followed by the Tretinoin group (20%) and the lowest was in the Velac group (12%).

Table No. 13
Subject Disposition in Study VLC.C.304

	Number (%) of subjects				
Timepoint	**Velac gel N (%)**	**Clindamycin gel N (%)**	**Tretinoin gel N (%)**	**Vehicle gel N (%)**	**Total N (%)**
Study Entry (baseline)	309 (100)	311 (100)	310 (100)	153 (100)	1083 (100)
Week 2	295 (95)	293 (94)	282 (91)	143 (93)	1013 (94)
Week 4	291 (94)	283 (91)	263 (85)	138(90)	975 (90)
Week 8	277 (90)	274 (88)	253 (82)	129 (84)	933 (86)
Week 12 (completed study)	271 (88)	270 (87)	247 (80)	121 (79)	909 (84)
Discontinued study early	38 (12)	41 (13)	63 (20)	32 (21)	174 (16)
Reasons for discontinuation					
Adverse experience	7 (2)	0 (0)	9 (3)	0 (0)	16 (1)
Subject non-compliance	1 (0)	2 (1)	2 (1)	1 (1)	6 (0)
Disease progression	0 (0)	2 (1)	1 (0)	1 (1)	4 (0)
Subject request to withdraw	10 (3)	7 (2)	11 (4)	6 (4)	34 (3)
Other	20 (6)	30 (10)	40 (13)	24 (16)	114 (11)
Subject died	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Source: Sponsor briefing document: Module 5, Volume 1.8

In the Velac group, out of the 38 subjects (12%) who discontinued study treatment early, 7 (2%) discontinued due to AEs which included application site reactions such as dryness, erythema, burning, non-compliance, depression aggravated and others were lost to follow-up or had other reasons. In the Tretinoin group, out of the 63 subjects (20%) who discontinued due to AEs, the majority of the reasons were application site reactions. The highest frequency of subjects discontinuing early due to an adverse experience was in the Tretinoin group (3%), followed by the Velac group (2%). The most frequent reason for discontinuation was 'Other' and was the highest in the Vehicle group (16%) followed by Velac gel (6%). Reasons for 'Other' included 109 subjects lost to follow-up, 1 subject who moved, 2 who became pregnant, 1 had a scheduled surgery and 1 had a family emergency. Out of a total of 4 patients discontinuing due to disease progression throughout the study, only 1 patient from the Vehicle gel group discontinued due to disease progression.

There were two patients in the Velac group in study VLC.C.304 who discontinued due to adverse reactions and used medications to treat these reactions.

1. Subject # 111-3292 reported dryness. 'Nature's Cure' (OTC product) was used to treat this reaction which resolved prior to study termination.
2. Subject # 117-3403 reported 'retinoid dermatitis, requiring corticosteroid'. This patient used Locoid Lipocream (hydrocortisone butyrate) and was lost to follow-up.

<u>Protocol Deviations for VLC.C.304:</u>
Following protocol deviations occurred during the study: 202 subjects missed > 16 applications; wrong treatment was assigned to 1 subject; 17 used prohibited medications; 6 entered the study while they did not satisfy eligibility criteria; 17 were randomized out of order and 4 did not have efficacy evaluations at baseline and week 12.

STUDY VLC.C.305:

Study Title: A Phase III, multi-center, randomized, double-blind, active and vehicle-controlled study of the safety and efficacy of Velac gel for the treatment of acne vulgaris.
Investigators and Study Centers: 19 investigators and study centers (Table No. 14)
Study Period: 16th December 2002 – 21st January, 2004.
Study Sponsor: Connetics Corporation, 3290 West Bayshore Rd., Palo Alto, CA 94303.
Study Objectives: Similar to VLC.C.304

Table No. 14
List of Investigators for Study VLC.C.305 (Source: Sponsor briefing document: Module 5, Volume 1.19)

Investigator	Site Number
Dan K. Chalker, MD, PC	110
Boni Elewski, MD	103
Toni Funicella, MD	149
J. John Goodman, MD	108
Carin Gribetz, MD	121
Terry M. Jones, MD	150
Alexa Kimball, MD	107
Robert Loss, MD	135
Christopher Moeller, MD	115
Eugene Monroe, MD	133
Amy Morris, MD	147
Alan Shalita, MD	134
Bruce Strober, MD	122
James Swan, MD	114
Leonard Swinyer, MD	130
Marvin Tankel, MD	144
Eduardo Tschen, MD	119
David Wilson, MD	132
John Wolf, Jr., MD	129

Table No. 15
List of IECs or IRBs (Source: Sponsor briefing document: Module 5, Volume 1.19)

Name of IRB	**Location**
Administrative Panel on Medical Human Subjects	Stanford, CA
Biomedics Research alliance of New York, LLC	Great Neck, NY
IRB, Mount Sinai School of Medicine	New York, New York
IRB, State University of New York	Brooklyn, NY
IRB for Human Subject Research at Baylor College of Medicine	Houston, TX
Office for the Protection of Research Subjects-IRB	Chicago, IL
University of Alabama IRB for Human Use	Birmingham, AL
Western IRB	Olympia, WA

Data Monitoring:
This was performed by independent contractors and Connetics Clinical Research Associates. Connetics Corporation personnel performed co-monitoring at various sites during the conduct of the study. There was no Data Safety Monitoring Board.

Study Population: Male and female subjects, 18 years of age and older with facial acne vulgaris (subjects could also have had acne on other parts of the body, but non-facial areas were not included in safety and efficacy assessments).
Duration of Study: 12 weeks.
Inclusion and exclusion criteria: Please refer to VLC.C.304.
Study design: This was similar to study design for VLC.C.304, except that labs, clinical photos and an interim analysis of study results was not performed in VLC.C.305.
Efficacy Assessments: Please refer to VLC.C.304.
Statistical Analysis:
Primary, secondary, tertiary efficacy endpoints and endpoints for subgroup analyses were similar to VLC.C.304.
Ethical Conduct of the Study:
This study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and the International Conference on Harmonization (ICH) harmonized Tripartite Guidelines for Good Clinical Practice and in compliance with local regulatory requirements.
Statistical Methods:

The comparisons between Velac, Clindamycin, Tretinoin and Vehicle groups were performed at a 0.04806 two-sided significance level (adjusted for interim analysis) with at least 80% power. The null hypotheses were that the efficacy estimate for Velac gel is equal to that of Clindamycin, Tretinoin and Vehicle gels respectively, versus the alternative hypotheses that these efficacy estimates are different. Demographics and baseline values for primary and secondary endpoints were compared across treatment groups to assure comparability of results.

The comparisons between Velac, Clindamycin, Tretinoin and Vehicle groups were performed at a 0.0500 two-sided significance level with at least 80% power. The null hypotheses were that the efficacy estimate for Velac gel is equal to that of Clindamycin, Tretinoin and Vehicle gels respectively, versus the alternative hypotheses that these efficacy estimates are different. Demographics and baseline values for primary and secondary endpoints were compared across treatment groups to assure comparability of results.

Primary Efficacy Analyses:

- Superiority based on percent reduction in lesion counts – The percent reduction from baseline to week 12 in each of the three lesion counts was analyzed using an ANOVA model with terms for treatment, center, and treatment-by-center interaction.
- Superiority based on ISGA – The proportion of subjects with an ISGA score of 0 or 1 were compared across the 4 treatment groups using the Cochran-Mantel-Haenszel test stratified by center. The pair wise comparisons between the Velac group and each of the other 3 groups were performed at the 0.0500 level.

Secondary Efficacy Analyses:

- Absolute reduction in lesion counts from baseline to week 12 was analyzed using the ANOVA model with terms for treatment, center and treatment-by-center interaction.

- Time to a 50% reduction in lesion counts was analyzed using Kaplan-Meier methodology. Median time to 50% reduction in total lesion counts was calculated by treatment group, when possible.

Tertiary Efficacy Analyses:
These were analyzed descriptively.

Additional Analyses:
Subgroup analyses were performed for the ITT population for all primary endpoints and the principal secondary endpoint. Each of these endpoints was grouped into the following demographic categories, but no statistical inferences were made within the subgroup analyses:

- Gender – male/female
- Age (years) – 12 to 16, 17 to 65, > 65 (if applicable)
- Race – Caucasian, African-American, Hispanic, 'Other'.

Revised sample size:
An interim analysis of the primary variables conducted after approximately one-half of the subjects had completed Study VLC.C.304 had been performed. The purpose of such an interim analysis was to estimate the sample size needed to detect treatment differences based on the percent reduction in lesion counts. This interim analysis had shown that the proposed sample size was sufficient to achieve the study objectives. Nonetheless, the sample size was increased by 196 subjects per study in both VLC.C.304 and VLC.C.305 to ensure robust study results and increase probability of success.

Table No. 16
Subject Enrollment and Disposition of ITT Population in Study VLC.C.305

Timepoint	**Number (%) of Subjects**				
	Velac gel N (%)	**Clindamycin gel N (%)**	**Tretinoin gel N (%)**	**Vehicle gel N (%)**	**Total N (%)**
Baseline (Day 1)	325 (100)	324 (100)	325 (100)	162 (100)	1136 (100)
Week 2	302 (94)	312 (96)	306 (94)	156 (96)	1078 (95)
Week 4	297 (91)	303 (94)	300 (92)	149 (92)	1049 (92)
Week 8	282 (87)	292 (90)	292 (90)	140 (86)	1006 (89)
Week 12 (completed study)	281 (86)	288 (89)	286 (88)	138 (85)	993 (87)
Discontinued study early	44 (14)	36 (11)	39 (12)	24 (15)	143 (13)
Reasons for discontinuation					
Adverse experience	4 (1)	0 (0)	8 (2)	0 (0)	12 (1)
Subject non-compliance	5 (2)	3 (1)	2 (1)	4 (2)	14 (1)
Disease progression	1 (0)	1 (0)	1 (0)	4 (2)	7 (1)
Subject request to withdraw	13 (4)	7 (2)	10 (3)	6 (4)	36 (3)
Other	21 (6)	25 (8)	18 (6)	10 (6)	74 (7)
Subject died	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Source: Sponsor Briefing Document: Module 5, Volume 1.19

Subject Disposition in VLC.C.305;
Overall, 87% of patients completed Study VLC.C.305. 13% of subjects discontinued prior to completion; the lowest incidence of patients discontinuing was in the Clindamycin group, while

the incidence was almost similar in the Velac (14%) and Vehicle (15%) groups. As in Study VLC.C.304, the most frequently reported reason for discontinuation was 'Other' which was reported by 7% (74/1136) of patients. Reasons for 'other' included 68 subjects who were lost to follow-up, 2 who moved, 1 who became pregnant, 1 did not meet study eligibility requirements and 2 who did not comply with study schedule. In the Velac group, only 1/325 discontinued due to disease progression, and in the Vehicle group, 4/162 discontinued due to disease progression.

In the Velac group, out of the 14% who discontinued early, 1% (4/44) of patients discontinued due to AEs. Following are the descriptions for these patients:

1. Subject No. 108-5039 had applications site dryness/erythema/desquamation, the AE continued post-study and medication was prescribed.
2. Subject No. 110-5217 had application site erythema/pruritus/burning/dryness
3. Subject No. 130-5939 had application site irritation, which lasted 5 days and no medication was prescribed.
4. Subject No. 149-6181 had application site erythema/vesicles/swelling/dryness. The edema, vesicles and swelling lasted 5 days resulting in early study termination.

There was one subject who discontinued in the Velac arm due to an adverse reaction and used medication to treat the reaction.

1. Subject # 110-5217 reported 'burning face at application site'. This subject used 'Complex 15' an OTC product (emollient and protective) to treat the reaction which resolved.

In general, study disposition patterns for subjects were similar across both studies VLC.C.304 and VLC.C.305.

Protocol deviations for VLC.C.305

The following protocol deviations occurred during the study (some subjects had > one protocol deviation): 180 subjects missed > 16 applications; 14 subjects were randomized out of order; 9 subjects entered the study while they did not satisfy eligibility criteria; 8 subjects used prohibited medications; 2 subjects had procedure errors; 2 subjects were un-blinded; 2 subjects did not have efficacy evaluations at baseline and week 12.

6.1.4 Efficacy Findings

Efficacy evaluation for the ITT population in the two pivotal studies VLC.C.304 and VLC.C.305 are presented in this section.

Data sets analyzed:

Two analysis populations were identified for both studies; the Intent-to-Treat (ITT) and the Per Protocol (PP) populations. The PP population results have been reviewed, and overall, the results for the PP population were similar to the ITT population.

In Study VLC.C.304, a total of 1083 subjects (ITT population) were enrolled at 18 investigative sites and were randomly assigned to one of four study drug treatments: Velac gel (309), Clindamycin gel (311), Tretinoin gel (310), and Vehicle gel (153). Overall, in the ITT population, there were 56% (602/1083) female and 44% (481/1083) male subjects. Distribution of age (ITT) was 47% (511/1083) between 12–16 years of age and 53% (571/1083) over 16

years of age. Majority of subjects (ITT) were Caucasian 62% (674/1083), African-American were 22% (234/1083), Hispanic were 11% (114/1083) and 'Other' were 6% (61/1083). The 'Other' group consisted of Asian subjects.

In Study VLC.C.305, a total of 1136 subjects (ITT population) were randomly assigned to one of four study drug treatments: Velac gel (325), Clindamycin gel (324), Tretinoin gel (325), and Vehicle gel (162). Overall, in the ITT population, there were 52% (594/1136) female subjects and 48% (542/1136) male subjects. Distribution of age (ITT) was 50% (570/1136) between 12-16 years of age and 50% (566/1136) over 16 years of age. Majority of subjects (ITT) were Caucasian 68% (768/1136), African-American were 18% (203/1136), Hispanic were 9% (104/1136) and 'Other' were 5% (61/1136). The 'Other' group consisted of Asian subjects.

Since the majority of patients were Caucasian across both studies, race distribution was not considered optimal, however, the age and gender distribution was more evenly represented in both studies.

Table No. 17
Analysis Populations for Study VLC.C.304

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel	Total
ITT Population	309 (100%)	311 (100%)	310 (100%)	153 (100%)	1083 (100%)
PP Population	257 (83%)	260 (84%)	227 (73%)	115 (75%)	859 (79%)

Source: Sponsor Briefing Document: Module 5, Volume 1.19

Table No. 18
Analysis Populations for Study VLC.C.305

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel	Total
ITT population	325 (100%)	324 (100%)	325 (100%)	162 (100%)	1136 (100%)
PP population	258 (79%)	274 (85%)	272 (84%)	134 (83%)	938 (83%)

Source: Sponsor Briefing Document: Module 5, Volume 1.19

In Study VLC.C.304, mean total, inflammatory and non-inflammatory lesion counts at baseline across the treatment groups respectively were: Velac group 74/25/49; Clindamycin gel group 74/25/49; Tretinoin gel group 74/25/49; Vehicle gel group 74/26/48. Overall, 62% (669/1083) of subjects had an ISGA score of 3 and the distribution was as follows: 61% in the Velac group, 62% in the Clindamycin and Tretinoin groups and 64% in the Vehicle group.

Subjects with a SGA score of 2 were as follows: 52% in the Velac group; 47% in the Clindamycin group; 43% in the Tretinoin group and 39% in the Vehicle gel group. Subjects with a SGA score of 3 were as follows: Velac group 32%; Clindamycin group 32%; Tretinoin group 38%; Vehicle group 43%.

9 out of the 18 investigative centers did not enroll 70 subjects and therefore, data from these sites was combined based on geographic and climatic similarities; hence there were 13 combined centers for analysis. This combination was done prior to unblinding the data.

Overall, 75% (231/309) of the Velac gel group, 76% (237/311) of the Clindamycin gel group , 67% (209/310) of the Tretinoin gel group and 73% (112/153) of the Vehicle gel group were at least 90% compliant (≤ 8 missed applications out of a total of 84 applications) with the treatment regimen.

It appears that in Study VLC.C.304, the Velac group had the highest frequency of patients with a SGA score of 2 and amongst the lowest frequency of patients with a SGA score of 3. By and large, the Velac group had patients with a SGA score of 2. Also, the frequency of patients with an ISGA score of 3 was lowest in the Velac group and highest in the Vehicle group.

In Study VLC.C.305, the mean total, inflammatory and non-inflammatory lesion counts across the treatment groups respectively were: Velac group 82/27/55; Clindamycin gel group 79/27/54; Tretinoin gel group 79/27/52; Vehicle group 82/27/55. Overall, 61% (690/1136) had an ISGA score of 3 and the distribution was as follows: 62% in the Velac group, 58% in the Clindamycin group, 63% in the Tretinoin group and 59% in the Vehicle group.

Subjects with a SGA score of 2 were as follows: Velac 44%, Clindamycin 45%; Tretinoin 44% and Vehicle 47%. Subjects with a SGA score of 3 were as follows: Velac 34%, Clindamycin and Tretinoin groups 37%, Vehicle group 33%.

10 out of the 19 investigative centers did not enroll 70 subjects and therefore data from these centers were combined and resulted in a total of 13 combined centers for the analyses. Combination of the investigative centers was completed prior to unblinding the data. All primary efficacy endpoints were analyzed across all investigative centers, as well as by-center (using combined centers) to estimate the consistency of responses at various centers.

Overall, 69% (224/325) of the Velac group, 75% (242/324) of the Clindamycin group, 73% (236/325) of the Tretinoin group and 70% (114/162) of the Vehicle group were at least 90% compliant (≤ 8 missed applications out of a total of 84 applications) with the treatment regimen.

Analysis of Efficacy:
Analyses of the primary and secondary efficacy endpoints were performed for both the ITT and the PP populations, but only the ITT population will be considered for purposes of this review.

Primary Efficacy analysis:
The two primary efficacy endpoints assessed for both studies were:

1) The percent reduction in lesion counts (total, inflammatory and non-inflammatory) from baseline to week 12 (end-of-treatment) and
2) The proportion of subjects who had ISGA scores of 0 or 1 at week 12.

1) Percent reduction in lesion counts
Study VLC.C.304
Lesion counts were performed at baseline and at weeks 2, 4, 8 and 12. Table No. 19 shows the percent reduction in lesion counts from baseline to week 12. In the ITT population, the mean percent reduction in total lesion counts was 46.2% in the Velac group, 33.8% in the Clindamycin group, 35.6% in the Tretinoin group and 20.0% in the Vehicle group. Mean percent reduction for inflammatory lesions were 52.3%, 46.2%, 39.3% and 27.2%; for non-inflammatory lesions, it was 41.5%, 25.5%, 32.9% and 14.3% in the respective treatment groups.

Table No. 19
Percent Reduction in Lesion Counts from baseline to week 12 (ITT population) VLC.C.304

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel
Number of subjects	309	311	310	153
Total lesions				
N	309	311	310	153
Mean (std)	46.2 % (35.3)	33.8 % (33.2)	35.6 % (30.8)	20.0 % (38.7)
Median	53.0	34.6	37.6	22.6
p-value*		<0.0001	<0.0001	<0.0001
Inflammatory lesions				
N	309	311	310	153
Mean (std)	52.3 % (36.2)	46.4 % (38.7)	39.3% (37.4)	27.2% (44.6)
Median	62.2	54.1	47.4	32.0
p-value		0.0503	<0.0001	<0.0001
Non-inflammatory lesions				
N	309	311	310	153
Mean (std)	41.5% (43.5)	25.0% (41.3)	32.9% (36.0)	14.3% (49.3)
Median	48.8	29.5	39.4	20.0
p-value		<0.0001	0.0065	<0.0001

Source: Sponsor Briefing Document: Module 5, Volume 1.8
* p- value based on ANOVA and tested at $\alpha = 0.04806$ level.

There was no treatment-by-center interaction for all comparisons, except for Velac vs. Vehicle gel for non-inflammatory lesions. Since this was statistically significant at 0.0383, further by-center analysis was performed. For all but one of the combined sites, the percent reduction in non-inflammatory lesion counts for Velac gel was greater than that for Vehicle gel. In this one combined site, the percent reduction in non-inflammatory lesion counts for Velac gel (53.9%/28 subjects) was lower than that for Vehicle gel (59.3%/ 14 subjects).

Superiority of Velac gel to Tretinoin and Vehicle gel was demonstrated for the mean percent reduction in all three lesion counts: Velac gel versus Tretinoin gel (total, $p < 0.0001$; inflammatory, $p < 0.0001$; and non-inflammatory, $p = 0.0065$) and Velac versus Vehicle (total $p < 0.0001$; inflammatory, $p < 0.0001$; and non-inflammatory, $p < 0.0001$). Superiority of Velac to Clindamycin gel was demonstrated in two out of the three lesion counts (total, $p < 0.0001$ and non-inflammatory, $p < 0.0001$). Mean percent reduction in inflammatory lesion counts for Velac gel was greater than that for Clindamycin gel with a borderline statistical significance, $p = 0.0503$.

Study VLC.C.305

For the primary efficacy analysis of percent reduction in lesion counts, lesion counts were performed at baseline and at weeks 2, 4, 8 and 12. Table No. 20 shows the percent reduction in lesion counts from baseline to week 12

In the ITT population, the mean percent reduction in total lesion counts was 51.1% in the Velac group, 42.5% in the Clindamycin group, 44.9% in the Tretinoin group and 26.2% in the Vehicle group. Mean percent reductions for inflammatory lesion counts were 54.5%, 48.6%, 47.2%, 33.3%; and for non-inflammatory lesions 48.8%, 37.8%, 42.7% and 22.5% in the respective groups.

Table No. 20:
Percent Reduction in Lesion Counts from baseline to week 12 (ITT population) - VLC.C.305

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel
Number of subjects	325	324	325	162
Total lesions				
Mean (std)	51.1 (28.4)	42.5 (31.7)	44.9 (31.0)	26.2 (38.5)
Median	56.5	47.8	49.3	31.4
p-value		0.0001	0.0034	< 0.0001
Inflammatory lesions				
Mean (std)	54.5 (35.5)	48.6 (37.2)	47.2 (33.9)	33.3 (46.9)
Median	63.0	54.9	52.4	43.1
p-value		0.0306	0.0041	< 0.0001
Non-inflammatory lesions				
Mean (std)	48.8 (31.3)	37.8 (39.7)	42.7 (37.1)	22.5 (45.5)
Median	54.7	44.0	49.4	26.0
p-value		< 0.0001	0.0121	< 0.0001

Source: Sponsor Briefing Document: Module 5, Volume 1.19
* p-value based on ANOVA and tested at $\alpha = 0.05$ level.

Superiority of Velac gel to Clindamycin, Tretinoin and Vehicle gels was demonstrated for the percent reduction in all three lesion counts: Velac versus Clindamycin gel (total, $p = 0.0001$; inflammatory, $p = 0.0306$; and non-inflammatory, $p < 0.0001$); Velac versus Tretinoin gel (total, $p = 0.0034$; inflammatory, $p = 0.0041$; and non-inflammatory, $p = 0.0121$); Velac versus Vehicle gel (total, $p < 0.0001$; inflammatory, $p < 0.0001$; and non-inflammatory, $p < 0.0001$).

2) Proportion of Subjects with an ISGA score of 0 or 1 at week 12 (end of treatment)
Study VLC.C.304

Subjects were assessed using the ISGA at baseline and at weeks 2, 4, 8 and 12 (end of treatment). Treatment success was defined as an ISGA score of 0 (clear skin) or 1 (almost clear skin) at week 12 (end of treatment). Table No. 21 shows the proportion of subjects in the ITT population with treatment success at week 12. At week 12, the proportion of subjects who attained treatment success were 35% (107/309) for Velac gel, 215 (66/311) for Clindamycin gel, 19% (60/310) for Tretinoin gel and 12% (19/153) for Vehicle gel. Pairwise comparisons performed between the Velac and Clindamycin group ($p = 0.0002$), Tretinoin group ($p < 0.0001$) and Vehicle group ($p < 0.0001$) were statistically significant for all comparisons. Velac gel was superior to all 3 comparators for this primary efficacy endpoint.

Table No. 21
Investigator's Static Global Assessment: Subjects with success at week 12 in ITT population - Study VLC.C.304.

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel
Number of subjects	309	311	310	153
Success	107 (35%)	66 (21%)	60 (19%)	19 (12%)
p-value*		0.0002	< 0.0001	< 0.0001

Source: Sponsor Briefing Document: Module 5, Volume 1.8
p-value is derived from Cochran-Mantel-Haenzel test ($\alpha = 0.04806$)

Study VLC.C.305:
Subjects were assessed using the ISGA at baseline and at weeks 2, 4, 8 and 12 (end of treatment). Treatment success was defined as an ISGA score of 0 (clear skin) or 1 (almost clear skin) at week 12 (end of treatment). Table No. 22 shows the proportion of subjects in the ITT population with treatment success at week 12. At week 12, the proportion of subjects who attained treatment success was 39% (128/325) for Velac gel, 32% (105/324) for Clindamycin gel, 31% (100/325) for Tretinoin gel and 15% (24/162) for Vehicle gel.

Table No. 22
Investigator's Static Global Assessment: Subjects with success at week 12 in ITT population - Study VLC.C.305.

	Velac	**Clindamycin gel**	**Tretinoin gel**	**Vehicle gel**
Number of subjects	325	324	325	162
Success	128 (39%)	105 (32%)	100 (31%)	24 (15%)
p-value		0.0441	0.0108	< 0.0001

Source: Sponsor Briefing Document: Module 5, Volume 1.19
p-value is derived from Cochran-Mantel-Haenzel test ($\alpha = 0.05$)

Secondary Efficacy Analysis:
The three endpoints assessed for both studies were:

1) Absolute reduction in lesion counts (total, inflammatory and non-inflammatory) from baseline to week 12.
2) Proportion of subjects who had a Subject's Global assessment (SGA) of 0 or 1 at week 12.
3) Time to a 50% reduction in total lesion counts.

1) Absolute reduction in lesion counts in the ITT population
Study VLC.C.304 (Table No. 23)

Table No. 23: Absolute reduction in lesion counts ITT population - Study VLC.C.304

	Velac	**Clindamycin gel**	**Tretinoin gel**	**Vehicle**
Number of subjects	309	311	310	153
Total lesions				
Mean (std)	35.0 (31.5)	23.7 (25.9)	25.6 (25.2)	12.9 (29.5)
p-value		< 0.0001	< 0.0001	< 0.0001
Inflammatory lesions				
Mean (std)	13.1(9.8)	11.3 (10.0)	11.3 (10.0)	6.8 (11.0)
p-value		0.0234	< 0.0001	< 0.0001
Non-inflammatory lesions				
Mean (std)	21.9 (26.8)	12.4 (21.2)	16.1 (20.0)	6.1 (24.3)
p-value		< 0.0001	0.0010	<0.0001

Source: Sponsor Briefing Document: Module 5, Volume 1.8
p- values based on ANOVA using a rank transform of the response

Mean absolute reduction in total lesion counts was 35.0 in the Velac group, 25.6 in the Tretinoin group and 12.9 in the Vehicle group. For inflammatory lesion counts, mean absolute reductions

were 13.1, 11.3, 9.5 and 6.8; and for non-inflammatory lesion counts, 21.9, 12.4, 16.1 and 6.1 in the respective groups.

Study VLC.C.305 (Table No. 24)
The mean absolute reduction in total lesion counts was 41.5 in the Velac gel group, 32.6 in the Clindamycin group, 35.5 in the Tretinoin group and 19.6 in the Vehicle group. For inflammatory lesion counts the reductions were 14.7, 12.9, 12.5 and 8.6, and for non-inflammatory lesion counts 26.8, 19.7. 23.0 and 10.9 in the respective treatment groups.

Table No. 24
Absolute reduction in lesion counts ITT population - Study VLC.C.305

	Velac	**Clindamycin gel**	**Tretinoin gel**	**Vehicle gel**
Number of subjects	325	324	325	162
Total lesions				
Mean (std)	41.5 (28.6)	32.6 (28.0)	35.5 (29.0)	19.6 (34.6)
p-value		< 0.0001	0.0036	< 0.0001
Inflammatory lesions				
Mean (std)	14.7 (10.3)	12.9 (10.8)	12.5 (10.0)	8.6 (13.9)
p-value		0.0141	0.0003	< 0.0001
Non-inflammatory lesions				
Mean (std)	26.8 (22.7)	19.7 (22.7)	23.0 (24.4)	10.9 (27.3)
p-value		< 0.0001	0.0102	< 0.0001

Source: Sponsor Briefing Document: Module 5, Volume 1.19
p- values based on ANOVA using a rank transform of the response

2) Subject's Global assessment (SGA) in the ITT population
Subjects performed a self evaluation of their acne at baseline and at weeks 2, 4, 8 and 12 using the SGA, where success was defined as a score of 0 or 1 at week 12.

Study VLC.C.304
In the ITT population, the proportion of subjects who attained success for SGA at week 12 were 60% for Velac gel, 51% for Clindamycin gel, 46% for Tretinoin gel and 37% for Vehicle gel.

Table No. 25: Subject's Global Assessment: Proportion of subjects with success at week 12 in ITT population – Study VLC.C.304

	Velac	**Clindamycin gel**	**Tretinoin gel**	**Vehicle gel**
Number of subjects	309	311	310	153
Success	184 (60%)	159 (51%)	143 (46%)	57 (37%)
p-value		0.0338	0.0007	< 0.0001

Source: Sponsor Briefing Document: Module 5, Volume 1.8
p-value derived from Cochran-Mantel-Haenszel test ($\alpha = 0.05$)

Study VLC.C.305
In the ITT population, the proportion of subjects who attained success for the SGA at week 12 were 63% for Velac gel, 55% for Clindamycin gel, 56% for Tretinoin gel and 44% for Vehicle gel.

Table No. 26: Subject's Global Assessment - Proportion of subjects with success at week 12 in ITT population – Study VLC.C.305

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel
Number of subjects	325	324	325	162
Success	206 (63%)	177 (55%)	182 (56%)	71 (44%)
p-value		0.0188	0.0478	< 0.0001

Source: Sponsor Briefing Document: Module 5, Volume 1.19
p-value derived from Cochran-Mantel-Haenszel test ($\alpha = 0.05$)

3) Time to a 50% reduction in total lesion counts in the ITT population

Study VLC.C.304

In the ITT population, the proportion of subjects with a 50% reduction in total lesion counts was higher in the Velac group compared to the other three groups at all study visits.

Table No. 27:
Subjects with 50% reduction in total lesion counts over time- ITT population in VLC.C.304

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel
Number of subjects	309	311	310	153
50% reduction				
Week 2	29 (9%)	17 (5%)	20 (6%)	6 (4%)
Week 4	86 (28%)	62 (20%)	60 (19%)	28 (18%)
Week 8	142 (46%)	104 (33%)	108 (35%)	39 (25%)
Week 12	183 (59%)	133 (43%)	140 (45%)	48 (31%)
p-value		< 0.0001	0.0044	< 0.0001

Source: Sponsor Briefing Document: Module 5, Volume 1.8
p-value is derived from the log-rank test ($\alpha = 0.05$) of the Odds Ratios at week 12 for Velac versus Clindamcyin, Tretinoin and Vehicle gels.

Study VLC.C.305

In the ITT population, the proportion of subjects with a 50% reduction in total lesion counts in the Velac and Tretinoin groups was the same at 15%, which was higher than the other two groups, whereas at all other study visits, the proportion was higher in the Velac group compared to the other groups.

Table No. 28
Subjects with 50% reduction in total lesion counts over time- ITT population in VLC.C.305

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel
Number of subjects	325	324	325	162
50% reduction				
Week 2	48 (15%)	32 (10%)	50 (15%)	10 (6%)
Week 4	113 (35%)	91 (28%)	98 (30%)	30 (19%)
Week 8	171 (53%)	149 (46%)	160 (49%)	48 (30%)
Week 12	217 (67%)	189 (58%)	194 (60%)	63 (39%)
p-value		0.0045	0.0539	< 0.0001

Source: Sponsor Briefing Document: Module 5, Volume 1.19
p-value is derived from the log-rank test ($\alpha = 0.05$) of the Odds Ratios at week 12 for Velac versus Clindamcyin, Tretinoin and Vehicle gels.

Interim Analysis:

The Interim Analysis was performed only in Study VLC.C.304 after 424 subjects were treated for 12 weeks. It was carried out by an in-house manager of Connetics Corporation who had signed a non-disclosure agreement and who performed the study at an undisclosed location. The conclusion of the interim analysis was that the original sample size of 847 subjects was sufficient to detect statistical significance at $\alpha = 0.04806$ level with 80% power for both objectives. After obtaining results of the study, the Executive Committee at Connetics Corporation chose to increase sample size by about 200 subjects for each study to "increase the probability of the positive trail outcome and to ensure robustness of the results" without apparently knowing specific details of the interim analysis. This number was adjusted to 196 subjects to account for the randomization block size. Table No. 29 shows results submitted by the sponsor in request to Agency request for information.

The interim analysis confirmed that the original sample size estimates were sufficient to detect statistically significant differences between the Velac gel group and each of the comparator groups for at least two out of the three lesion counts with 80% power at the 0.04806 significance level. The original sample size estimates were not sufficient in comparing Velac gel to Clindamycin and Tretinoin for inflammatory lesions, but this was one out of the three lesion types. The Interim Analysis has been reviewed in detail in the statistical review by Dr. Soukup and it states the following 'The overall conclusion reached from this exploration is that the decision to increase sample size after the interim did not inflate the likelihood of success which would thereby yield favorably biased conclusions for the sponsor. Thus, with the information provided by the sponsor and from the data of the two pivotal studies, it appears as if the conclusions of efficacy are not negatively impacted by results of the interim analysis (i.e. no favorable bias towards efficacy is seen by increasing sample size).'

Table No. 29
Results of the Interim Analysis as submitted by the Sponsor

	Velac	**Clindamycin**	**Tretinoin**	**Vehicle**
	N = 123	N = 120	N = 123	N = 123
Total lesions				
Mean (SD) N to maintain 80% power	44.2% (29.3%)	35.1% (35.2) 242*	36.1% (29.2%) 211*	23.7% (39.1%) 45*
Non-inflammatory lesions				
Mean (SD) N to maintain 80% power	40.7% (35.8%)	24.7% (46.9%) 138*	31.1% (32.3%) 222*	17.9% (55.3%) 71*
Inflammatory lesions				
Mean (SD) N to maintain 80% power	48.0% (35.9%)	48.2% (35.0%) x	41.3% (34.8%) 460	30.2% (39.0%) 58*
Investigator Global Assessment				
Percent Success N to maintain 80% power	32.5%	Not calculated NA	Not calculated NA	16.4% 87*

Source: Statistical Review – Dr. Matt Soukup
* Denotes cases when the required N to maintain 80% power and declare significance of Velac gel to comparator at $\alpha = 0.04806$ was less than or equal to the original sample size estimate (242 active, 121 vehicle)

Tertiary Analysis:

The five tertiary endpoints included in both studies VLC.C.304 and VLC.C.305 for which only descriptive analyses were performed are as follows:

1. The proportion of subjects who had an ISGA scores of 0 or 1 at weeks 2, 4 and 8.
2. The percent reduction in lesion counts (total, inflammatory and non-inflammatory and non-inflammatory) from baseline to weeks 2, 4 and 8.
3. Absolute reduction in lesion counts (total, inflammatory and non-inflammatory) from baseline to weeks 2, 4 and 8.
4. Proportion of subjects who had a SGA score of 0 or 1 at week 2, 4 and 8.
5. Change in quality of life as measured by the DLQI or the CDLQI questionnaire from baseline to week 12.

These endpoints have limited regulatory utility and as such, have not been discussed in this review.

Subgroup Analysis of Results

Three additional subgroup analyses of the two primary efficacy endpoints (percent reduction in lesion counts from baseline to week 12 and the proportion of subjects with an ISGA score of 0 or 1 at week 12) were performed on the ITT population in Studies VLC.C.304 and VLC.C.305. These analyses were performed for the following demographic categories: gender (male, female), age (12-16 years, over 16 years) and race (Caucasian, African-American, Hispanic, 'Other'). In both studies, subjects categorized as Asian were combined with the 'Other' race category because of the small number of Asian subjects enrolled.

Lesion Count Analysis by Gender

In Study VLC.C.304, the overall enrollment by gender in the ITT population was 56% female (602 subjects) and 44% male (481 subjects). In study VLC.C.305, in the ITT population, there were 52% female (594 subjects) and 48% male (542 subjects).

The active treatment groups were associated with greater reductions in lesion counts than the Vehicle group. Across all comparator groups, female subjects had greater reduction in lesion counts than male subjects.

Table No. 30
Mean Percent Reduction in Lesion Counts by Gender - Study VLC.C.304

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel
Males				
Total lesions	43.4%	30.2%	34%	20.2%
Inflammatory	47.9%	41.8%	37.0%	24.1%
Non-inflammatory	39.6%	22.2%	32.3%	15.8%
Females				
Total Lesions	48.7%	36.8%	36.6%	19.9%
Inflammatory	56.2%	50.1%	40.7%	30%
Non-inflammatory	43.2%	27.4%	33.3%	13.1%

Source: Sponsor Briefing Document, Module 2, Volume 1.4

Table No. 31
Mean Percent Reduction in Lesion Counts by Gender - Study VLC.C.305

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel
Males				
Total lesions	50%	44.2%	41.6%	23%
Inflammatory	52.7%	45.4%	44.7%	28.6%
Non-inflammatory	56%	51.6%	49%	39.4%
Females				
Total lesions	52%	41%	47.5%	30.2%
Inflammatory	56%	51.6%	49%	39.4%
Non-inflammatory	49.8%	33%	45.8%	26%

Source: Sponsor Briefing Document, Module 2, Volume 1.4

Lesion Count Analysis by Age

In VLC.C.304, 47% (511/1083) subjects were between 12-16 years of age, and 53% (571/1083) subjects were > 16 years of age. In VLC.C.305, 50% (570/1136) subjects were between 12-16 years of age, and 50% (566/1136) subjects were > 16 years of age.

In both studies, the active treatment groups were associated with greater reductions in lesion counts compared to the Vehicle group and the highest reductions were in the Velac group.

Table No. 32
Mean Percent Reduction in Lesion Counts by Age – Study VLC.C.304

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel
Ages 12-16 years				
Total lesions	44%	30%	31%	5.8%
Inflammatory	47.6%	44.6%	37.7%	16.4%
Non-inflammatory	40.7%	22%	27.4%	- 2.4%
Ages > 16 years				
Total lesions	48.3%	37.2%	39.4%	30.8%
Inflammatory	57.1%	48%	40.8%	35.4%
Non-inflammatory	42.4%	27.9%	37.6%	27%

Source: Sponsor Briefing Document, Module 2, Volume 1.4

Table No. 33
Mean Percent Reduction in Lesion Counts by Age – Study VLC.C.305

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel
Ages 12-16 years				
Total lesions	51.9%	41.9%	42.7%	24.2%
Inflammatory	54%	46.75	41.5%	31%
Non-inflammatory	50%	38.9%	42.8%	20.6%
Ages > 16 years				
Total lesions	50.3%	43%	46.6%	29.6%
Inflammatory	55%	50.3%	51.7%	37.2%
Non-inflammatory	47.4%	36.9%	42.6%	25.7%

Source: Sponsor Briefing Document, Module 2, Volume 1.4

Lesion Count Analysis by Race

In VLC.C.304, the majority of subjects enrolled were Caucasian 62% (674/1083), African-American were 22% (234/1083), Hispanic were 11% (114/1083) and 'Other' were 6% (61/1083).

In VLC.C.305, the majority of subjects enrolled were also Caucasian 68% (768/1136), African-American were 18% (203/1136), Hispanic were 9% (104/12136) and 'Other' were 5% (61/1136).

Table No. 34
Mean Percent Reduction in Lesion Counts by Race – VLC.C.304

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel
Caucasian				
Total lesions	46.5%	33.9%	39%	22.5%
Inflammatory	50.5%	46.3%	41.9%	28.3%
Non-inflammatory	43%	25.3%	36.3%	18%
African-American				
Total lesions	42.95	28.7%	28.5%	21.4%
Inflammatory	56.8%	46.2%	39.8%	36.3%
Non-inflammatory	32.9%	17.7%	21.4%	11%
Hispanic				
Total lesions	48.3%	34.6%	26.5%	- 4.3%
Inflammatory	49%	39%	18.3%	4.8%
Non-inflammatory	46.6%	28.9%	33%	- 11.6%
Other				
Total lesions	51%	51.2%	41.7%	38.7%
Inflammatory	63.2%	61.2%	43.9%	28.7%
Non-inflammatory	43.7%	44%	41.6%	43.4%

Source: Sponsor Briefing Document, Module 2, Volume 1.4

Table No. 35
Mean Percent Reduction in Lesion Counts by Race – VLC.C.305

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel
Caucasian				
Total lesions	52%	43.3%	45%	24.5%
Inflammatory	53.9%	48%	46%	28.8%
Non-inflammatory	50.3%	38.7%	43.5%	21.3%
African-American				
Total lesions	51%	34.3%	44.4%	33%
Inflammatory	65%	42%	50%	51.4%
Non-inflammatory	44.8%	29.4%	40.5%	25%
Hispanic				
Total lesions	43.4%	46%	56%	32.6%
Inflammatory	38.5%	54.6%	54.8%	38%
Non-inflammatory	46.6%	41%	58.4%	32%
Other				
Total lesions	49.9%	50%	24%	12.5%
Inflammatory	58%	59%	39.9%	15%
Non-inflammatory	42.8%	44.8%	13.7%	13%

Source: Sponsor Briefing Document, Module 2, Volume 1.4

In both studies, the active treatment groups of all race groups were associated with greater reductions in ach of the lesion counts than the Vehicle groups. In VLC.C.304, the Velac group achieved the greatest reductions in all race groups, except for the 'Other' race group, which had similar reductions in the Velac and Clindamycin groups.

In VLC.C.305, Caucasians and African-Americans in the Velac groups achieved the greatest reductions in all lesions counts. Hispanic subjects achieved greatest reduction in all lesion counts in the Tretinoin group, while subjects in the 'Other' group had greatest reduction in the Clindamycin group. It is possible

ISGA Score Analysis by Gender, Age and Race:

Treatment success was defined as the proportion of subjects with an ISGA score of 0 or 1 at week 12. The active treatment groups were associated with higher rates of treatment success than the Vehicle gel group and the Velac group had the highest rate of treatment success. In general, female subjects had higher rates of treatment success than males, and this pattern was seen across all treatment groups.

Table No. 36
ISGA Score Analysis by Gender, Age and Race – VLC.C.304

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel
Gender				
Females	38%	23%	22%	14%
Males	31%	19%	16%	11%
Age				
12-16 years	29%	19%	14%	11%
> 16 years	41%	23%	24%	14%
Race				
Caucasian	33%	23%	18%	14%
African-American	32%	13%	19%	9%
Hispanic	46%	19%	20%	6%
Other	44%	35%	30%	25%

Source: Sponsor Briefing Document, Module 2, Volume 1.4

Table No. 37
ISGA Score Analysis by Gender, Age and Race – VLC.C.305

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel
Gender				
Females	45%	38%	35%	19%
Males	32%	27%	265	12%
Age				
12-16 years	36%	30%	23%	9%
> 16 years	43%	34%	37%	25%
Race				
Caucasian	39%	30%	28%	14%
African-American	48%	29%	36%	25%
Hispanic	23%	30%	43%	8%
Other	40%	60%	29%	0%

Source: Sponsor Briefing Document, Module 2, Volume 1.4

In both studies, subjects > 16 years of age had higher rates of treatment success than subjects 12-16 years of age and this pattern was seen across all age groups. In both studies, the active treatment groups of all races had higher success than the Vehicle group. In VLC.C.304, the Velac group achieved the highest rate of success across all treatment groups. In VLC.C.305, Caucasians and African-Americans in the Velac group had the highest rate of success, while the Hispanic subjects had the highest rate of success with the Tretinoin and Cindamycin treatments. Subjects in the 'Other' group also had the highest rate of success in the Clindamycin group. This most likely was due to a very small sample size in the 'Other' group (37 subjects overall).

Race representation was considered sub-optimal across both studies, since the majority of patients were Caucasian.

6.1.5 Clinical Microbiology

No microbiology studies were performed for this NDA.

6.1.6 Efficacy Conclusions

Results of the two pivotal efficacy studies, VLC.C.304 and VLC.C.305 indicate that Velac gel was able to meet the pre-defined primary and secondary efficacy endpoints and demonstrate effectiveness in the treatment of lesions of acne vulgaris.

In Study VLC.C.304, Velac gel demonstrated statistically significant superiority to Clindamycin gel for the primary efficacy endpoint based on the mean percent reduction in two of the three lesion counts: total ($p < 0.0001$) and non-inflammatory ($p < 0.0001$). For inflammatory lesion counts, the statistical significance was borderline at $p = 0.0503$. However, per pre-defined protocol agreements, Velac gel achieved its objective of demonstrating superiority in 2 out of 3 lesion counts.

Statistically significant superiority was demonstrated against Tretinoin based on mean percent reduction for all three lesion counts: total ($p < 0.0001$), inflammatory ($p < 0.0001$) and non-inflammatory ($p = 0.0065$).

Statistically significant superiority was also demonstrated against Vehicle gel based on mean percent reduction for all three lesion counts: total ($p < 0.0001$), inflammatory ($p < 0.0001$) and non-inflammatory ($p < 0.0001$).

For the second primary efficacy endpoint, i.e., the ISGA of 0 (clear) or 1 (almost clear) at week 12, Velac gel demonstrated statistically significant superiority to Clindamycin gel ($p = 0.0002$), Tretinoin gel ($p < 0.0001$) and Vehicle gel ($p < 0.0001$).

Velac gel also demonstrated statistically significant superiority for the three secondary efficacy endpoints against Clindamycin, Tretinoin and Vehicle gels.

In Study VLC.C.305, Velac gel demonstrated statistically significant superiority to Clindamycin gel for the primary efficacy endpoint based on the mean percent reduction in all three lesion counts: total ($p = 0.0001$), inflammatory ($p = 0.0306$) and non-inflammatory ($p < 0.0001$).

Statistically significant superiority was demonstrated against Tretinoin based on mean percent reduction for all three lesion counts: total ($p = 0.0034$), inflammatory ($p = 0.0041$) and non-inflammatory ($p = 0.0121$).

Statistically significant superiority was demonstrated against Vehicle gel based on mean percent reduction for all three lesion counts: total ($p < 0.0001$), inflammatory ($p < 0.0001$) and non-inflammatory ($p < 0.0001$).

For the second primary efficacy endpoint, i.e., the ISGA of 0 (clear) or 1 (almost clear) at week 12, Velac gel demonstrated statistically significant superiority to Clindamycin gel ($p = 0.0441$), Tretinoin gel ($p < 0.0108$) and Vehicle gel ($p < 0.0001$).

Velac gel also demonstrated statistically significant superiority for the three secondary efficacy endpoints against Clindamycin and Vehicle gels. In the case of Tretinoin gel, Velac gel demonstrated statistically significant superiority for the secondary efficacy endpoints of mean absolute reduction of lesion counts and SGA assessment at week 12. However, for the time to 50% reduction of total lesion counts, Velac gel had borderline statistical significance ($p = 0.0539$).

After obtaining the results of the interim analysis conducted in Study VLC.C.304, the sample size of subjects was increased, so as to increase the probability of success; however, based on the Agency statistical review, the overall conclusion reached was that the decision to increase sample size after the interim analysis did not inflate the likelihood of success which would yield favorably biased conclusions for the sponsor (no favorable bias towards efficacy was seen by increasing sample size).

Results of the combined efficacy analysis of the two studies and results from the Per Protocol analysis supported above results obtained for the ITT population. Results from the subgroup analyses of the two primary efficacy endpoints for age, gender and race for both studies demonstrated that in general, female subjects had better results than male subjects and those patients > 16 years of age performed somewhat better than patients 12-16 years of age.

Efficacy Analysis Conclusion**:** The results of the two pivotal studies VLC.C.304 and VLC.C.305 indicate that Velac gel applied once a day for 12 weeks is effective in the treatment of lesions of facial acne vulgaris. No claims of efficacy should be made for non-facial areas, since they were not included in the efficacy analysis. Since Clindamycin is a topical antibiotic, it is expected to be more efficacious in inflammatory lesions; this probably explains the slightly higher p-values seen for inflammatory lesions in comparing Velac to Clindamycin gel in both studies for the primary efficacy endpoint of percent reduction in lesion counts.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The integrated summary of clinical safety for Velac gel combines safety results from the following:

1) Three studies of Velac gel (2 safety and efficacy, and 1 PK study) in patients with acne vulgaris conducted in the US by Connetics *and*
2) Six safety and efficacy studies of Velac gel in patients with acne vulgaris conducted in Europe by Yamanouchi.

The formulation of Velac gel differed in the two studies, in that the concentration of the (b) (4) methylparaben was (b) (4) in the Yamanouchi studies and (b) (4) in the Connetics studies. The Connetics studies (ITT population) consisted of two pivotal, Phase 3, multi-center, randomized, double-blind, safety and efficacy studies i.e. VLC.C.304 and VLC.C.305 and the bioavailability study VLC.C.201 in which Velac gel was compared to Clindamycin gel, Tretinoin gel and Vehicle gel in patients with mild to moderate acne vulgaris. The Yamanouchi studies (ITT population) consisted of two sets of studies in patients with moderate-to severe acne vulgaris, each consisting of a pilot study and two Phase 3 safety and efficacy studies.

The ISS ITT population refers to the Integrated Summary of Safety/Intent-to-Treat population which is a combination of the US and European studies. 1083 subjects were enrolled in VLC.C.304, 1136 subjects in VLC.C.305, and 15 subjects in VLC.C.201, while the European studies enrolled 769 subjects. Overall, the combined studies enrolled 2988 subjects and 2958 received at least one dose of study drug and are included in the overall safety population. Across all studies, subjects applied the study medication over the entire face (including forehead, nose, cheeks and chin). Safety of Velac gel over non-facial areas was not assessed in these studies. Duration of treatment was 12 weeks in all studies, except VLC.C.201 where it was 28 days. Safety of Velac gel was evaluated in the Connetics and Yamanouchi studies by an assessment of vital signs, adverse events, changes in signs and symptoms of facial acne vulgaris and clinical labs. (In the US studies, labs were performed only in a subset of patients enrolled in VLC.C.304)

European Studies:

The Yamanouchi (European) studies in patients with moderate-severe acne vulgaris consisted of two sets. In one set of studies, Velac gel was compared to clindamycin containing products (Clindamycin gel or Dalacin® T lotion); studies 95-CTC-01, 91-CTC-01 and 96-CTC-01. In the second set, Velac gel was compared to tretinoin containing products (Tretinoin gel or Aberela® gel); studies 92-CTC-01, 91-CTC-02 and 91-CTC-04.

The Yamanouchi studies did not contain a vehicle group and were conducted only in Caucasian patients. All studies enrolled patients based on an acne severity of grade 3 or higher based on the Cook scale (described below); the IGA scale was not used. Patients were evaluated in all studies at baseline and weeks 2, 4, 8 and 12.

Velac gel versus Clindamycin

1. Protocol # 95-CTC-01 - open label, randomized, two-center, parallel-group pilot study of Velac gel compared to Dalacin T lotion (1% clindamycin lotion). 40 patients were enrolled in a 1:1 ratio; Velac gel was administered once daily and Dalacin T lotion twice daily for 12 weeks.
2. Protocol # 91-CTC-01 – investigator-blinded, randomized, multi-center, parallel-group study of Velac gel compared to Clindamycin gel 1%. 162 subjects were enrolled in a 1:1 ratio and all treatments were administered once at night for 12 weeks.
3. Protocol # 96-CTC-01 – investigator-blinded, multi-center, randomized study of Velac gel compared to Dalacin T lotion. 209 subjects enrolled in a 1: 1 ratio, Velac gel was administered once daily and Dalacin T lotion twice daily.

Velac gel versus Tretinoin

1. Protocol # 92-CTC-01 – double-blind, randomized, comparative, two-center pilot study of Velac gel compared to Aberela gel (0.025% tretinoin). 40 subjects enrolled in a 1: 1 ratio and all treatments were administered once at night for 12 weeks.
2. Protocol # 91-CTC-02 – double-blind, randomized, multi-center, comparative study of Velac gel compared to Tretinoin gel. 157 subjects enrolled in a 1:1 ratio and all treatments were administered once at night for 12 weeks.
3. Protocol # 91-CTC-04 – double-blind, multi-center, randomized, parallel-group study of Velac gel compared to Aberela gel. 161 subjects enrolled in a 1: 1 ratio and all treatments were administered once daily for 12 weeks.

Cook scale for assessing facial acne (European Studies)

Grade	Description
0	Skin need not be perfectly clear. A few scattered small comedones or papules may be present; but these should be visible only upon examination.
2	About ¼ of facial area involved with small papules (6-12) and comedones (may be a few large comedones or as many as 20-30 small closed comedones). Very few pustules or large prominent papules present.
4	About ½ of facial area involved with small papules and large or small comedones. A few pustules or large prominent papules usually present.
6	About ¾ of facial area involved with papules and/or large open comedones. Numerous pustules present, some of them large.
8	Practically all of the facial area involved with lesions. Large prominent pustules usually quite visible. Lesions usually inflammatory. Other types of acne (eg. Conglobate, including sinus and cystic types) may be present.

Severity scales of 1, 3, 5 and 7 may be assigned for intermediate cases.
Source: Sponsor's briefing document Module 5, Vol. 1.34

Table No. 38
Study Drug Exposure for VLC.C.304, VLC.C.305 and European studies - ITT population

	Velac	Clindamycin gel	Tretinoin gel	Vehicle gel (US studies)
No. of subjects Total/European	1003/369	836/201	804/169	315
Days on study drug				
Mean (std)	73.5 (22.6)	74.4(22.8)	70.0(26.3)	68.1(27.5)
Median	81.0	82.0	80.0	80.0
Min, max	(1, 115)	(1, 113)	(1, 133)	(1, 107)

Demographics:

In the ISS ITT population of the US and European studies, the number of subjects enrolled was 2973 (2958 subjects received at least one dose of study medication). There were 52% females and 48% males; subjects 12-16 years of age constituted 45% and those > 16 years of age 55%; one subject was > 65 years of age. Caucasians constituted 74%, African-Americans 15%, Hispanics 7% and Asians 2% of the ISS ITT population.

In studies VLC.C.304 (n=1083) and VLC.C.305 (n=1136), females constituted 54% of the ITT population and males 46% and 51% of subjects were > 16 years of age. In these studies, Caucasians constituted 65%, African-Americans 20%, Hispanics 10% and Asians 2% and 'Others' 3%. In study VLC.C.201, there were 9 males and 6 females, all subjects received Velac gel for 28 days; 12 subjects were 12-16 years of age and 3 subjects were 17-65 years of age. Only Caucasians were enrolled in this study.

In the European studies (n=739), females constituted 45% and males 55%; subjects 12-16 years of age were 32% and 62% of patients were > 16 years of age. Only Caucasians were enrolled in the European studies.

Across the US and European studies, there is no pharmacokinetic information available for non-Caucasian patients.

Adverse events (AEs):

Adverse events have been described for the ISS/ITT population. Overall, the most significant and frequent adverse events were local and included application site reactions. These were mild to moderate in most cases and generally decreased in intensity after a few weeks of therapy. The description of these AEs is similar to the well described AE profile of Tretinoin and it was felt that most of these events could be attributed to the Tretinoin component of Velac gel.

Incidence of Severe or Life-Threatening Adverse Experiences in the ISS ITT population:
There were two life-threatening adverse experiences reported for Study VLC.C.304, both in the Velac gel group.
1) A 21 year old male who was hospitalized for status asthmaticus and convulsions about 21 days after initiating treatment. His past medical history included asthma and an unspecified demyelinating disorder. This patient recovered without sequelae and although study treatment was discontinued for 6 days during hospitalization, he went on to complete study treatment.
This event appears unrelated to study drug treatment.

2) A 36 year old male patient was hospitalized with diabetic ketoacidosis about 2 months after initiating treatment. His past medical history included type I diabetes mellitus, treated with insulin. The patient recovered without sequelae and although study drug was discontinued during the 3 days of hospitalization, he went on to complete study treatment.
This event appears unrelated to study drug treatment

Incidence of Treatment-Related Severe Adverse Events in the ISS/ITT population:
Severe AEs in the ISS ITT population were reported by 2% (65/2958) of subjects; Velac gel 3% (33/1003), Clindamycin gel 1% (11/836), Tretinoin gel 2% (18/804), Vehicle gel 1% (3/315).

There were no treatment-related life-threatening AEs for any subjects in any of the studies. Treatment-related severe AEs in the ISS/ITT population (Table No. 39) were reported by 1% of subjects overall; Velac gel 2%, Clindamycin gel 0%, Tretinoin gel 1%, Vehicle 0%. Most significant of these AEs were local events, related to study drug treatment.

Table No. 39
Treatment-Related Severe Adverse Experiences – ISS ITT population

System Organ Class Preferred Term	Velac N (%)	Clindamycin gel N (%)	Tretinoin gel N (%)	Vehicle gel N (%)	Total N (%)
Number of subjects	1003	836	804	315	2958
Subjects with severe or life-threatening treatment-related AE	17(2)	2(0)	12(1)	0(0)	31(1)
GASTROINTESTINAL DISORDERS	1(0)	0(0)	0(0)	0(0)	1(0)
Desquamation mouth	1(0)	0(0)	0(0)	0(0)	1(0)
GENERAL DISORDERS & ADMINISTRATIVE SITE CONDITIONS	14(1)	1(0)	10(1)	0(0)	25(1)
Application site burning	4(0)	0(0)	4(0)	0(0)	8(0)
Application site desquamation	3(0)	0(0)	3(0)	0(0)	6(0)
Application site dryness	5(0)	0(0)	1(0)	0(0)	6(0)
Application site erythema	5(0)	0(0)	3(0)	0(0)	8(0)
Application site irritation	3(0)	1(0)	2(0)	0(0)	6(0)
Application site pruritus	2(0)	0(0)	3(0)	0(0)	5(0)
Application site rash	0(0)	0(0)	1(0)	0(0)	1(0)
Application site swelling	1(0)	0(0)	0(0)	0(0)	1(0)
Application site vesicles	1(0)	0(0)	0(0)	0(0)	1(0)
INVESTIGATIONS	0(0)	1(0)	0(0)	0(0)	1(0)
Lab test abnormal NOS	0(0)	1(0)	0(0)	0(0)	1(0)
SKIN & SUBCUTANEOUS TISSUE DISORDERS	2(0)	0(0)	2(0)	0(0)	4(0)
Dermatitis NOS	1(0)	0(0)	1(0)	0(0)	2(0)
Erythema	0(0)	0(0)	1(0)	0(0)	1(0)
Localized exfoliation	1(0)	0(0)	0(0)	0(0)	1(0)

Source: Sponsor briefing document Module 2, volume 1.4.

From Table No. 39, it is clear that the majority of treatment-related severe AEs were local and related to study drug application site. There were no statistically significant differences between the treatment groups, although the incidence of clinically significant application site reactions was highest in the Velac gel group, followed by the Tretinoin gel group. No treatment-related severe AEs were reported for Study VLC.C.201.

7.1.1 Deaths

There were no deaths reported in either the Connetics (US) or the Yamanouchi (European) studies. Although the drug was approved for marketing in France, it was never marketed; therefore there is no post-marketing information available.

7.1.2 Other Serious Adverse Events (SAEs)

There were 7 SAEs in the Connetics studies; 3 subjects in the Velac gel group and 1 subject in the Clindamycin gel group in Study VLC.C.304, and 3 subjects in VLC.C.305, all of which were in the Tretinoin groups. There were no SAEs in VLC.C.201 and only 1 SAE was reported in the European studies. None of the SAEs appear to be related to study drug, narratives are provided below.

Table No. 40
Serious Adverse Events – ISS ITT Population

Preferred Term	Velac N (%)	Clindamycin Gel N (%)	Tretinoin Gel N (%)	Vehicle Gel N (%)	Total N (%)
Number of subjects	1003	836	804	315	2958
Subjects with a SAE	3(0)	1(0)	3(0)	0(0)	7(0)
Abdominal pain upper	0(0)	0(0)	1(0)	0(0)	1(0)
Gastroenteritis NOS	0(0)	1(0)	0(0)	0(0)	1(0)
Ankle fracture	0(0)	0(0)	1(0)	0(0)	1(0)
Diabetic ketoacidosis	1(0)	0(0)	0(0)	0(0)	1(0)
Convulsions NOS	1(0)	0(0)	0(0)	0(0)	1(0)
Depression aggravated	1(0)	0(0)	0(0)	0(0)	1(0)
Menometrorrhagia	0(0)	0(0)	1(0)	0(0)	1(0)
Pelvic pain NOS	0(0)	0(0)	1(0)	0(0)	1(0)
Respiratory failure (Excl Neonate)	1(0)	0(0)	0(0)	0(0)	1(0)

Source: Sponsor briefing document Module 2, volume 1.4.

Narratives of SAEs:

1. VLC.C.304 – Velac arm - Subject 106-3216, SAE Case ID 2003S1000028, was a 28 year old male hospitalized for status asthmaticus. (This case has been described previously under Severe/Life-Threatening AEs). This patient completed study treatment.
This event does not appear to be related to study treatment.

2. VLC.C.304 – Velac arm - Subject 112-3115, SAE Case ID 2003S1000029, was a 14 year old female hospitalized for aggravated depression one day after starting Velac gel. She had a past medical history (PMH) of depression. The patient's mother withdrew consent to participate in the study a month later.
This event does not appear to be related to study treatment.

3. VLC.C.304 – Velac arm - Subject 126-3848, SAE Case ID 2003S1000076 was a 36 year old male hospitalized for diabetic ketoacidosis. (This case has been described previously under Severe/Life-Threatening AEs). This patient completed study treatment.
This event does not appear to be related to study treatment.

4. VLC.C.304 – Clindamycin arm - Subject 105-3034, SAE ID 2003S1000060 was a 25 year old female hospitalized for severe gastroenteritis about 40 days after initiating treatment with Clindamycin gel. This was preceded by several days of nausea, vomiting and diarrhea and the patient was discharged a day later after standard treatment. No action was taken with the study drug; patient recovered without sequelae and went on to complete study drug treatment.

This event occurred in the Clindamycin arm; cultures for Clostridium difficile were not performed. An ova and parasites test was performed, which was negative and a stool culture for Salmonella, Shigella, Campylobacter, E.Coli 0157 and Yersinia was negative. However, since this patient recovered within a few days and went on to continue treatment with Clindamycin, it is unlikely that this was a case of pseudomembranous colitis.

5. VLC.C.305 – Tretinoin arm – Subject 108-5026, SAE Case ID 2003S1000011 was a 27 year old male hospitalized for abdominal pain about 29 days after starting Tretinoin gel. Abdominal pain had started about 3 days prior to admission, PMH was not significant and patient was discharged after 4 days following standard medical treatment. He recovered without sequelae and although study drug was interrupted during hospitalization, he went on to complete treatment.
This event does not appear to be related to study treatment.

6. VLC.C.305 – Tretinoin arm – Subject 108-5837, SAE Case ID 2003S1000099 was a 17 year old male who was hospitalized for 1 day for a bone graft, about 2 and a half months after starting treatment secondary to a fractured wrist that had occurred 11 days after starting treatment. Study drug was interrupted during hospitalization, but patient completed treatment.
This event does not appear to be related to study treatment.

7. VLC.C.305 – Tretinoin arm – Subject 150-6041, SAE Case ID 2003S1000094, was a 35 year old female who had an exacerbation of menometrorrhagia and exacerbation of pelvic pain due to uterine fibroids. About a month after starting treatment, the patient was hospitalized for a total abdominal hysterectomy and bilateral salpingo-oophorectomy with lysis of adhesions. PMH included being HIV positive, uterine fibroids, menstrual problems, cervical dysplasia and pelvic inflammatory disease. No action was taken with study drug and patient recovered without sequelae and completed treatment.
This event does not appear to be related to study treatment.

8. 91-CTC-01 – Velac arm – Subject 110, Report # CTCV9400001 was a 25 year old male who was hospitalized for arthroscopic meniscectomy secondary to an accidental injury. He discontinued treatment on day 59 because of the injury and outcome was described as 'recovered'.
This event does not appear to be related to study treatment.

7.1.3 Dropouts and Other Significant Adverse Events

In the ISS ITT population, 2% of subjects discontinued study participation early because of AE/SAEs; Velac gel 2%, Clindamycin gel 0%, Tretinoin gel 3%. No subjects discontinued in the Vehicle group because of an AE.

Table No. 41
Reasons for Study Discontinuation – ISS ITT population

	Velac Gel N (%)	Clindamycin Gel N (%)	Tretinoin Gel N (%)	Vehicle Gel N (%)
Number of subjects	1003	836	804	315
Subjects who completed study	887(88)	744(89)	686(85)	259(82)
Subjects who discontinued	116(12)	92(11)	118(15)	56(18)
Reasons for discontinuation				
Adverse experience	23(2)	3(0)	27(3)	0(0)
Subject non-compliance	7(1)	5(1)	4(0)	5(2)
Disease progression	1(0)	3(0)	2(0)	5(2)
Subject request to withdraw	31(3)	17(2)	24(3)	12(4)
Acute deterioration	1(0)	2(0)	1(0)	0(0)
Subject died	0(0)	0(0)	0(0)	0(0)
Other reason	53(5)	62(7)	60(7)	34(11)

Source: Sponsor briefing document Module 2, volume 1.4.

7.1.3.1 Overall profile of dropouts

As evident in Table No. 41, the highest incidence of study discontinuation in the ISS ITT population was in the vehicle arm; disease progression was also the highest in the Vehicle arm. The highest incidence of patients discontinuing in the ISS ITT population because of an AE was in the Tretinoin arm 3%, followed by the Velac arm 2%. This was also true for the Connetics ITT population and the European studies ITT population.

Similarly, in the combined ITT population of the Connetics studies, 1% of subjects discontinued study participation early because of AE/SAE; 2% of subjects in the Velac group and 3% in the Tretinoin group. None of the subjects in the Clindamycin or Vehicle groups or Study VLC.C.201 discontinued because of an AE.

In the European studies, 25/739 (3%) subjects discontinued study participation early because of an AE. 12/369 (3%) in the Velac gel groups, 3/201 (1%) in the Clindamycin group and 10/169 (6%) in the Tretinoin group.

7.1.3.2 Adverse events associated with dropouts

Study VLC.C.304:
7/309 (2%) subjects in the Velac gel group and 9/310 (3%) subjects in the Tretinoin group discontinued because of an AE. One subject in the Velac gel group discontinued because of aggravated depression (described before, PMH of depression +). The other 6 patients reported applications site reactions that ranged from mild (in 2 patients) to moderate to severe dryness, erythema, burning, pain and irritation and rash. In the Tretinoin gel group, the 9 patients who discontinued treatment also reported application site reactions that ranged from mild rash (1 patient) to moderate to severe reactions such as burning, dryness, erythema, bleeding and rash.

Study VLC.C.305:
4/325 (1%) subjects in the Velac gel group and 8/325 (2%) in the Tretinoin gel group discontinued because of AEs. In the Velac gel group, application site reactions again ranged from moderate to severe erythema, burning, dryness, irritation, pruritus and vesicles. In the

Tretinoin group, reactions ranged from mild (in 3 patients) to moderate to severe reactions such as dryness, desquamation, erythema, pruritus, burning and pigmentation changes. Pigmentation changes were reported mainly in the Tretinoin group.

7.1.3.3 Other significant adverse events

No significant systemic adverse events or laboratory abnormalities were noted in the ISS ITT population.

7.1.4 Other Search Strategies

Not applicable

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were derived from the two pivotal safety and efficacy studies conducted by Connetics in the US: VLC.C.304 and VLC.C.305 as well as the studies conducted by Yamanouchi in Europe. There was a difference in the formulation between the two studies, the European studies used a formulation of Velac gel that had a methylparaben (b) (4) (b) (4) while the US studies were conducted using a formulation that had a methylparaben (b) (4)

Study visits were conducted at baseline (week 0), week 2, week 4, week 8 and week 12 (end of treatment) across all studies. Safety was assessed by recording all adverse events (local and systemic) that occurred during the course of the study, conducting physical exams, monitoring vital signs and assessing labs that were conducted in a select number of patients in VLC.C.304 and some European studies (described later). In addition, local signs (scaling, dryness, erythema) and symptoms (burning, itching) of facial acne vulgaris were also assessed at each study visit across all studies.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

For the ISS ITT population, the most frequently reported AEs were in the MedDRA SOCs of Infections and Infestations – 14% (404/2958), followed by General Disorders and Administration Site Conditions – 12% (345/2958). The sponsor grouped these AEs appropriately and these have been described below.

7.1.5.3 Incidence of common adverse events

<u>Infections and Infestations:</u>

Three AEs were reported by ≥ 2% of subjects: nasopharyngitis 4% (112 subjects), influenza 2% (59 subjects) and upper respiratory tract infection NOS 2% (53 subjects).

Nasopharyngitis was reported for 4% (38 subjects) in the Velac group, 3% (27 subjects) in the Clindamycin gel group, 4% (32 subjects) in the Tretinoin group and 5% (15 subjects) in the Vehicle gel group.

Influenza was reported for 2% (22 subjects) in the Velac group, 2% (18 subjects) in the Clindamycin group, 2% (13 subjects) in the Tretinoin group and 2% (6 subjects) in the Vehicle gel groups.

Upper respiratory tract infection NOS was reported for 2% (20 subjects) in the Velac group, 1% (11 subjects) in the Clindamycin group and 1% (11 subjects) in the Tretinoin group and 3% (11 subjects) in the Vehicle gel groups.

Nasopharyngitis, influenza and upper respiratory tract infection are commonly seen in teenagers and young adults; these infections are usually viral. There is no clinically or statistically significant difference in the incidence of the three infections between the treatment groups. These events do not appear to be related to study drug treatments.

General Disorders and Administrative Site Conditions:

Four AEs were reported by ≥ 2% of subjects under this heading; application site dryness 5% (137 subjects), application site desquamation 3% (103 subjects), application site burning 3% (97 subjects) and application site erythema 3% (83 subjects).

Application site dryness was reported in 7% (68 subjects) in the Velac group, 1% (12 subjects) in the Clindamycin group, 7% (54 subjects) in the Tretinoin group and 1% (3 subjects) in the Vehicle gel group. The incidence of dryness in the Velac and Tretinoin groups was similar. A greater proportion of patients reported application site dryness in the Velac gel groups versus the Clindamycin and Vehicle gel groups ($p < 0.0001$ for both)

Application site desquamation was reported for 5% (52 subjects) in the Velac group, 0% (2 subjects) in the Clindamycin group, 6% (47 subjects) in the Tretinoin gel group and 1% (2 subjects) in the Vehicle group. The incidence of desquamation was similar in the Velac and Tretinoin groups and a greater proportion of patients reported application site desquamation in the Velac groups versus the Clindamycin group ($p < 0.0001$) or the vehicle group ($p = 0.0004$).

Application site burning was reported for 4% (44 subjects) in the Velac group, 0% (4 subjects) in the Clindamycin group, 5% (44 subjects) in the Tretinoin group and 2% (5 subjects) in the Vehicle gel group. The incidence of burning was similar in the Velac and Tretinoin groups and a greater proportion of subjects reported burning in the Velac groups versus the Clindamycin group ($p < 0.0001$) or the vehicle group ($p = 0.0220$).

Application site erythema was reported for 4% (37 subjects) in the Velac group, 1% (6 subjects) in the Clindamycin group, 5% (37 subjects) in the Tretinoin group and 1% (3 subjects) in the Vehicle group. The incidence of erythema was similar in the Velac and Tretinoin groups and a greater proportion of subjects reported erythema in the Velac group versus the Clindamycin group ($p < 0.0001$) or the vehicle group ($p = 0.0135$).

The description of the local adverse events such as dryness, desquamation, erythema and burning was similar in the Velac and Tretinoin groups for all events and was statistically significantly higher in both those groups compared to the Clindamycin and Vehicle groups. It is expected that Tretinoin contributed to the majority of adverse events seen in the Velac groups; this is in keeping with the known AE profile of Tretinoin.

7.1.5.4 Common adverse event tables

Common Adverse Events:
The common AEs reported in the ISS ITT population were similar to the ITT population in the Connetics and European studies individually, with minor changes in ranking order of frequency. In the Connetics studies, the most frequently reported AE was application site dryness 6%, application site desquamation 5%, nasopharyngitis 4%, and application site burning 4%, application site erythema 4%, application site pruritus 3% and upper respiratory site infection 2%. In the European studies, the most frequently reported AEs were influenza 5%, application site irritation 4%, headache NOS 4%, nasopharyngitis 2%, application site dryness 2% and skin irritation 2%.

Table No. 42
Adverse Experiences Reported in ≥ 2% of Subjects in the ISS ITT Population

Preferred Term	Velac, N (%)	Clindamycin gel, N (%)	Tretinoin gel N (%)	Vehicle gel N (%)	Total N (%)
Number of subjects	1003	836	804	315	2958
Subjects with AE	353(35)	240(29)	273(34)	91(29)	957(32)
Application site dryness	68(7)	12(1)	54(7)	3(1)	137(5)
Nasopharyngitis	38(4)	27(3)	32(4)	15(5)	112(4)
Application site desquamation	52(5)	2(0)	47(6)	2(1)	103(3)
Application site burning	44(4)	4(0)	44(5)	5(2)	97(3)
Application site erythema	37(4)	6(1)	37(5)	3(1)	83(3)
Application site pruritus	27(3)	7(1)	23(3)	6(2)	63(2)
Headache NOS	20(2)	17(2)	21(3)	3(1)	61(2)
Influenza	22(2)	18(2)	13(2)	6(2)	59(2)
Upper Respiratory Tract Infection NOS	20(2)	11(1)	11(1)	11(3)	53(2)

Source: Sponsor briefing document Module 2, Vol.1.4

In study VLC.C.201, 60% of subjects reported AEs, out of which application site dryness was 40%, headache NOS 27%, application site erythema 20%, application site burning 13%, application site pruritus 7%, application site pustules 7%, application site rash 7%, application site reaction NOS 7% and pharyngolaryngeal pain 7%.

7.1.5.5 Identifying common and drug-related adverse events

Treatment-emergent adverse events:
For the ISS ITT population, 32% of subjects overall reported adverse events: Velac gel 35% (353/1003); Clindamycin gel 29% (240/836); Tretinoin gel 34% (273/804); Vehicle gel 29% (91/315). All adverse events were compared at a 0.1 significance level based on a two-sided chi-square test ($\alpha = 0.10$) when the incidence was at least five percent in any one treatment group. The incidence of adverse events was similar in the Velac and Tretinoin gel groups; however, the incidence of AEs in the Velac gel group (35%) was significantly higher compared to the Clindamycin gel group (29%; $p = 0.0030$) or subjects in the Vehicle gel groups (29%; $p = 0.0389$).

33% of patients reported treatment-emergent AEs in the ITT population in the Connetics studies: Velac gel 37% (232/634); Clindamycin gel 27% (172/635); Tretinoin gel 37%

(232/635); Vehicle gel 29% (91/315). Incidence of AEs in Study VLC.C.201 (Velac gel only) was 60% (9/15) and he incidence of AEs was similar in the Velac gel and Tretinoin groups.

31% of patients reported treatment-emergent AEs in the ITT population in the European studies: Velac gel 33% (121/369); Clindamycin gel 34% (68/201); Tretinoin gel 24 % (41/169). There was no Vehicle gel group in the European studies. A significantly greater proportion of subjects in the Velac gel group reported AEs compared to the Tretinoin group (p = 0.0453).

The overall incidence of treatment-emergent AEs in the combined ITT population in the Connetics studies and the combined ITT population in the European studies was similar to the combined ISS ITT population. As discussed later, most of the treatment emergent AEs were local and it is expected that most of these are related to Tretinoin, since they fit in with the known AE profile of Tretinoin.

Treatment Related Adverse Events:

In the ISS ITT population, (Table No. 43) 12% of patients reported AEs that were related to study drug; 16% (160/1003) in the Velac group, 5% in the Clindamycin group (p < 0.0001), 15% in the Tretinoin group (p 0.5989) and 5% in the Vehicle group (p < 0.0001).

In the combined ITT population of the Connetics studies VLC.C.304 and VLC.C.305 (Table No 44), a total of 12% of patients reported treatment related AEs; 19% of patients reported an AE related to Velac, 5% reported an AE related to Clindamycin (p < 0.0001), 17% reported an AE related to Tretinoin (p = 0.3716) and 5% reported an AE related to the Vehicle gel (p < 0.0001).

In study VLC.C.201, a total of 53% of patients reported treatment-related AEs (study included only Velac gel). 8/15 (53%) patients had a treatment related AE under General Disorders and Administrative Site conditions. They were as follows: Application site - burning 13%, dryness 40%, erythema 20%, pruritus 7%, rash 7%, reaction NOS 7%, pustules 7%.

In the combined ITT population of the European studies (Table No. 45) 9% of subjects reported treatment –related AEs; 11% in the Velac group, 5% in the Clindamycin group (p 0.0255) and 8% in the Tretinoin group (p 0.3150). In the organ class ‘General Disorders and Administrative Site Conditions’, 9% in the Velac group, 3% in the Clindamycin group (p=0.0088) and 7% in the Tretinoin group (p=0.3150) reported AEs.

Generally, the overall incidence of treatment-related AEs for the combined ITT population of the Connetics studies was similar to the ISS ITT population. A significantly greater proportion of patients reported treatment-related AEs in the Velac gel group compared to the Clindamycin and Vehicle gel groups, while patients in the Tretinoin gel groups had a comparable incidence of AEs to the Velac group. The majority of these AEs were local and included dryness, desquamation, burning, erythema and pruritus; these AEs fit in with the known AE profile of Tretinoin.

Table No. 43
Incidence of Significant Treatment-Related Adverse Experiences - ISS ITT population

Preferred term	Velac N (%)	Clindamycin Gel N (%)	Tretinoin Gel N (%)	Vehicle Gel N (%)	Total N (%)	P-value
Number of subjects	1003	836	804	315	2958	
Subjects with treatment-related adverse experience	160(16)	45(5)	121(15)	16(5)	342(12)	<0.0001 0.5989 <0.0001
Eye swelling	0(0)	0(0)	1(0)	0(0)	1(0)	
Eyelid pruritus	1(0)	0(0)	0(0)	0(0)	1(0)	
Abdominal pain upper	1(0)	0(0)	0(0)	0(0)	1(0)	
Chapped lips	1(0)	0(0)	1(0)	0(0)	2(0)	
Desquamation mouth	1(0)	0(0)	0(0)	0(0)	1(0)	
Application site bleeding	0(0)	0(0)	1(0)	0(0)	1(0)	<0.0001 0.9659 <0.0001
Application site burning	44(4)	3(0)	44(5)	5(2)	96(3)	<0.0001 0.2866 0.0220
Application site desquamation	51(5)	2(0)	47(6)	2(1)	102(3)	<0.0001 0.4778 0.0005
Application site dryness	67(7)	12(1)	52(6)	3(1)	134(5)	<0.0001 0.8565 <0.0001
Application site erythema	36(4)	6(1)	37(5)	3(1)	82(3)	<0.0001 0.2772 0.0160
Application site irritation	29(3)	7(1)	7(1)	1(0)	44(1)	
Application site edema	1(0)	0(0)	1(0)	0(0)	2(0)	
Application site pain	4(0)	0(0)	0(0)	0(0)	4(0)	
Application site pigmentation changes	1(0)	1(0)	6(1)	0(0)	8(0)	
Application site pruritus	26(3)	7(1)	23(3)	6(2)	62(2)	
Application site rash	5(0)	0(0)	7(1)	0(0)	12(0)	
Application site reaction NOS	4(0)	0(0)	5(1)	0(0)	9(0)	
Application site swelling	2(0)	0(0)	0(0)	0(0)	2(0)	
Sunburn	10(1)	5(1)	5(1)	3(1)	23(1)	
Dermatitis NOS	1(0)	0(0)	1(0)	0(0)	2(0)	

Source: Sponsor briefing document Module 2, volume 1.4.
P-values based on comparing Velac gel versus Clindamycin gel (top), Tretinoin gel (middle) and Vehicle gel (bottom). Based on the Chi-square test ($\alpha = 0.10$) and are calculated when the incidence is at least 5% in any one treatment group.

Table No. 44
Incidence of Treatment-Related Adverse Experiences ITT Population-VLC.C.304 and VLC.C.305

Preferred term	Velac	Clindamycin Gel N (%)	Tretinoin Gel N (%)	Vehicle gel N (%)	Total	P-value
Number of subjects	634	635	635	315	2219	
Subjects with treatment-related adverse experience	119(19)	34(5)	107(17)	16(5)	276(12)	<0.0001 0.3716 <0.0001
Eye swelling	0(0)	0(0)	1(0)	0(0)	1(0)	
Eyelid pruritus	1(0)	0(0)	0(0)	0(0)	1(0)	
Abdominal pain upper	1(0)	0(0)	0(0)	0(0)	1(0)	
Chapped lips	0(0)	0(0)	1(0)	0(0)	1(0)	
Application site bleeding	0(0)	0(0)	1(0)	0(0)	1(0)	
Application site burning	40(6)	3(0)	41(6)	5(2)	89(4)	<0.0001 0.9144 0.0013
Application site desquamation	51(8)	2(0)	47(7)	2(1)	102(5)	<0.0001 0.9144 0.0013
Application site dryness	57(9)	12(2)	48(8)	3(1)	120(5)	<0.0001 0.3547 <0.0001
Application site erythema	35(6)	6(1)	33(5)	3(1)	77(3)	<0.0001 0.7980 0.0007
Application site hyperesthesia	1(0)	0(0)	0(0)	0(0)	1(0)	
Application site irritation	6(1)	1(0)	3(0)	1(0)	11(0)	
Application site pain	4(1)	0(0)	0(0)	0(0)	4(0)	
Application site pigmentation changes	1(0)	1(0)	6(1)	0(0)	8(0)	
Application site pruritus	24(4)	7(1)	21(3)	6(2)	58(3)	
Application site rash	4(1)	0(0)	7(1)	0(0)	11(0)	
Application site reaction NOS	1(0)	0(0)	4(1)	0(0)	5(0)	
Application site swelling	2(0)	0(0)	0(0)	0(0)	2(0)	
Sunburn	9(1)	5(1)	5(1)	3(1)	22(1)	

Source: Sponsor briefing document Module 2, volume 1.4.
P-values based on comparing Velac gel versus Clindamycin gel (top), Tretinoin gel (middle) and Vehicle gel (bottom). Based on the Chi-square test ($\alpha = 0.10$) and are calculated when the incidence is at least 5% in any one treatment group.

Table No. 45
Incidence of Significant Treatment-Related Adverse Experiences in ITT population - European studies

Preferred Term	Velac N (%)	Clindamycin gel N (%)	Tretinoin gel N (%)	Total N (%)	p-value
Subjects with AE	41(11)	11(5)	14(8)	66(9)	0.0255 0.3150
Application site burning	4(1)	0(0)	3(2)	7(1)	
Application site dryness	10(3)	0(0)	4(2)	14(2)	
Application site erythema	1(0)	0(0)	4(2)	5(1)	
Application site inflammation	1(0)	0(0)	0(0)	1(0)	
Applications site irritation	23(6)	6(3)	4(2)	33(4)	0.0918 0.0566
Application site edema	1(0)	0(0)	0(0)	1(0)	
Application site paresthesia	1(0)	0(0)	0(0)	1(0)	
Application site pruritus	2(1)	0(0)	2(1)	4(1)	
Application site rash	1(0)	0(0)	0(0)	1(0)	
Application site reaction NOS	3(1)	0(0)	1(1)	4(1)	
Sunburn	1(0)	0(0)	0(0)	0(0)	

Source: Sponsor briefing document Module 2, volume 1.4.
P-values based on comparing Velac gel versus Clindamycin gel (top) and Tretinoin gel (bottom). Based on the Chi-square test ($\alpha = 0.10$) and are calculated when the incidence is at least 5% in any one treatment group.

7.1.5.6 Additional analyses and explorations

Two additional analyses have been explored:

A) Signs and Symptoms of Acne Vulgaris
B) Safety subgroup analyses in Special Groups- Race, Age and Gender

A) **Signs and symptoms of Acne Vulgaris**:
In the Connetics studies, the severity of the signs (scaling, dryness, erythema) and symptoms (burning, itching) were graded using an ascending scale from 0 (normal) to 5 (severe) at baseline, and at weeks 2, 4, 8 and 12 (end of treatment). The mean change in scores for scaling was highest at week 2 compared to all study visits and were highest in the Tretinoin groups, followed by Velac. The mean change in scores for dryness was also highest at week 2 compared to all study visits and were highest in the Tretinoin groups, followed by Velac. Scaling and dryness was more pronounced for Velac gel than for Clindamycin gel and Vehicle gel, but at all study visits, changes in scaling and dryness indicated a trend in favor of Velac gel as compared to Tretinoin gel. There was an increase in erythema scores at week 2 in the Velac and Tretinoin groups and a decrease in erythema scores for Clindamycin and Vehicle groups. At weeks 4, 8 and 12, erythema scores indicated a trend in favor of Velac gel compared to Tretinoin gel and was more pronounced in the Velac groups compared to Clindamycin or Vehicle groups.

Burning scores at all visits were higher in the Velac group compared to Clindamycin and Vehicle groups. At week 2, burning scores were lower in the Velac group compared to the Tretinoin group, but by weeks 4, 8 and 12, burning scores were similar for Velac and Tretinoin gel.

Table No. 46
Evaluation of signs (Scaling, Dryness, Erythema)

None	0 =	Normal
Trace	1 =	Mild and localized
Mild	2 =	Mild and diffuse
Moderate	3 =	Moderate and diffuse
Marked	4 =	Moderate and dense
Severe	5 =	Prominent and dense

Source: Sponsor briefing document Module 5, Vol 1.8 & 1.9

Table No. 47
Evaluation of Symptoms (Burning and Itching)

None	0 =	Normal, no discomfort
Trace	1 =	An awareness, but no discomfort and no intervention required
Mild	2 =	A noticeable discomfort that causes intermittent awareness
Moderate	3 =	A noticeable discomfort that causes continuous awareness
Marked	4 =	A definite discomfort that causes continuous awareness and interferes occasionally with normal daily activities
Severe	5 =	A definite continuous discomfort interferes with normal daily activities

Source: Sponsor briefing document Module 5, Vol 1.8 & 1.9

At week 2, changes in itching scores were similar for Velac and Tretinoin, but there was a decrease in itching scores for Clindamycin and Vehicle gel. By weeks 4, 8 and 12, there was a slight decrease in itching scores from baseline for all treatment groups.

Overall, the results from the US studies appear to indicate that the dryness, scaling, erythema, burning and itching were highest around week 2 in the Velac and Tretinoin groups, after which there was a progressive decline. The scores were higher in the Tretinoin group compared to the Velac group. In the Clindamycin and Vehicle groups, scores for all signs and symptoms were lesser compared to the other two groups across all visits, and by week 2, there was a decrease in erythema and itching scores for both Clindamycin and Vehicle.
This maximization of scores for signs and symptoms of acne vulgaris around week 2, followed by a progressive decline is consistent with the known adverse event profile of Tretinoin.

In the 6 European studies, irritation at application site (scaling, induration, erythema, burning sensation and pruritus) was assessed using an ascending scale from 0 (none) to 4 (severe). Velac and Tretinoin gels showed slight increases in scaling and slight decreases in induration scores. Scaling was more pronounced for Velac compared to Clindamycin, while induration scores decreased for Velac compared to Clindamycin.

Erythema scores decreased from baseline to Visit 12 for Clindamycin and Tretinoin gels and were unchanged in the Velac group. Erythema was more pronounced for Velac than for Clindamycin gel. The change from baseline to visit 12 in burning scores indicated a trend in favor of Velac gel as compared to Tretinoin gel. Burning was more pronounced for Velac gel than for Clindamycin gel. Pruritus scores for Velac gel and Tretinoin gel were similar from week

2 to week 8. At week 12, slight reduction in pruritus scores was observed for Tretinoin gel; no change from baseline to week 12 was observed for Velac gel.

Table No. 48
Scale used for assessment of signs and symptoms of acne vulgaris in European Studies

Category	Score	Description
Erythema	0	No erythema
	1	Very slight erythema, barely perceptible
	2	Well defined erythema
	3	Moderate to severe erythema
	4	Severe erythema
Scaling, pruritus, burning sensation	0	None
	1	Slight
	2	Moderate
	3	Marked
	4	Severe

Source: Sponsor briefing document: Module 5

It is noted that the erythema scores declined for the individual Clindamycin and Tretinoin groups but not for the Velac group and erythema was more pronounced in the Velac group compared to Clindamycin. This observation was different from the US studies, where erythema had been more pronounced in the Tretinoin group. The clinical significance of this observation is unclear since the vehicle for both studies was almost similar with the exception of methylparaben. Unfortunately, there were no vehicle groups in the European studies for comparison.

B) **Safety in Special Groups**:
An analysis of AEs was performed for studies VLC.C.304 and VLC.C.305 within the subgroups of gender, age and race; these analyses were performed for AEs that were ≥ 5% in any treatment group. Such analysis was not performed for Study VLC.C.201 because of the different study duration (28 days) and because of a very small sample size (15 patients).

Subgroup Analysis by Gender:

Females constituted 52% (1532/2958) of the ISS ITT population and males 48% (1426/2958). The incidence of AEs was slightly higher in females (35%) compared to males (30%) and a significantly greater proportion of AEs were reported for both male (33%) and female (38%) patients in the Velac groups compared to the Clindamycin groups (25% for males, $p = 0.0137$; 32% for females, $p = 0.0692$).

The AEs reported by males most frequently (14%) were in the SOC of Infections and Infestations, while females reported AEs most frequently (14%) in the SOC of General Disorders and Administrative Site Conditions. In the SOC of General Disorders and Administrative Site Conditions, a significantly greater proportion of males and females reported AEs in the Velac group compared to the Clindamycin group ($p < 0.0001$for males and females) or the Vehicle gel group ($p = 0.0866$ for males and $p = 0.0006$ for females).

For both males and females, the AE reported most frequently in the SOC of Infections and Infestations was nasopharyngitis (3% for females and 4% for males) and the most frequently reported AE in the SOC of General Disorders and Administration Site Conditions was application site dryness for both males (4%) and females (6%). A significantly greater proportion

of both males and females in the Velac gel group reported application site dryness as compared to the Clindamycin group ($p < 0.0001$ for both males and females) or the vehicle group ($p = 0.0020$ for males, $p = 0.0091$ for females).

Applications site desquamation was reported by a significantly greater proportion of males and females in the Velac group compared to the Clindamycin group ($p = 0.0001$ for males, $p < 0.0001$ for females) and to the vehicle group ($p = 0.0472$ for males, $p = 0.0034$ for females). Application site burning was reported by a significantly greater proportion of female subjects in the Velac group as compared to the Clindamycin group ($p < 0.0001$) and the vehicle group ($p = 0.0140$); this difference was not observed in males.

Application site erythema was reported by a significantly greater proportion of males in the Velac group compared to the Clindamycin group ($p = 0.0025$) and the vehicle group ($p = 0.0573$); this difference was not seen in females.

In the SOC of Gastrointestinal Disorders, females in the Velac group reported a greater proportion of AEs as compared to the Tretinoin group ($p = 0.0521$); this difference was not seen in males.

There were no other statistically significant differences reported by male or female subjects.

Subgroup Analysis by Age:

The incidence of AEs in the ISS ITT population was broken down into two age groups, the 12-16 years group and the > 16 years group. Subjects 12-16 years of age constituted 45% and those > 16 years 55%. The incidence of AEs in the two groups was almost similar, in the 12-16 years group, it was 32% (416/1318) and the incidence in the > 16 years age group was 33% (541/1639).

Subjects in both age groups had a significantly greater incidence of AEs in the Velac arm as compared to the Clindamycin group ($p = 0.0120$ for ages 12-16, $p = 0.0838$ for > 16 years). Subjects in the > 16 years group also reported a significantly greater proportion of AEs in the Velac gel group as compared to the Vehicle gel group ($p = 0.0406$); this was not seen in the 12-16 years age group.

Both age groups reported AEs in the SOC of Infections and Infestations most frequently; 14% for the 12-16 years group and 13% for the 16 years group and nasopharyngitis was the most frequently reported AE (4%).

The SOC with the second most frequently reported number of AEs was General Disorders and Administrative Site conditions: 10% (137/1318) for ages 12-16 years and 13% (208/1639) for > 16 years. In both groups, a statistically significantly greater proportion of patients reported AEs in the Velac group as compared to the Clindamycin group ($p < 0.0001$for both age categories) and the Vehicle gel group ($p = 0.0534$ for ages 12-16 years, $p = 0.0014$ for > 16 years).

The most frequently reported AE was application site dryness, which was reported by 4% of subjects in the 12-16 years group and 5% in the > 16 years group. A statistically significantly greater proportion of patients from both age categories reported dryness in the Velac group compared to the Clindamycin ($p = 0.0025$ for 12-16 years and $p < 0.0001$ for > 16 years) and vehicle group ($p = 0.0088$ for 12-16 years and $p = 0.0040$ for > 16 years). The pattern for desquamation was similar as dryness across both age groups. Application site burning was reported in greater proportions by both age categories in the Velac gel group than in the

Clindamycin gel group (p = 0.0003 for ages 12-16 years, p = 0.0001 for > 16 years); but only the 12-16 years group had a greater proportion of these AEs in the Velac versus the Vehicle gel (p = 0.0528).

Application site erythema was reported by a greater proportion of Velac gel patients in the 12-16 years category versus Clindamycin (p = 0.0054); but Tretinoin gel patients reported erythema in greater proportions than Velac gel (p = 0.0133). In the > 16 years group, there was no statistically significant difference across treatment groups for application site erythema.

In general, the incidence of application site AEs was slightly higher in the 12-16 years age group compared to the > 16 years age groups. Erythema was higher in the Tretinoin groups versus the Velac groups, and the overall incidence of application site AEs was higher in the Velac groups compared to the Clindamycin and Vehicle groups. Although application site AEs are expected to be most frequent in the first few weeks after starting therapy, and improve progressively in most patients, these may lead to discontinuation of treatment in a certain segment of the population. Since acne is most commonly seen in teenagers, this may have some clinical significance and could be incorporated in labeling.

Subgroup Analysis by Race:

The European studies enrolled only Caucasians, while the Connetics studies included Caucasians, African-Americans, and Hispanics and 'Others' which included Asians in a small proportion. Thus, the largest proportion of patients in the ISS ITT population were Caucasians who constituted 74%, African-Americans were 15%, Hispanics were 7% and the 'Other' 4% group made up the rest.

The incidence of AEs in these groups was as follows: Caucasians 32% (704/2181), African-Americans 30% (132/437), Hispanics 30% (65/218) 'Other' 46% (56/122). A statistically significantly greater proportion of Caucasian (p = 0.0150) and African-American (p = 0.0764) subjects in the Velac gel groups reported AEs than in the Clindamycin groups. This difference was not seen in the Hispanic and 'Other' groups.

Overall, AEs were reported most frequently in the General Disorders and Administration Site Conditions SOC by African-Americans (14%, 63/437), Hispanics (13%, 29/218) and 'Other' (25%, 30/122). Caucasians reported AEs most frequently in the Infections and Infestations SOC (15%, 321/2181). In the General Disorders and Administration site Conditions SOC, a significantly greater proportion of Caucasian and African-American subjects reported AEs in the Velac group than in the Clindamycin group (p <0.0001 for Caucasians, p = 0.0026 for African-Americans) or the Vehicle gel group (p = 0.0002 for Caucasians, p = 0.0338 for African-Americans). This statistically significant difference was not seen in the Hispanic and Other groups. In the Infections and Infestations SOC, there were no statistically significant differences across treatment groups.

For all race groups, the most frequently reported AE in the General Disorders and Administrative Site Conditions SOC was application site dryness: Caucasian 4% (79/2181), African-American 6% (25/437), Hispanic 6% (12/218), 'Other' 17% (21/122).

From the above, it appears that the incidence of AEs in the Velac arm was statistically significantly higher in the Velac groups compared to the Clindamycin and Vehicle groups. Application site AEs were noted to be higher in the Caucasian group compared to the other

groups, but it should be noted that 74% of the ISS ITT population was Caucasians. Pigmentation changes were significantly higher in the African-American group; however, post-inflammatory hypo or hyper-pigmentation is expected to be higher in this group of patients.

In general, AEs in subgroups were in keeping with those noted in the comprehensive safety review; however, certain aspects can be incorporated in labeling.

Table No. 49
Significant AEs in the General Disorders and Administration Site Conditions SOC by Race In the ISS ITT population

	Caucasians	**African-Americans**	**Hispanic**	**Other (Asians)**
Number of Subjects	74% (2181/2958)	15% (437/2958)	7% (218/2958)	4% (122/2958)
DRYNESS Velac vs. Clindamycin Velac vs. Vehicle	 P < 0.0001 P = 0.0018	 P = 0.0130 P = 0.0841		 P = 0.0227 P = 0.0327
DESQUAMATION Velac vs. Clindamycin Velac vs. Vehicle	 P < 0.0001 P = 0.0032	 P = 0.0018 P = 0.0224	 P = 0.0128 P = 0.0806	
BURNING Velac vs. Clindamycin Velac vs. Vehicle	 P < 0.0001 P = 0.0068	 P = 0.0082		
ERYTHEMA Velac vs. Clindamycin Velac vs. Vehicle	 P = 0.0003 P = 0.0191			 P = 0.0243
PIGMENTATION CHANGES Tretinoin vs. Velac		 P = 0.0752		
PRURITUS Velac vs. Clindamycin		 P = 0.0146		

7.1.6 Less Common Adverse Events

Following are clinically significant less common adverse events. These were all reported as treatment-related adverse events in the ISS ITT population and are described in Table No. 43, Section 7.1.5.5.

1) Mouth desquamation was reported in 1/1003 (0%) patients in the Velac group of the ISS ITT population.
2) Chapped lips were reported by 1/1003 (0%) patients in the Velac group and 1/804 (0%) patients in the Tretinoin group.

3) Application site pigmentation changes were reported by 6/804 (1%) patients in the Tretinoin group and 1/1003 (0%) patients in the Velac group.
4) Sunburn was reported by 10/1003 (1%) patients in the Velac group, 5/836 (1%) in the Clindamycin group, 5/804 (1%) in the Tretinoin group and 3/315 (1%) in the Vehicle group.

Most of these reactions are local and fit in with the adverse event profile of Tretinoin, although sunburn was reported by subjects in the Clindamycin and Vehicle groups too. There were no other clinically significant less common adverse events.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Clinical lab evaluations were performed at baseline and at week 12 (end of treatment) in Study VLC.C.304 for 318 subjects at 4 selected investigative sites. Labs included a complete blood count (CBC) and a serum chemistry panel (sodium, potassium, bicarbonate, chloride, calcium, phosphorus and uric acid). No clinically significant changes were noted in these labs from baseline to end of treatment and across all treatment groups.

In the European studies, labs were performed at baseline and week 12 (end of treatment) for all subjects in 3 studies (91-CTC-01, 92-CTC-01 and 91-CTC-02), at selected sites in 2 studies (96-CTC-01, 91-CTC-04) and were not performed in Study 95-CTC-01. Labs were performed in 490 patients and included a CBC and a serum chemistry panel (sodium, potassium, calcium, chloride, total protein, bilirubin, creatinine, alkaline phosphatase and liver function tests). Results showed no significant changes from baseline to week 12 and no correlation with study drug use.

Overall, across both the European and the US studies, there were no clinically meaningful differences in mean or median hematology or chemistry lab results across all treatment groups and from baseline to end of treatment.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs (systolic and diastolic blood pressure and pulse rates) were measured at baseline and week 12 (end of treatment) visits in all studies. There were no clinically meaningful differences in mean or median vital sign measurements between treatment groups from baseline to week 12.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Not conducted for this NDA.

7.1.8.3 Standard analyses and explorations of vital signs data

Not conducted for this NDA.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Electrocardiogram testing was not performed as part of the drug development program.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not conducted for this NDA.

7.1.9.3 Standard analyses and explorations of ECG data

Not conducted for this NDA.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

No malignancies were reported to have developed during the six week clinical studies as conducted for this NDA.

7.1.12 Special Safety Studies

In addition to the two pivotal safety and efficacy studies, dermal safety studies were performed for Velac gel. Only one study, VLC.C.101 – a cumulative irritation and skin sensitization study was performed in the US with the final to-be-marketed-formulation (methylparaben (b) (4) The other studies were conducted using the older formulation (methylparaben (b) (4) in Europe. The dermal safety studies are illustrated in Table No. 50:

A spectrophotometric analysis of Velac gel was also conducted to check UV absorption spectra.

Table No. 50
Dermal safety studies conducted for Velac gel

Study No.	Objective	Study Design	Test Product	No Pts	Patient type	Duration of treatment
VLC.C.101	Evaluate cutaneous irritation & allergic contact sensitization	Treatment site randomized; vehicle-controlled	Velac, vehicle gel, sodium lauryl sulfate, distilled water	243	Healthy subjects	21 days for irritation, 48-72 hours for sensitization
91-CTC-05	Compare irritation	Treatment site randomized, active and vehicle controlled	Velac, Acid-a-Vit cream (tretinoin 0.05%)	20	Healthy subjects	18 days
94-CTC-01	Photoirritation & Phototoxicity	Treatment site randomized, active and vehicle controlled	Velac, tretinoin in vehicle gel, vehicle gel	10	Healthy subjects	24 hours
94-CTC-02	Irritation & Sensitization in a Repeat Insult Patch Test	Treatment site randomized, active and vehicle controlled	Velac, tretinoin in vehicle gel, clindamycin in vehicle gel, vehicle gel	196	Healthy subjects	21 days for irritation, 72 hours for sensitization
94-CTC-03	Irritation & Photosensitizatio n	Treatment site randomized, active and vehicle controlled	Velac, tretinoin in vehicle gel, vehicle gel.	26	Healthy subjects	21 days for irritation, 24 hours for sensitization
94-CTC-04	Determine Irritancy	Treatment site randomized, active and vehicle controlled	Velac, tretinoin in vehicle gel, clindamycin in vehicle gel, Aberela gel (tretinoin 0.025%), Antibio-Aberela gel, vehicle gel	27	Healthy subjects	21 days
94-CTC-05	Contact Irritancy	Treatment site randomized, active and vehicle controlled	Velac, tretinoin in vehicle gel, clindamycin in vehicle gel, vehicle gel	10	Healthy subjects	15-30 minutes

Study VLC.C.101 (US study):

This was a Phase 1 cumulative irritation and skin sensitization study of Velac gel to evaluate the cutaneous irritation and allergic contact sensitization potential of Velac gel under maximal stress in healthy volunteer subjects. 243 subjects were enrolled; male (76) and female (167) between 18-73 years of age. Ethnicity was as follows: Caucasian 65%, Hispanic 19%, Black 14%, Asian 3%, 'Other' races 2%.

This was a single-center, evaluator-blinded study of repeated insult patch testing in healthy adult volunteers. Test articles administered during the Induction, Challenge and Repeat Challenge phase were Velac gel, Vehicle gel, sodium lauryl sulfate (positive control) and distilled water (negative control), while test articles administered during the Second Repeat Challenge Phase were Velac gel, Vehicle gel, Clindamycin gel and Tretinoin gel.

Treatment was applied to the upper arms of volunteers under occlusive patches three times per week for 21 days (Induction Phase), followed by a Rest Phase (2 weeks) and then a single application of test articles was applied to the upper back of volunteers to assess for sensitization (Challenge Phase). Subjects suspected of having contact sensitization during the

Challenge Phase underwent a Repeat Challenge (single application of test articles applied to the upper arm) to confirm possible sensitization exhibited during Challenge. Test articles applied were identical to those used during the Induction and Challenge Phases of the study. A Second Repeat Challenge (single application of test articles applied to upper back) was performed to further evaluate reactions exhibited during the Repeat Challenge. Test articles applied during the Second Repeat Challenge Phase were Velac gel, Vehicle gel, Clindamycin gel and Tretinoin gel and were applied under occlusive and non-occlusive patches.

An evaluation of skin reactions (Table No. 52) was made at each test site after patch removal using a grading scale for irritation and contact sensitization.The total irritation score for each test article was calculated (converted irritation score). If severe irritation (grade 2) was noted at a site during the Induction Phase that patch site was moved to a naïve adjacent site. A maximum of two patch site moves per test article was permitted with the exception of sodium lauryl sulfate, in which case the patch site was terminated once an irritation score of 2 was observed.

Study Results:
243 subjects were enrolled in the study; 195 reached study completion, excluding the Repeat Challenge and Second Repeat Challenge Phase.

Table No. 51- Disposition of Subjects for Study VLC.C.101 (Sponsor document Module 5, Vol.1.5)

	Treated
Total Number of Subjects	243
Subjects who Completed Each Phase	
Induction	204 (84%)
Rest	201 (83%)
Challenge	195 (80%)
Repeat Challenge	12 (5%)
Second Repeat Challenge	6 (2%)

Table No. 52
Grading scale for Irritation and Contact Sensitization (Sponsor document, Module 5, Vol. 1.5)

Numerical Score	**Inflammatory Response**
0	No visible reaction
0.5	Slight, confluent or patchy erythema
1	Mild erythema (pink)
2	Moderate erythema (definite redness)
3	Strong erythema (very intense redness)
Letter Score	**Definition of letter grades appended to numerical grade**
J	Burning, stinging, itching
E	Edema – swelling, spongy feeling when palpated
P	Papule – red, solid, pinpoint elevation
V	Vesicle – small elevation containing fluid
B	Bulla reaction – fluid-filled lesion (blister)
S	Spreading – evidence of the reaction beyond the pad area
W	Weeping – result of a vesicular or bulla reaction-serous exudates
I	Induration – solid, elevated, hardened, thickened skin
*	Residual reaction to earlier application after absence

Table No. 53
Test Article Mean Irritation and Cumulative Irritation Scores

Test Article	Mean irritation Score	Number of Test Article Evaluations	Cumulative skin Reaction Score
Velac gel	1.40	1790	2504.5
Vehicle gel	0.83	1738	1443.5
Sodium lauryl sulfate	1.36	1744	2366.5
Distilled water	0.11	1740	197

Source: Sponsor briefing document, Module 5, Volume 1.5

The mean irritation score was calculated by dividing the cumulative skin reaction score for each test article by the total number of evaluations completed for that test article. The irritation level observed in Velac gel was similar to the irritation level observed for sodium lauryl sulfate, while the irritation for Vehicle gel was higher than distilled water. During the Challenge Phase, 21 subjects exhibited reactions, considered to be consistent with potential allergic contact sensitization. 13 out of the 21 subjects agreed to participate in the Repeat Challenge Phase; 12 out of these 13 subjects completed the Repeat Challenge Phase, while 1 patient did not complete all study visits. The results of the Repeat Challenge showed that for Velac gel, potential sensitization was confirmed in 6 out of the 12 subjects and for Vehicle gel, this was confirmed in 4 out of the 12 subjects.

To further evaluate the source and type (true allergic contact sensitization versus irritant contact reaction) of the Repeat Challenge reactions, a Second Repeat Challenge was conducted about 11 weeks later with the active ingredients of Velac gel, i.e. Clindamycin phosphate and Tretinoin. Thus, the four test articles included Velac gel, Vehicle gel, and Clindamycin and Tretinoin gels. To evaluate the possibility that occlusion resulted in 'false positive' interpretations of sensitization, the test articles were applied using occlusive and non-occlusive (open) patches for the Second Repeat Challenge phase. It was hypothesized that a true sensitization reaction should occur under occlusive and non-occlusive conditions; therefore, if a reaction was exhibited under occlusion, but not reproduced under non-occlusive conditions, the reaction was more likely to be that of an irritant contact reaction rather than an allergic contact sensitization reaction.

In the Second Repeat Challenge Phase, a potential sensitization for Velac gel was further confirmed under occlusive conditions in 5 of 6 subjects. Under non-occlusive conditions, sensitization was confirmed in only 2 of the 6 subjects. This led to the assumption that occlusion may lead to exaggerated 'false-positive' reactions suggestive of allergic contact sensitization that would not be observed in normal use conditions. An isolated reaction to Clindamycin was seen in the Second Repeat Challenge test and another isolated reaction was seen to Vehicle gel.

Conclusion:
The irritation level observed with Velac gel was similar to the level of irritation seen with sodium lauryl sulfate 0.1%. Results from the Repeat Challenge and Second Repeat Challenge demonstrated that Velac gel induced allergic contact sensitization rarely. Sensitization seen in the Velac group at the time of Repeat Challenge may have been due to Tretinoin which is known to cause irritation. It is assumed from the Second Repeat Challenge test that occlusion leads to false-positive reactions suggestive of allergic contact sensitization that may not be observed under normal use conditions.

Overall, it appears from this study that Velac gel is a low-level irritant and can occasionally induce sensitization. The irritation is most likely to be contributed by Tretinoin, since this fits in with the known AE profile of Tretinoin.

Study No. 91-CTC-05: Irritation Study (European study):
This was a single-blind, single-center study, comparing skin irritation in 20 healthy volunteers who were dosed for 18 days with Velac gel, Vehicle gel or Acid-a-Vit® cream (tretinoin 0.05%, w/w), or left untreated. Patients were dosed twice a day with all 3 test articles on the flexor surface of both underarms and skin irritation was assessed by ChromaMeter measurements and by a dermatologist. ChromaMeter readings indicated significantly more erythema with Velac gel as compared to Vehicle gels, but comparable to Acid-a-Vit cream. Clinical ratings showed a significantly greater degree of irritation with Velac gel as compared to Vehicle gel and Acid-a-Vit cream. The level of irritation was clinically mild for all treatments.

Study No. 94-CTC-01: Photo-Irritation Study (European study):
10 healthy, adult subjects were dosed with Velac gel, Tretinoin 0.025% gel and Vehicle gel, where the test products were applied to the back or upper arms of subjects. The sites were irradiated with Woods light Inspectolamp at 9 inches for 45 minutes; this UVA irradiation was followed by exposure to 2/3 MED from a Kromayer lamp. When the site was scored after 24 hours, there was no evidence of phototoxicity to any of the test formulations.

Study No. 94-CTC-02: Sensitization Study (European study):
This was a modified Draize study, where 196 healthy adult volunteers were dosed with Velac gel, Tretinoin gel 0.025%, Clindamycin 1% gel and Vehicle gel and were assessed for sensitization. In the 3 week induction period, occlusive patches were applied three times a week for 48-72 hours on the forearm or back of subjects. About 2 weeks after the sensitization phase, a challenge patch was applied to a previously unpatched site and removed after 72 hours. Repeat testing was conducted for those who tested positive, and in this study, all formulations caused cumulative irritation under occlusion, but not allergic sensitization.

Study No. 94-CTC-03: Photo-Sensitization Study (European study):
This was a modified Draize study, where 26 healthy adults were dosed with Velac gel, Tretinoin gel 0.025% and Vehicle gel to assess sensitization. In the 3-week induction period, occlusive patches were applied three times weekly for 24 hours to the upper arm or back of subjects. After patch removal, the site was irradiated with ~ 3 MED of unfiltered light. About 2 weeks after the sensitization phase, a challenge patch was applied to a previously unpatched site, removed after 24 hours and the site irradiated. This study showed that some formulations had a cumulative irritancy potential when applied to the skin under an occlusive patch, but they did not induce allergic or photo-allergic dermatitis.

Study No. 94-CTC-04: 21 Day Cumulative Irritation Study (European study):
This was a double-blind study, where 25 subjects were treated with six test formulations, including Velac gel, tretinoin 0.025% gel, clindamycin 1% gel, Aberela® gel (tretinoin 0.025%), Antibio-Aberela® gel (tretinoin 0.025%, erythromycin) and vehicle gel. Here, test materials

were applied to the patch at the same site 5 days per week for 21 days. This study showed that Aberela gel had the greatest irritation potential, tretinoin was next in irritation potential and Velac gel had irritation potential comparable to that of Clindamycin and Vehicle gel.

Study No. 94-CTC-05: Allergenicity Study (European study):
This was a double-blind study, where 10 subjects were dosed with 4 test formulations including Velac, Vehicle, Tretinoin 0.025% gel and Clindamycin gel. Test materials were applied to the forehead and the site was read 15 and 30 minutes after application of test material to determine the presence of absence of contact urticarial (non-immunogenic potential). In this study, contact urticaria was not elicited by any of the formulations.

Overall, the results from the European studies indicate that irritation observed with Velac gel was mild and was more than likely contributed by Tretinoin. Velac gel can occasionally induce contact sensitization, but does not appear to induce contact urticaria or allergic dermatitis. There were only 10 patients in the Phototoxicity study and 26 patients in the Photosensitization study and these studies were conducted using the older formulation of Velac gel. If the spectrophotometric analysis of a topical drug formulation shows UV and visible light absorption in the 290-700 nm. range, the Agency recommends that 30 patients be included for Photoirritation studies and 50 for Photosensitivity studies, and that these studies be conducted with the final to- be-marketed-formulation of the drug product. The sponsor will therefore be asked to conduct appropriate studies in an increased number of patients.

Study TC-VEL-045R - Photosensitivity Evaluation of Velac Gel Formulations Containing Different levels of Methylparaben:

This study compared the ultraviolet/visible radiation absorption spectra for the 2 formulations of Velac gel containing (b) (4) methylparaben (b) (4). Yamanouchi originally developed two formulations for Velac gel which differed in the levels of methylparaben (b) (4) but chose to develop the (b) (4) formulation. Connetics chose to develop the second version of Velac gel ((b) (4)), because it produced better antimicrobial effectiveness test results and had a higher potential for chemical stability and longer shelf life.

The spectroscopic analysis of the (b) (4) formulation is almost similar to the (b) (4) formulation; the (b) (4) formulation showed absorption in the 290-440 nm. range, with the peak being at ~ 359 nm.

The sponsor concluded that since the absorption spectra of the two formulations appear to be similar when overlaid on one another, the photosafety studies conducted by Yamanouchi in Europe would suffice, and that no additional studies would be needed. However, as mentioned above, the Agency requires that dermal safety studies be conducted with the final to be marketed formulation of the drug product in the appropriate number of patients.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No instances of drug abuse were reported in subjects treated with any of the study drugs or their vehicles in any of the US or European studies, and none of the topical drugs used in these studies have a known potential for drug abuse.

No instances of withdrawal or rebound were reported in subjects treated with any of the study drugs or their vehicles in the US or European studies and none of the drugs used in these studies have a known potential for withdrawal or rebound.

No instances of a study drug effect on the ability to drive or operate machinery or of impairment of mental ability were reported in subjects treated with any of the study drugs or their vehicles in the US or European studies. None of the topical drugs used in these studies have a known potential to affect the ability to drive or operate machinery or to impair mental ability.

7.1.14 Human Reproduction and Pregnancy Data

Table No. 54
Pregnancy Outcomes in Studies VLC.C.304 & VLC.C.305

Subject Number	Velac	Clindamycin	Tretinoin	Vehicle
146-4007 (VLC.C.304)		Withdrew after 56 days of treatment. Had a normal baby.		
118-3493 (VLC.C.304)			Withdrew after 56 days of treatment. Pregnancy was aborted.	
112-3618 (VLC.C.304)			Completed study. Had a normal baby	
118-4018 (VLC.C.304)	Completed study. Had a normal baby.			
125-3752 (VLC.C.304)	Completed study. Had a normal baby.			
130-5150 (VLC.C.305)	Completed study. Had a normal baby.			
110-5372 (VLC.C.305)		Completed study. Lost to follow-up.		
135-5514 (VLC.C.305)	Withdrew from study after 55 days of treatment. Had a healthy baby.			
150-6151 (VLC.C.305)		Completed study. Had a spontaneous abortion.		

Velac gel carries a Pregnancy Category C rating. Therefore, pregnant or breastfeeding females were excluded from participating in the Connetics studies and females of childbearing potential were required to use medically acceptable methods of birth control throughout the studies. Urine pregnancy tests were performed at baseline and week 12 for females of childbearing potential.

Nine subjects became pregnant during the conduct of these studies: 5 subjects in Study VLC.C.304 and 4 subjects in VLC.C.305. In the Tretinoin group, there was one normal outcome and one pregnancy was aborted. There was one spontaneous abortion in the Clindamycin arm. No untoward pregnancy outcome effects were reported for the European clinical studies.

7.1.15 Assessment of Effect on Growth

Not conducted for this study.

7.1.16 Overdose Experience

No instances of overdose were reported in subjects treated with any of the study drugs or their vehicles across the Connetics (US) and Yamanouchi (European) studies.

7.1.17 Post-marketing Experience

The previous formulation of Velac gel was tested in Europe and approved for marketing in France; however, it was never marketed due to corporate reasons of the previous sponsor. There is no post-marketing data available for Velac gel from US or foreign experience and ODS has not conducted any safety assessments for Velac gel.

7.2 Adequacy of Patient Exposure and Safety Assessments

Local and Systemic Safety:

The integrated safety analysis of Velac gel was assessed from the 2988 subjects enrolled in the three clinical Connetics studies in the US and the six clinical studies conducted by Yamanouchi (previous sponsor) in Europe in patients with acne vulgaris; the US studies enrolled 2219 subjects in the two pivotal studies. Because of the differences between the European (b) (4) methylparaben) and the US ((b) (4) methylparaben) formulations, the sponsor had chosen to perform a bridging program between the two studies to assess safety and efficacy. As part of this program, a bioavailability study and a dermal safety study were also done using the new formulation. The bioavailability study was done to assess the bioavailability of the individual ingredients when combined into a single drug product and the dermal safety study was done to assess cutaneous irritation and sensitization.

The integrated safety analysis of the ISS ITT population showed that treatment-related adverse effects seen most frequently were local/application type events eg., dryness, desquamation, erythema, burning and pruritus. The incidence of such events in the Velac and Tretinoin arms were similar, suggesting the well-known adverse effect profile of Tretinoin probably contributed to a significant extent to the AE profile of Velac gel.

On evaluation of the signs and symptoms of acne vulgaris, at all study visits, changes in scaling and dryness scores indicated a trend in favor of Velac gel as compared to Tretinoin gel. In general, the AEs for Velac gel appeared to be most frequent about 2 weeks after initiation of treatment, after which there was a progressive decline.

No significant systemic adverse events were noted during the conduct of these studies and labs (complete blood counts, comprehensive metabolic profile) conducted in Study VLC.C.304 showed no significant abnormalities. Electrocardiograms were not conducted as part of this submission.

Dermal safety studies:
The dermal cumulative irritation and skin sensitization study of Velac gel conducted in the US showed that Velac gel has cumulative irritancy properties under occlusion and it induces contact sensitization rarely. The sponsor conducted a spectroscopic analysis of Velac gel which showed absorption between the 290-700 nm range; there was no difference in the UVA/UVB or visible absorption between the (b) (4) methylparaben formulations of Velac gel. In the European studies, there was no evidence of photoirritation (10 patients) and photoallergenicity (26 patients); however, these studies were conducted with the old formulation of Velac gel and the recommended numbers of patients were not enrolled

Non-clinical studies:
The submission for Velac gel included a mouse Tg.AC carcinogenicity study conducted by the sponsor in the US with the to-be-marketed formulation of Velac gel. Results from this study showed that there was an increase in papillomas in all treated animals, including the vehicle control, when compared to the untreated animals. Treatment with the vehicle and clindamycin phosphate together, produced an even higher tumor incidence than the vehicle alone. These study results caused significant concern when reviewed by the Agency Executive Carcinogenicity Assessment Committee. The Committee concluded that an adequate study had been done and the vehicle of Velac gel was determined to be a carcinogen.

Conclusion:
The sponsor assessed local and systemic safety for Velac gel in > 2000 patients and the studies were conducted over a 12 week period, which is the standard period for testing drug products for acne vulgaris. However, dermal safety tests are inadequate; the numbers of patients in the phototoxicity (10) and photoallergenicity (26) studies are less than the recommendations provided by the Agency. Since the Agency requires testing in 30 patients for phototoxicity, and in 50 patients for photoallergenicity studies, the sponsor will be asked to conduct these studies in the appropriate number of patients with the final to be marketed formulation of Velac gel. Clinical labs were performed in the appropriate number of patients and since no cardiac effects of either drug product was expected, electrocardiograms were not performed in any of the studies.

Non-clinical carcinogenicity studies conducted in the pre-approved mouse model showed significant papilloma formation in all treated animals, including vehicle controls; the risk assessment of this finding will have to be taken into account for product approval.
Overall, the assessment of local and systemic safety was assessed appropriately by the sponsor; however, while such 12 week studies are considered adequate for testing an anti-acne drug product, they do not provide information about long-term safety. Also, since Velac gel has never

been marketed before, a safety analysis of post-marketing data is not possible. Per ICH E1A criteria, long-term safety studies would be required, since acne vulgaris is a chronic indication.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The summary of clinical safety for Velac gel combines safety results from three Connetics studies of Velac gel in patients with acne vulgaris in the US, and six clinical studies of Velac gel conducted by Yamanouchi in Europe.

Please see Sections 1.3.1 and 7.1.

Please also refer to Section 4 (Data Sources, Review Strategy and Data Integrity) for tabular description of studies.

7.2.1.1 Study type and design/patient enumeration

Please see Section 4 for description of patients enrolled in the US and European Phase 3 studies.

Since both topical Clindamycin and Tretinoin are pre-approved drug products for the treatment of acne vulgaris, and Velac gel had been tested originally in Europe (b) (4) methylparaben formulation), the sponsor did not conduct Phase 1 or 2 studies in the US with the to-be-marketed formulation ((b) (4) methylparaben formulation) of Velac gel.

7.2.1.2 Demographics

Subgroup analyses by age, gender and race were done for safety and efficacy in Phase 3 studies for the ISS ITT population. Please refer to Section 7.1.5.6 Integrated Review of Safety for a detailed review of Safety in Special Groups.

7.2.1.3 Extent of exposure (dose/duration)

The sponsor did not conduct dose-duration studies for Velac gel, but is relying on the pharmacology, pharmacokinetics and toxicology literature reports of both tretinoin and clindamycin. In addition, the sponsor is also relying on the clinical use of both products over the years that have helped establish their safety profile. While Clindamycin and Tretinoin have been used in conjunction in clinical practice, the specific safety issues that may arise for a fixed-combination product such as Velac gel were addressed by the sponsor by conducting bridging non-clinical and clinical studies.

The non-clinical studies included single and repeat dose (dose-ranging and dermal toxicity) animal toxicity studies, genotoxictiy, carcinogenicity and dermal safety studies. The sponsor also conducted a bioavailability study of Velac gel to assess the effect of the individual drug products on the absorption of each other when present in a fixed-combination form.

Safety and efficacy studies, as well as dermal safety studies had been performed in Europe using the previous formulation of Velac gel. As part of the bridging program, the sponsor

has performed two pivotal safety and efficacy studies in the US, a dermal safety study and a spectroscopic analysis on the to be marketed formulation of Velac gel.

Thus, the dose-duration profile of Velac gel has been assessed by a combination of literature reports regarding the two individual products Clindamycin and Tretinoin, as well as the drug development program in Europe and the US.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The Integrated Review of Safety for Velac gel was derived from the two pivotal safety and efficacy studies conducted in the US together with the six efficacy and safety studies conducted in Europe (by Yamanouchi). Yamanouchi conducted two sets of clinical studies of Velac gel, each consisting of a pilot study and two Phase 3 safety and efficacy studies. In one set, Velac gel was compared to clindamycin-containing products (Clindamycin gel or Dalacin® T Lotion) and in the second set, Velac gel was compared to tretinoin-containing products (Tretinoin gel or Aberela® gel). These studies were conducted in patients with moderate-severe acne vulgaris, but did not contain a vehicle group. The criteria for diagnosing severity of acne vulgaris was based on Cook's scale, which is different from the ISGA scale recommended by the Agency; however, since the European studies were included only for the safety analysis and not efficacy analysis, this was found to be acceptable. Safety was assessed by evaluating signs and symptoms of acne, adverse experiences and lab tests.

The information regarding study drug usage in European studies was not available. Only Caucasians were included in the Europeans studies, and therefore the studies were lacking in ethnic diversity. Out of the ITT population of 739 subjects in the European studies, females constituted 45% (336/739) and males 55% (403/739). Subjects 12-16 years of age constituted 32% (237/739) and those > 16 years of age were 68% (502/739).

The overall incidence of AEs was similar in the ITT population of the US and European studies.

Please refer to Section 7 for the detailed review.

7.2.2.1 Other studies

Dermal safety studies conducted in Europe using the previous formulation of Velac gel were also included in the safety analysis. These studies included irritation, contact sensitization, phototoxicity and photoallergenicity studies. Please refer to Section 7 for the detailed review.

7.2.2.2 Postmarketing experience

Although Velac gel was approved for marketing in France, it was never marketed. The sponsor states that a marketing authorization was granted for Velac gel in 1998 in France; however, Velac gel was never launched in France (b) (4) Thus, there is no post-marketing information available for Velac gel.

7.2.2.3 Literature

The sponsor has submitted literature references in support of the use of Clindamycin and Tretinoin both individually and in combination for the treatment of acne vulgaris, in addition to providing references for comparisons of various formulations of both drugs against other anti-acne drugs. Supportive pharmacokinetic literature reports have been provided for Clindamcyin and Tretinoin.

In addition, the sponsor has provided literature reports regarding the role of retinoic acid in papilloma formation in mice models, i.e. its role as a tumor promoter. Interestingly, there has been speculation in the literature that topical retinoids may decrease skin papilloma formation, but that resistant papillomas treated with Tretinoin may be at high risk for malignant conversion and the sponsor has provided literature information in this regard.

The sponsor has also referred to the Agency Guidance Document 'Skin irritation and sensitization testing of generic transdermal drug products'. Overall, the sponsor has provided adequate literature information in support of their fixed combination drug product.

7.2.3 Adequacy of Overall Clinical Experience

The Integrated Safety Analysis for Velac gel was assessed in 2,988 patients with acne vulgaris across the combined US and European 12 week studies. The two pivotal US studies were multi-center, randomized, double-blind and vehicle-controlled studies, while 3 of the European studies were single-blind and 3 were double-blind. While there was a vehicle arm in the two pivotal US studies, there was no vehicle arm across all the European studies. Also, only Caucasians were enrolled in the European studies, while the US studies included a subject population that was more ethnically diverse. Age and gender were more or less similarly and adequately represented across the US and European studies. The US studies were conducted in patients with mild-moderate acne vulgaris, while the European studies in moderate-severe acne vulgaris and the scale used to grade acne in the European studies (Cook scale) was different from the US studies (ISGA).

Local and systemic safety as well as the signs and symptoms of acne vulgaris were able to be adequately assessed; however, non-facial areas were excluded from the safety analysis. Patients with a history of concurrent use of photosensitizing agents were excluded from the studies (to avoid a concurrent effect with tretinoin) and patients using neuromuscular blocking agents were also excluded from these studies (to avoid a concurrent effect with clindamycin); the label for Velac gel would be expected to include this information. Overall, an adequate number of patients were assessed for the integrated safety analysis and the duration of studies was in keeping with other studies testing anti-acne drug products.

During the review cycle, the non-clinical Tg.AC mouse carcinogenicity study conducted by the sponsor was reviewed by the Agency Executive Carcinogenicity Assessment Committee and was found to be positive for carcinogenicity. There was an increase in papillomas in all treated animals, including the vehicle control and treatment with vehicle and clindamycin phosphate together produced an even higher tumor incidence than the vehicle alone. The findings indicated that the vehicle is either a complete carcinogen or at the very least a promoter. The Integrated Safety Analysis of Velac gel did not reveal the development of cutaneous

malignancies; however, such malignancies are not expected to develop over a 12 week period. If Velac gel is approved, long-term safety data per ICH E1A guidelines would be required, it is even possible that long-term cancer registries may be required to elucidate this concern.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Although the pharmacology, pharmacokinetics and toxicology of both tretinoin and clindamycin have been well described in literature, to address specific toxicity issues relating to a fixed-combination topical drug product consisting of Tretinoin and clindamycin phosphate, the sponsor conducted pivotal studies, which are described in the Pharmtox and Biopharm reviews.

Overall, the pharmacokinetic (PK) evaluations conducted by the sponsor demonstrated that the absorption profiles of clindamycin phosphate and Tretinoin following topical administration of Velac gel are consistent with known PK profiles of both drugs. These studies also showed that the PK characteristics of the individual drugs were not affected by the fixed-combination product, Velac gel.

The toxicity profiles of the individual ingredients, clindamycin phosphate and Tretinoin are well known; however, the toxicity program conducted by the sponsor, in agreement with the Agency focused on evaluations specific to Velac gel along with carcinogenicity testing on clindamycin phosphate and tretinoin. Focusing on carcinogenicity, National Cancer Institute sponsored studies have demonstrated that Tretinoin is a weak promoter in mice, but is also capable of reducing tetradeconyl-phorbol-13-acetate (TPA)-induced tumor production. The sponsor has acknowledged that the potential of systemically absorbed Tretinoin to promote tumor formation will be reflected in the eventual drug label.

The carcinogenic potential of clindamycin phosphate was evaluated in a 26-week dermal carcinogenicity study in transgenic Tg.AC mice. Results from this study indicated that there was an increase of papillomas in all treated animals, including the vehicle control, when compared to the untreated animals. This vehicle effect on papilloma formation was accentuated by the administration of Clindamycin phosphate in the Velac gel vehicle at 3% and 5%. This study has been reviewed by the Agency Executive Carcinogenicity Assessment Committee and it was concluded that the vehicle is either a promoter or a complete carcinogen. The Committee noted that although the sponsor believes that application site irritation led to papilloma formation, there have been other studies in Tg.AC mice, where irritation alone did not lead to papilloma formation. The Pharmtox reviewer determined that the sponsor performed appropriate studies in a pre-approved animal model and that based upon results form this study, Velac gel is non-approvable.

Please see Pharmtox review for a detailed discussion.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing, including vital signs, evaluation of signs and symptoms of facial acne vulgaris and labs was considered adequate in study subjects. Dermal safety assessed from the data provided was not complete since the phototoxicity and photoallergenicity studies were considered inadequate for a complete assessment.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

As such, a drug-drug interaction program was not conducted for Velac gel. Patients with a history of concurrent use of photosensitizing agents were excluded from the studies (to avoid a concurrent effect with tretinoin) and patients using neuromuscular blocking agents were also excluded from these studies (to avoid a concurrent effect with clindamycin); the label for Velac gel would be expected to include this information.

Please see Biopharm review for a detailed analysis.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Given the chronic nature of acne vulgaris and that the majority of treatment-related AEs were local, and highest in the Velac groups, as discussed at the pre-NDA meeting, long-term safety data would be needed per ICHE 1A guidelines. Although the sponsor had been asked to submit a proposal for addressing long-term safety, this has not been submitted. Given the non-clinical carcinogenicity study, if Velac gel were to be approved, long-term cancer registries would be required to assess the development of cutaneous cancers.

7.2.8 Assessment of Quality and Completeness of Data

Overall, the data submitted for the safety review of Velac gel was complete and allowed for an assessment of local and systemic adverse events that may be associated with 12 week use. There was no post-marketing data available for Velac gel itself since it had not been marketed elsewhere and since it is a new combination product, safety comparisons could not be made to other such products.

7.2.9 Additional Submissions, Including Safety Update

A four-month safety update provided by the sponsor on 1/7/2005 contained no new information. At the request of the Agency, the sponsor submitted the French label for Velac gel; this did not contain any new information either.

However, the mouse Tg.AC carcinogenicity study conducted by the sponsor was reviewed and presented before the Agency's Executive Carcinogenicity Assessment Committee on 3/29/2005. The Committee concluded that there was an increase in papillomas in all treated animals, including the vehicle control, when compared to the untreated animals. Treatment with the vehicle and clindamycin phosphate together produced an even higher tumor incidence than the vehicle alone. While non-clinical studies have shown that Tretinoin acts as a promoter of skin tumorigenesis, it is concerning that in this mouse study, the vehicle itself was noted to cause the increase in papillomas and that the addition of Clindamycin increased this effect. This study indicates that the vehicle of Velac gel has the potential to be a carcinogen; the implications of this positive non-clinical carcinogenicity results have affected the safety profile of Velac gel. The risk benefit ratio of a topical acne drug product that has the potential of causing cutaneous

cancers does not lend itself to product approval; therefore Velac gel is not approvable given the positive non-clinical carcinogenicity study.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In the ISS ITT population, 12% of patients reported AEs that were related to study drug; 16% (160/1003) in the Velac group, 5% in the Clindamycin group ($p < 0.0001$), 15% in the Tretinoin group (p 0.5989) and 5% in the Vehicle group ($p < 0.0001$). The highest incidence of AEs was in the system organ class 'General Disorders and Administrative Site Conditions'. Here, the incidence of AEs was 14% (144/1003) in the Velac group, similar to the AEs in the Tretinoin group 14% (116/804), while the incidence in the Clindamycin group 4% (116/836) was similar to the Vehicle group 4% (14/315). The following are the treatment-related AEs seen most frequently:

1) Application site dryness – incidence in Velac group 7%
2) Application site desquamation – incidence in Velac group 5%
3) Application site burning – incidence in Velac group 4%
4) Application site erythema - incidence in Velac group 4%
5) Application site pruritus – incidence in Velac group 3%
6) Application site irritation– incidence in Velac group 3%

Patients in the Tretinoin groups reported a similar incidence of AEs to the Velac groups and as such, these AEs fit in with the known AE profile of Tretinoin; it is therefore likely that Tretinoin contributed largely to the treatment-related AE profile of Velac gel.

Please refer to Section 7.1.5.5 for a detailed review of treatment-related AEs.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The integrated safety analysis was done in the ISS ITT population of the European and US studies. Safety analyses for all adverse events were provided for the ITT Connetics population and the ITT European population in addition to the ISS ITT population of both studies. Pooling of data of the European and US studies was allowed to yield a larger patient database from which a safety analysis could be done.

7.4.1.2 Combining data

For the two US pivotal studies, the multi-center trials pooled the centers by geographic location when centers contained small numbers of subjects. This resulted in 13 pooled centers for each study. Combination of the investigative centers was completed prior to unblinding the data for both studies.

In Study VLC.C.304, 9 out of the 18 investigative centers did not enroll 70 subjects and therefore, data from these sites was combined based on geographic and climatic similarities; hence there were 13 combined centers for analysis.

In Study VLC.C.305, 10 out of the 19 investigative centers did not enroll 70 subjects and therefore data from these centers were combined and resulted in a total of 13 combined centers for the analyses.

7.4.2 Explorations for Predictive Factors

Please see Section 7.1.5.6 for safety analysis by subgroups of age, race and gender. Application site reactions were the most frequently seen treatment-related AEs. These reactions were higher in the Caucasian group compared to the other groups, but it should be noted that 74% of the ISS ITT population was Caucasians. Pigmentation changes were significantly higher in the African-American group; post-inflammatory hyper or hypo pigmentation can be higher in this group of patients.

In general, the incidence of application site AEs was slightly higher in the 12-16 years age group compared to the > 16 years age groups, and the overall incidence of application site AEs was higher in the Velac groups compared to the Clindamycin and Vehicle groups. Since acne is most commonly seen in teenagers, this may have some clinical significance. Although such AEs are expected to be most frequent in the first few weeks after starting therapy and improve progressively in most patients, they could lead to discontinuation in a certain segment of the population.

7.4.2.1 Explorations for dose dependency for adverse findings

Not conducted for this NDA.

7.4.2.2 Explorations for time dependency for adverse findings

At all study visits, the signs and symptoms of acne vulgaris were sought; this showed that the majority of treatment-related AEs were local and appeared to be maximum two weeks after initiation of treatment, after which there was progressive decline. This information would be useful to convey in the label.

7.4.2.3 Explorations for drug-demographic interactions

Subgroup analyses for age, gender and race were conducted. Please refer to Section 7.1.5.6.

7.4.2.4 Explorations for drug-drug interactions

Not conducted for this NDA.

7.4.3 Causality Determination

As discussed in the safety review, application site reactions such as dryness, desquamation, erythema and pruritus were the most frequently seen treatment-related AEs and the incidence of these events was almost similar in the Velac and Tretinoin groups. Also, these AEs were seen most frequently in the first two weeks after starting treatment, after which there was a progressive decline. The description of such treatment-related AEs is in keeping with the well known AE profile of Tretinoin and it is possible that most of these AEs were related to the Tretinoin component of Velac gel.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Velac gel was studied in patients who applied study treatment once at night for 12 weeks. The nightly application was chosen to avoid the undesirable side-effects of Tretinoin application and sun exposure which can exacerbate local AEs described above. The 12 week study duration that was chosen, is in keeping with most other acne trials.

8.2 Drug-Drug Interactions

Not conducted for this NDA and no drug-drug interactions observed during the clinical trials.

8.3 Special Populations

Velac gel was studied in patients more than 12 years of age, since acne vulgaris is more prevalent in that age group, and, if approved would be indicated in similar age groups. Efficacy and safety of Velac gel was tested in the subgroups - age, race and gender, and based on those findings, there are no special dosing considerations for different demographic populations. Pregnant and breast-feeding subjects were excluded form the study (this was based on the teratogenic adverse effects of Tretinoin) and if approved, Velac gel would have a Pregnancy Category C.

8.4 Pediatrics

The studies for Velac gel were conducted in compliance with PREA regulations. Since acne is commonly seen in teenagers, patients more than 12 years of age were included in these studies. The sponsor has requested a pediatric waiver since acne is not usually seen in patients less than

12 years of age and it would be difficult to enroll appropriate patients in that age group. A partial pediatric waiver will be granted to the sponsor.

8.5 Advisory Committee Meeting

No advisory committee meetings were held to discuss Velac gel.

8.6 Literature Review

Please see Section 7.2.2.3.

8.7 Post-marketing Risk Management Plan

No Post-Marketing risk management plan has been submitted with the NDA. Based on the non-clinical carcinogenicity study, where the vehicle was found to be a carcinogen, Velac gel is not approved for use.

However, it is recommended that the sponsor conduct adequate photosafety studies for Velac gel, bearing in mind that based on the non clinical carcinogenicity study conducted for Velac gel, this would involve a de novo clinical development program.

8.8 Other Relevant Materials

The Division of Drug Marketing, Advertising and Communications (DDMAC) was consulted to review Velac and the Division of Medication Errors and Technical Support (DMETS) were consulted to review the trade name Velac and identify potential name confusion with other proprietary or established drug names.

DDMAC found the proprietary name Velac acceptable from a promotional perspective. However, the Expert Panel discussion held by DMETS to gather professional opinions on the safety of the name Velac concluded that there were six other proprietary names (Cedax, Penlac, Velban, Valtrex, Teslac, Valnac) that had the potential for confusion with Velac. Also, through independent review, Keralac and Carac were also determined to have potential for confusion with the proposed name.

DMETS recommended the following:

1. The proprietary name Velac was not recommended.
2. Label revisions were recommended to minimize potential errors with the use of this product.

This information was conveyed to the sponsor who suggested two additional proprietary names instead of Velac: (b) (4) Veltin. Appropriate labeling and product packaging changes were also submitted by the sponsor.

9 OVERALL ASSESSMENT

9.1 Conclusions

Connetics Corporation has submitted a NDA application for Velac gel, which is a fixed-combination product, containing Clindamycin 1% and Tretinoin 0.025%, for the treatment of acne vulgaris. Velac gel was originally developed in Europe for the treatment of acne vulgaris but was never marketed. The only difference between the US and European formulations was that the concentration of methylparaben was (b) (4) in the European studies and (b) (4) in the US studies; the sponsor therefore conducted a bridging bioequivalence clinical and non-clinical program to address this difference in formulations.

The efficacy of Velac gel was determined based on the two pivotal Phase 3 safety and efficacy studies conducted in the US, while safety was derived from these two studies as well as six safety and efficacy studies conducted in Europe. Efficacy analysis of Velac gel showed it to be statistically superior to its individual constituents, Clindamycin and Tretinoin as well as its Vehicle in the treatment of mild-moderate lesions of facial acne vulgaris. The Integrated Safety Analysis of Velac gel showed local and systemic safety under study conditions; in addition, tests for dermal safety demonstrated Velac gel to be safe, although the number of patients in the photoxicity and photoallergenicity tests were found to be inadequate.

However, it is concerning that the non-clinical 26 week carcinogenicity study in the Tg.AC mouse model conducted by the sponsor showed that the vehicle of Velac gel alone caused a statistically significantly increased incidence of skin papillomas compared to the untreated controls and that the addition of Clindamcyin further augmented this effect. The Agency's Executive Carcinogenicity Assessment Committee (CAC) concluded that the study was conducted in an adequate manner and that the positive results indicate that that the vehicle is a carcinogen. The Pharmtox reviewer has deemed Velac gel not approvable based on this study.

Velac gel was shown to be safe and effective in the clinical trials as conducted for this NDA; however, based on the non-clinical carcinogenicity study, it is deemed non-approvable.

9.2 Recommendation on Regulatory Action

Please see Section 1.1

9.3 Recommendation on Postmarketing Actions

Please see Section 1.2

9.3.1 Risk Management Activity

Not applicable because of Non-Approvable action.

9.3.2 Required Phase 4 Commitments

Please see Section 1.2.2

9.3.3 Other Phase 4 Requests

Not applicable because of Non-Approvable action.

9.4 Labeling Review

There is no labeling review in view of the Non Approvable action.
The Division of Medication Errors and Technical Support had conducted a review for the proprietary trade name 'Velac' and their recommendation included a change of name because other drug products had similar sounding names.
Please refer to Section 8.8

9.5 Comments to Applicant

Recommendations for Sponsor (To be conveyed to Sponsor):
The sponsor could choose to explore the Velac gel formulation to determine what ingredient/ingredients contributed to its carcinogenicity profile. It is also recommended that photosafety studies be performed in the appropriate number of patients; although, given the non-clinical carcinogenicity findings, this would be included in a *de novo* clinical development program.

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/s/

Bindi Nikhar
5/16/05 04:16:47 PM
MEDICAL OFFICER

Markham Luke
5/20/05 05:11:02 PM
MEDICAL OFFICER
Concur with primary review. See also Pharm/Tox review regarding carcinogenicity concern.

Jonathan Wilkin
6/7/05 05:05:49 PM
MEDICAL OFFICER
The results of the Tg.AC do not show that the drug product, specifically, one or more of the inactive ingredients in the product, is sufficiently safe for the treatment of acne, a chronic indication.

45 DAY MEETING CHECKLIST for (b) (4) VELAC GEL(clindamycin 1% - tretinoin 0.025%)

FILEABILITY:

On initial overview of the NDA application:	YES	NO

CLINICAL:

		YES	NO
1.	Identify the general format that has been used for this application. This NDA is in the Common Technical Document format as described by ICH and FDA guidance documents and has been submitted in paper. Some items have been submitted electronically as follows: Draft labeling, SAS datasets and associated files, clinical and non-clinical references and clinical photographs.		
2.	On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	X	
3.	Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X	
4.	On its face, is the clinical section of the NDA legible so that substantive review can begin?	X	
5.	If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose- ranging studies)? The Sponsor did not conduct dose-ranging studies, but has relied on information available from the six Yamanouchi studies conducted in Europe using Velac gel (different formulation). Connetics (current sponsor) licensed Velac gel from Yamanouchi (previous sponsor) in May 2002. The formulation used in the Yamanouchi studies was identical to that in the Connetics' studies, except for (b) (4) methylparaben (b) (4) in the Yamanouchi and Connetics formulations respectively.		X
6.	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? Application Type: 505(b)(2) because it is supported in part by reference to published literature for topical Clindamycin Phosphate and Tretinoin (for non-clinical studies, including fertility and peri/postnatal development). The Sponsor does not have rights of reference to the underlying data for both products and will be relying on the Agency's findings of safety for both. Reference drug: None	X	

7. Identification of pivotal trials:

Pivotal Study #1: Protocol Number: VLC.C.304
Location in NDA: Module 5, Section 5.3.5, Efficacy and Safety Studies.
Study Title: A Phase 3, multi-center, randomized, double-blind, active and vehicle controlled study of the safety and efficacy of Velac® Gel for the treatment of Acne Vulgaris.
Study design: Randomized (Y), Double Blind (Y), Placebo controlled (Y), Multi-centered (Y)
Indication: Treatment of Acne Vulgaris.
Study arms: Four arms: Velac gel vs. Clindamycin 1% gel vs. Tretinoin 0.025% gel vs. Vehicle gel, once daily application for 12 weeks each.

Pivotal Study #2: Protocol Number: VLC.C.305
Location in NDA: Module 5, Section 5.3.5, Efficacy and Safety Studies.
Study Title: A Phase 3, multi-center, randomized, double-blind, active and vehicle-controlled study of the safety and efficacy of Velac® Gel for the treatment of Acne Vulgaris.
Study design: Randomized (Y), Double Blind (Y) Placebo controlled (Y), Multi-centered (Y)
Indication: Treatment of Acne Vulgaris
Study arms: Four arms: Velac gel vs. Clindamycin 1% gel vs. Tretinoin 0.025% gel vs. Vehicle gel, once daily application for 12 weeks each.

		Yes	No
8.	Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	X	

9. Proposed indication from sponsor's draft labeling: Topical treatment of Acne Vulgaris

10. Endpoints in pivotal trial #1:

Primary Efficacy Endpoints:

1. Percent reduction in lesion counts (total, inflammatory and non-inflammatory) from baseline to week 12 (end of treatment).
2. Proportion of subjects with an Investigator's Static Global Assessment (IGA) score of 0 or 1 at week 12 (end of treatment).

Secondary Efficacy Endpoints:

1. Absolute reduction in lesion counts (total, inflammatory and non-inflammatory) from baseline to week 12.
2. Proportion of subjects with a Subject's Global assessment score of 0 or 1 at week 12.
3. Time to a 50% reduction in total lesion counts.

Other Endpoints :

1. Proportion of subjects who had an IGA score of 0 or 1.
2. Percent reduction in lesion counts from baseline.
3. Absolute reduction in lesion counts from baseline.
4. Proportion of subjects who had a SGA score of 0 or 1.
5. Change in quality of life from baseline to week 12.

Endpoints in pivotal trial #2:
Same as above.

11. Are all data sets for pivotal efficacy studies complete for all indications (indication) requested? (this is a stat question?)
Yes.

12. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?
Yes
Pre IND Mtg: Yes
IND number: 65,369
Pre IND Mtg Date: 8/26/02
EP2 Meeting Date: 8/26/02
Agency response to Phase 3 protocols:
Pre NDA meeting date: 5/27/04

13. Do endpoints in pivotal Study 1 conform to previous agency commitments?
Yes.
Do endpoints in pivotal Study 2 conform to previous agency commitments?
Yes.

14. Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?
Yes.

15. Has the application submitted a rationale for assuming the applicability of foreign data (disease specific, microbiologic specific) in the submission to the US population?
Six studies were conducted by Yamanouchi (previous sponsor for Velac gel) in Europe for establishing the safety and efficacy of Velac gel in the treatment of acne vulgaris. The Sponsor has conducted two pivotal trials in the US for establishing safety and efficacy for Velac gel and data from the European studies has been used for dose ranging purposes as well as for augmenting the safety database in the US studies. The rationale behind this was that the formulation used in the Yamanouchi studies was the same as the US studies except (b) (4) methylparaben (b) (4) in the European studies and (b) (4) the US studies.
Bridging studies, which include a pharmacokinetic study (in patients with acne vulgaris, under maximal usage conditions) and a dermal safety study (cumulative irritation and skin sensitization in 195 healthy subjects) have been conducted to show that (b) (4) methylparaben would not adversely affect the outcome of any safety data obtained from the Yamanouchi-sponsored studies.

16. Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division?
Not applicable.

17. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?
Yes.

18. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?
Yes.

19. Has the applicant submitted draft -labeling consistent with 21CFR 201.56 and 21CFR 201.57, current divisional policies, and the design of the development package?
Yes.

20. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor?
The Sponsor has conducted one dermal safety study, a cumulative irritation and contact sensitization study with the to be marketed formulation of Velac gel. The potential for the Sponsor's formulation to effect a change in the photosensitization properties of Velac gel beyond that documented in the Yamanouchi studies was evaluated in a photosensitivity study. This study demonstrated that there was no difference in UVA/UVB or visible absorption between the (b) (4) methylparaben formulations of Velac gel. The Sponsor concluded that the two formulations are comparable and has submitted additional dermal safety studies conducted by Yamanouchi in support of their application.
The Sponsor has also conducted subgroup efficacy analyses based on age, race and gender for both pivotal studies.

21. Has the applicant complied the requirements of PREA?
a) Is this an indication that would be applicable to the pediatric population?
b) What pediatric ages are included in the protocol(s)?
c) Does the sponsor request pediatric labeling? If yes, what age groups?
The Sponsor has complied with PREA requirements. Since acne is commonly seen in teenagers, patients > 12 years of age were included in the studies. The Sponsor has requested a pediatric waiver since acne is not usually seen in patients < 12 years of age and it would be difficult to enroll appropriate patients in that age group.

22. Financial disclosure of investigator:
Does the NDA contain the appropriate form to comply with the filing requirement for Financial Disclosure for Investigators?
Yes.

23. From a clinical perspective, is this NDA fileable? If "no", please state below why it is not. If certain claims are not fileable please state which claims they are and why they are not fileable.
Yes.

24. Please identify and list any potential review issues to be forwarded to the Sponsor for the 74-day letter.

Bindi Nikhar,
Reviewing Medical Officer

Markham Luke,
Clinical Team Leader/Dermatology

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

/s/

Bindi Nikhar
10/20/04 02:13:43 PM
MEDICAL OFFICER

Markham Luke
10/20/04 03:21:51 PM
MEDICAL OFFICER
Concur with fileable from Clinical.