CLINICAL STUDY REPORT SYNOPSIS

Name of Sponsor/Company:	VERISFIELD (UK) Ltd, Greek branch
Name of Finished Product:	Clindamycin-Tretinoin/Verisfield, gel, (1.0+0.025)%
Name of Active Ingredient:	Clindamycin (as phosphate) Tretinoin
ATC Code:	D10A X30
Title of Study: Multicenter, randomized, double-blind comparative study with the reference products, for assessment of therapeutic superiority of the combination clindamycin-tretinoin/verisfield, gel, (1.0+0.025)%, (versus the monotherapy with clindamycin or tretinoin) for the topical treatment of acne.	
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Study centers: Venereal and Skin Diseases Hospital , Andreas Syggros, I. Dragoumi 5, 161 21, Athens, Greece, Telephone: +30 210-7265100 Fax: +30 210-7235546 • First, A' Dermatological Clinic of University of Athens, Andreas Syggros Hospital • Second, B' Department of Dermatology, Andreas Syggros Hospital • Third, C' Department of Dermatology, Andreas Syggros Hospital	
Publication (reference): N/A	
Phase of Development	Therapeutic superiority
Study period:	The duration of the study was from 13 December 2010 (date of first patient enrolled) to 14 November 2011 (last visit of last patient), a total of 336 days (or about 11 months).
(date of first enrollment) ***(date of last completed)***	13 December 2010 (first patient enrolled) 14 November 2011 (last visit of last patient)
Objectives:	The purpose of this study is to provide evidence that the Verisfield formulation Clindamycin-Tretinoin (1.0+0.025%) w/w is therapeutically superior to both the reference monotherapies of clindamycin and tretinoin in patients diagnosed with common acne (acne vulgaris).
Methodology:	This is a randomized, double-blind, parallel group, therapeutic superiority study.
Number of patients (planned and analyzed):	Planned: 134 Enrolled: 133 Analyzed:126(Treated Patients Set), 120 (Full analysis set)
Diagnosis and main criteria for inclusion: Volunteers, aged 12 - 35 years old, diagnosed with mild to moderate acne, who have acne lesions, divided into regions (forehead, cheeks, jaw). Acne lesions consisting of inflammatory and non inflammatory acne characteristics, but not cysts and nodules. Patients that are willing, in good physical condition based on their medical history and are able to attend the scheduled study visits.	
Test product:	Clindamycin-Tretinoin/Verisfield gel (1.0+0.025%) w/w
Dose:	0.5 g of gel (pea size) is spread to the affected skin surface with dimensions 10cm x 10cmbefore bedtime

Mode of administration:	Topical application	
Batch Number:	00150710	
Reference products:	Dalacin-C/Pfizer, gel 1.0%	Retin-A/Janssen-Cilag, gel, 0.025%
Dose:	0.5 g of gel (pea size) is spread to the affected skin surface with dimensions 10 cm x 10 cm before bedtime	0.5 g of gel (pea size) is spread to the affected skin surface with dimensions 10 cm x 10 cmbefore bedtime
Mode of administration:	Topical application	Topical application
Batch number:	0A885	ABS0Q00
Duration of treatment	84 days ± 3 days	

Criteria for evaluation:

Efficacy:

The percent change in total number of the total number of acne lesions [inflammatory (papules, pustules) and non-inflammatory (comedones)] between 1st and 3rd visit.

Efficacy: Secondary parameters:

- Scale IGII (Investigator Global Improvement Index).
- Scale PGII (Patient Global Improvement Index).

Safety: Main Parameters:

- Physical examination/Vital signs
- Topical reactions
- Adverse events
- Discontinuation of therapy

Statistical methods:

I. Tests regarding the homogeneity of three treatment groups: Fisher exact test will explore the relation of study treatment with the variables of gender and skin photo type. Analysis of variance technique will test the relation between study treatment and the variables of age, disease duration, number of Closed and open comedones, number of Papules and pustules, and total number of lesions.

II. Analysis of the Adherence scale: The Adherence scale at the third visit will be tested for statistically significant differences between the test drug and the two reference groups, with the implementation of Mann-Whitney test (two-tailed).

III. Analysis of the main parameter of efficacy - Therapeutic Superiority: To assess the superiority of Clindamycin-Tretinoin/Verisfield, gel (1.0+0.025%) against the original formulation the percent change of the total number of lesions from baseline will be used, defined as the difference of the total number of lesions at the third visit minus the total number of lesions at the first visit over the total number of lesions at first visit. These percent changes from baseline will be compared between the test drug and each of the reference ones – using Student's t-test – to assess the hypothesis of the superiority of the test drug at an alpha=0.05 level.

IV. Analysis of the secondary parameters of efficacy: The values of secondary parameters at the 3rd visit will be compared between the test drug and each of the reference ones, using the Mann-Whitney test, at a (one-sided) alpha=0.05 level.

V. Safety & Adverse Events (AE) / Local reactions assessment: The frequency of withdrawals from the study and adverse events will be presented in cross tabulation form and the relative differences between the test drug and the two reference groups will be tested, using Fisher's Exact Test. Assessments of local reactions at the third visit, will be tested for statistically significant differences between the test drug and the two reference groups, with the implementation of Mann-Whitney test (two-tailed).

Summary – Conclusions:

EFFICACY RESULTS:

Primary parameter – Therapeutic Superiority

The test product Clindamycin – Tretinoin gel (1.0+0.025)% w/w performed excellent, averaging 80.1% decrease from baseline in 38 patients (SD=12.1%). On the contrary monotherapy with tretinoin produced a 72.1% decrease from baseline (SD=14.9%), while monotherapy with clindamycin only 66.0% decrease from baseline (SD=19.7%).

Based on the statistical methodology pre-defined in the approved protocol, the test product was therapeutically superior to both monotherapies.

Secondary parameter – IGII

Based on the results from this scale in the Full Analysis Set, the combination of clindamycin and tretinoin proved to be statistically significantly superior than the monotherapies. In the Full analysis Set, at the 3rd Visit, the median value of IGII was 2.0 ("moderately improved") in both Clindamycin and Tretinoin treatments, while the median PGII values in the Clindamycin+Tretinoin treatment was 3.0 ("significantly improved"). Mann Whitney test also showed that the values corresponding to the combination therapy were statistically significantly higher than those corresponding to the Clindamycin therapy and those corresponding to the Tretinoin one. (Mann Whitney test p-value (one-sided) <0.001 and 0.041 respectively).

Secondary parameter – PGII

Based on the results from this scale in the Full Analysis Set, the combination of clindamycin and tretinoin proved to be statistically significantly superior than the monotherapy with clindamycin, however it was borderline not superior to the monotherapy with tretinoin. In the Full analysis Set, at the 3rd Visit, the median value of PGII was 2.0 ("moderately improved") in both Clindamycin and Tretinoin treatments, while the median PGII values in the Clindamycin+Tretinoin treatment was 3.0 ("significantly improved"). Mann Whitney test also showed that the values corresponding to the combination therapy were statistically significantly higher than those corresponding to the Clindamycin therapy (Mann Whitney test p-value (one-sided) <0.001) but it didn't detect any statistically significant difference between the combination therapy and the Tretinoin therapy (Mann Whitney test p-value (one-sided) = 0.056).

SAFETY RESULTS:

No serious or unexpected adverse events were recorded during the study. Overall the test product, Clindamycin – Tretinoin gel (1.0+0.025)% w/w, has a well understood and described safety profile, similar to that of tretinoin alone. Adverse events are of local nature and mild severity, as described in the SmPC of the product.

CONCLUSION:

The primary efficacy endpoint provides clear evidence of the therapeutic superiority of the test product Clindamycin – Tretinoin gel (1.0+0.025)% w/w, against the monotherapies with clindamycin or tretinoin. This result is not unexpected, since the combination of two active substances against acne lesions is expected to produce better results than using only one. It is also worth mentioning that these two active substances act by a different mechanism, producing synergistic effects and providing a better therapeutic outcome. The secondary efficacy parameters provide supportive data to the superiority of the test product against the monotherapies.

By taking into consideration the results of the primary efficacy parameter for the Full Analysis Set, as well as the supportive data from the secondary efficacy parameters, the test product Clindamycin – Tretinoin gel (1.0+0.025)% w/w is therapeutically superior to both the monotherapies with tretinoin or clindamycin.

Date of the report:	5/4/2012