CLINICAL STUDY REPORT SYNOPSIS

Name of Sponsor/Company:	VERISFIELD (UK) Ltd, Greek branch
Name of Finished Product:	Erythromycin-Isotretinoin/Verisfield, gel, (2.0+0.05)%
Name of Active Ingredient:	Erythromycin Isotretinoin
ATC Code:	D10AX30
Title of Study: Multicenter, randomized, double-blind comparative with the reference product clinical study to demonstrate the safety and efficacy of the therapy with the combination erythromycin-isotretinoin/Verisfield, gel, (2.0+0.05)% w/w for the topical treatment of mild to moderate acne	
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Study centers: Venereal and Skin Diseases Hospital, Andreas Syggros, I. Dragoumi 5, 161 21, Athens, Greece • 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 equivalence
Study period:	The duration of the study was from 28 March 2012 (date of first patient enrolled) to 29 October 2012 (last visit of last patient), a total of 216 days (or about 7 months).
(date of first enrollment)	28 March 2012 (first patient enrolled)
(date of last completed)	29 October 2012 (last visit of last patient)
Objectives:	The purpose of this study was to provide evidence that the Verisfield formulation Erythromycin-Isotretinoin (2.0+0.05%) w/w is therapeutically equivalent to the reference formulation of Erythromycin-Isotretinoin (2.0+0.05)% w/w (Isotrexin/Stiefel Labs.) in patients diagnosed with common acne (acne vulgaris).
Methodology:	This was a randomized, double-blind, parallel group, therapeutic equivalence study.
Number of patients (planned and analyzed):	Planned: 90 Enrolled: 90 Analyzed: 78 (Per Protocol Set), 90 (Full analysis set)
Diagnosis and main criteria for inclusion: Volunteers, aged 12 - 35 years old, diagnosed with mild to moderate acne, which had 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 were willing, in good physical condition based on their medical history and were able to attend the scheduled study visits.	
Test product:	Erythromycin-Isotretinoin/Verisfield gel (2.0+0.05%) w/w

Dose:	0.5 g of gel (pea size) was spread to the affected skin surface with dimensions 10cm x 10cm before bedtime
Mode of administration:	Topical application
Batch Number:	00261110
Reference product:	Isotrexin/Stiefel Labs, gel (2.0+0.05)% w/w
Dose:	0.5 g of gel (pea size) was spread to the affected skin surface with dimensions 10cm x 10cm before bedtime
Mode of administration:	Topical application
Batch number:	1308N
Duration of treatment	60 ± 3 days

Criteria for evaluation:

Efficacy:

The absolute change 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:

Continuous variables have been summarized with the use of descriptive statistical measures [mean value, standard deviation (SD), median and range]. Categorical/distinct variables have displayed as frequency tables (N, %).

For the evaluation of the primary endpoint of the study, which referred to the assessment of the therapeutic equivalence between the two therapies, the confidence interval approach was used. Specifically, the 90% confidence interval (CI) for the difference between the two sample mean reductions in the total number of lesions of the two treatments was calculated.

The confidence interval calculation was based on the formula $[\overline{X}_R - \overline{X}_T \pm t_{n_R+n_T-2} \cdot S_p]$, where:

$\overline{X}_R, \overline{X}_T$ are the estimators of μ_R and μ_T and

$$S_p^2 = \frac{(n_R-1)S_R^2 + (n_T-1)S_T^2}{n_R+n_T-2},\ S_R^2 = \sum_{i=1}^{8} w_{iR}^2 S_{iR}^2,\ S_T^2 = \sum_{i=1}^{8} w_{iT}^2 S_{iT}^2,\ w_{iR} = \frac{n_{iR}}{n_R},\ w_{iT} = \frac{n_{iT}}{n_T}$$

where S_{iR}^2 and S_{iT}^2 are the variances of the reference and the test group, respectively within stratum *i*, n_{iR} and n_{iT} are the sample sizes of the reference and the test group respectively in stratum *i*, and n_R and n_T are the sample sizes of the reference and test group, respectively.

Additionally, for the evaluation of differences between the two treatment groups in the IGII and the PGII scores as well as in the evaluation of the severity/grade of the local reactions experienced at the 30-day post-treatment visit and at the 60-day post-treatment visit the Mann-Whitney test has been performed.

Summary – Conclusions:

EFFICACY RESULTS:

Primary parameter – Therapeutic Equivalence

The primary efficacy parameter for testing therapeutic equivalence was the difference in the total number of lesions during the 3rd visit, as compared to baseline. This is a well defined and validated form of measurement, relevant to the combinational nature of the test product, which targets both inflammatory and non-inflammatory lesions.

The test product Erythromycin-Isotretinoin/Verisfield, gel (2.0+0.05)% w/w showed excellent results, with an average 59.92% decrease from baseline in the total number of lesions. Similarly, the reference product Isotrexin/Stiefel Labs induced an average decrease of 60.16% from baseline in the total number of lesions. Therefore, the absolute difference between the two treatments was of the range of 0.24%, further demonstrating the therapeutic equivalence of the two products.

Moreover, the point estimate of the difference $\bar{x}_R - \bar{x}_T$ is almost zero (-0.21) in the PPS. This indicates that the best estimate for the difference between the test and the reference formulations is zero.

In addition, the estimated 90% CI (-2.78 to 2.36) for the difference between the mean reductions in the total lesion counts of the two treatment arms lies within the critical bounds of -6.32 to 6.32 ($-0.43\mu_T$, $0.43\mu_T$), thus indicating the therapeutic equivalence between the test and the reference medicinal product.

Secondary parameter – IGII

Mann-Whitney test showed no statistically significant difference between the test and the reference treatment groups regarding IGII scores (p-value=0.523).

Secondary parameter – PGII

Mann-Whitney test showed no statistically significant difference between the test and the reference treatment groups regarding PGII scores (p-value=0.642).

SAFETY RESULTS:

In terms of safety, the results of this study are reassuring, since both products were characterized by a low incidence of adverse reactions. The statistical analysis failed to show significant differences between the two products. This was expected, since both products are identical in terms of composition.

Conclusion:

Both products succeeded in reducing about 60% of the total acne lesions in the treated patients, after two months of treatment. Moreover, the difference in the reduction of the total number of acne lesions between the third visit and baseline (primary endpoint) is almost zero (-0.21). This difference is considered therapeutically insignificant. Based on the primary efficacy parameter of the study, the test product can be considered therapeutically equivalent to the reference product, since the estimated 90% CI (-2.78 to 2.36) for the difference between the mean reductions in the total lesion counts of the two treatment arms lies within the critical bounds of -6.32 to 6.32 ($-0.43\mu_T$, $0.43\mu_T$). The results from the secondary efficacy parameters, i.e. the Investigator's and the Patient's Global Improvement Index, are similar, since both treatment groups scored similar values. There is no statistically significant difference between the test and the reference treatment groups. Therefore, based on the primary and secondary efficacy parameters, the two products are considered therapeutically equivalent.

In terms of safety, the results of this study are reassuring, since both products were characterized by a low incidence of adverse reactions. The statistical analysis failed to show significant differences between the two products. This was expected, since both products are identical in terms of composition.

In conclusion, Verisfield's formulation Erythromycin-Isotretinoin/Verisfield, gel, (2.0+0.05)% w/w is therapeutically equivalent to Isotrexin/Stiefel Labs, gel, (2.0+0.05)% w/w.

Date of the report:	10/12/2012