CLINICAL STUDY REPORT SYNOPSIS

Name of Sponsor/Company:	Verisfield (UK) Ltd, Greek branch
Name of Finished Product:	Lidocaine-Prilocaine/Verisfield (2.5+2.5)% w/w cream
Name of Active Ingredient:	Lidocaine Prilocaine
ATC Code:	N01BB20

Title of Study: A Multicenter, randomized, double-blind (patient and investigator), placebo-controlled, crossover clinical study of Lidocaine-Prilocaine/Verisfield (2.5+2.5) % cream and EMLA/AstraZeneca cream, in patients undergoing haemodialysis.

Coordinating Investigator:

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Principal Investigators:

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- Dr. K. Stamatelou, Nephrologist

Director of the Nephrology Unit of the Hospital "Kyanous Stavros"
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Study centers:

- Artificial Kidney Unit of "Attikon" Hospital
- Artificial Kidney Unit of "Kyanous Stavros" Hospital and Diagnostic Center.

Publication (reference):N/A

Phase of Development	Therapeutic equivalence
Study period:	The duration of the study was from 01 April 2013 (date of first patient enrolled) to 04 July 2013 (last visit of last patient), a total of 95 days (or about 3 months).
(date of first enrollment)	01 April 2013 (first patient enrolled)
(date of last completed)	04 July 2013 (last visit of last patient)

Objectives:	The purpose of this study was to assess the therapeutic equivalence of local treatment with ***Lidocaine-Prilocaine/Verisfield (2.5+2.5)% w/w cream*** and the original formulation EMLA/AstraZeneca cream in terms of the management of pain associated with arteriovenous fistula cannulation in haemodialysis patients.
Methodology:	This was a randomized, double-blind (patient and investigator), placebo-controlled, crossover therapeutic equivalence study.
Number of patients (planned and analyzed):	Planned: 60 Enrolled: 60 Analyzed: 59 (Per Protocol Set), 60 (Full analysis set)
Diagnosis and main criteria for inclusion: Volunteers, aged ≥ 18 years old undergoing chronic haemodialysis. Patients that were willing and were able to attend the scheduled study visits.	
Test product:	Lidocaine-Prilocaine/Verisfield (2.5+2.5%) w/w cream
Dose:	2.0 g of cream were applied per 10 cm^2 surface area and the area was subsequently covered with an occlusive dressing for 1 hour
Mode of administration:	Topical application
Batch Number:	112262
Reference product:	EMLA/AstraZeneca (2.5+2.5)% w/w cream
Dose:	2.0 g of cream were applied per 10 cm^2 surface area and the area was subsequently covered with an occlusive dressing for 1 hour
Mode of administration:	Topical application
Batch number:	OF5521
Placebo product:	Placebo/Verisfield (0.0+0.0)% w/w cream
Dose:	2.0 g of cream were applied per 10 cm^2 surface area and the area was subsequently covered with an occlusive dressing for 1 hour
Mode of administration:	Topical application
Batch number:	112263
Duration of treatment	3 consecutive haemodialysis sessions (approximately 1 week)

Criteria for evaluation:

Efficacy: Primary parameter:

The determination of the difference in the mean VAS (Visual Analogue Scale) scores (mm) between the local treatment with Lidocaine-Prilocaine/Verisfield (2.5+2.5)% w/w cream and the reference treatment EMLA/AstraZeneca cream, as recorded by the eligible study population undergoing chronic haemodialysis immediately following the insertion of the cannula in the arteriovenous fistula.

Efficacy: Secondary parameters:

- Determination of the difference in the mean VAS scores (mm) between the Lidocaine-Prilocaine/Verisfield (2.5+2.5)% treatment and the placebo.
- Determination of the difference in the mean VAS scores (mm) between the EMLA/AstraZeneca (2.5+2.5)% treatment and the placebo.
- Assessment of the difference between the Verbal Rating Scale (VRS) score of the Lidocaine-Prilocaine/Verisfield (2.5+2.5)% w/w cream and that of the EMLA/AstraZeneca cream.
- Assessment of the difference between the VRS score of the EMLA/AstraZeneca (2.5+2.5)% w/w cream and that of the placebo cream

Safety: Main Parameters:

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

Statistical methods:

Descriptive statistical analysis was performed for all study data. Continuous variables have been summarized with the use of descriptive statistical measures [mean value, standard deviation (SD), median and range]. Categorical/distinct variables are being displayed as frequency tables (N, %).

Primary Endpoint Analysis:

For the evaluation of the primary endpoint which referred to the determination of the difference in the mean VAS scores (mm) between the local treatment with Lidocaine + Prilocaine/Verisfield (2.5+2.5)% w/w cream and the reference treatment EMLA/AstraZeneca cream the confidence interval approach has been used. In order to declare therapeutic equivalence, the estimated two-sided 95% confidence interval for the difference between the mean VAS Scores of the reference and test treatment will lie entirely in the interval (-13 mm, 13 mm).

The aforementioned confidence interval has been generated from a linear model analysis, where all effects were fixed effects. In order to achieve the best fit for the aforementioned linear model, according to Akaike criterion (AIC), the period and the sequence effects were excluded from the model.

Secondary Endpoint Analyses:

Superiority of test treatment versus the placebo has been declared if the one-sided 97.5% confidence interval calculated for the difference of the mean VAS scores (μ_T - μ_P) is below zero. The 97.5% confidence interval for the difference of the means has been derived from a linear model analysis with terms for treatment, period, sequence and subject within sequence where all effects will be fixed effects. For achieving a better fit according to AIC the effects of period and sequence were removed from the aforementioned model.

Likewise, the superiority of the reference treatment versus the placebo in reducing patients' pain has been evaluated by considering as null hypothesis ($H0:\mu_R-\mu_P\geq 0$) (the reference treatment is not more efficacious than the placebo), versus the alternative of superiority ($H1:\mu_R-\mu_P<0$), where μ_R denotes the mean VAS score (mm) reported for the reference treatment (EMLA/AstraZeneca cream) and μ_P denotes the mean VAS score (mm) reported for the placebo cream. Superiority of reference treatment has been declared by calculating one-sided 97.5% confidence interval for the difference of the mean VAS scores (μ_R - μ_P) and examining if it is below zero.

With regard to the third and the fourth secondary endpoints of the study, the distribution of patients by the intensity of the pain recorded on the 6-point VRS by applied product has been displayed in frequency tables (N,%). In addition to the aforementioned analysis, descriptive statistics (mean, SD, median and range) of the VRS scale has been presented per applied product (reference, test, and placebo). For the evaluation of differences between products in the VRS score the Friedman's test has been used. In order to detect differences between reference treatment and test treatment or placebo, pairwise comparisons will be performed using the Wilcoxon Signed-Rank test.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Primary parameter – Therapeutic Equivalence

According to the results, the estimated 95% CI, (-6.5 to 5.9) for the difference between the mean VAS scores recorded by the participants after the application of reference and test treatments, lies entirely within the critical bounds of (-13mm, 13mm), indicating the therapeutic equivalence between the test and the reference medicinal product.

Secondary parameters

In regards to the first secondary endpoint pertaining to the assessment of the superiority of test treatment over placebo, the estimated 97.5% CI derived from a linear model including the effects of treatment and subject within subjects, for the difference between the mean of VAS scores of the test treatment and placebo, is below zero (-42.2 to -27.6), indicating the superiority of the former versus the latter.

Likewise the examination of the null hypothesis (H0 :μ_r-$\mu_p \geq 0$) that the placebo product is more efficacious than the reference treatment pertaining to the second secondary endpoint was performed. The one-sided 97.5% CI (-41.9 to -27.3) derived from a linear model declares the superiority of the reference treatment over the placebo.

With regards to the third and fourth secondary endpoints, the efficacy of the test product compared to the reference product and of the reference treatment versus the placebo in terms of pain management using the VRS score has been assessed. The differences in the VRS score between the test and reference treatments have been evaluated as not statistically significant, p-value>0.05, whereas the differences in the VRS score between the reference and placebo treatments have been evaluated as statistically significant, p-value<0.05.

SAFETY RESULTS:

In terms of safety, the results of this study are reassuring since no (N)SAEs were reported during the study, which is consistent with both hospitals' records.

According to the SPC of the reference product, the incidence of the most common adverse events associated with the use of this product (paleness, erythema or oedema at the application site) can be as rare as 1 case in 100. Therefore, a low incidence of adverse reactions was expected in this study.

Overall, the safety results of the present study indicate an excellent safety profile of the two products. In addition, the two products (Test and Reference) are equivalent in terms of safety. This was expected, since both products are identical in terms of composition.

CONCLUSION:

The purpose of this study was to assess the therapeutic equivalence of local treatment with *Lidocaine-Prilocaine/Verisfield (2.5+2.5)% w/w cream* and the original formulation EMLA/AstraZeneca cream in terms of the management of pain associated with arteriovenous fistula cannulation in haemodialysis patients.

The primary outcome of the study was the assessment of pain by the patient using the VAS scale. Based on the statistical analysis of the primary endpoint, the estimated 95% CI, (-6.5 to 5.9) for the difference between the mean VAS scores recorded by the participants after the application of reference and test treatments, lies entirely within the critical bounds of (-13mm, 13mm), indicating the therapeutic equivalence between the test and the reference medicinal product.

Moreover, the analysis of the secondary endpoints of the study revealed that both the Test and the Reference product are efficient in reducing pain (both significantly superior to placebo) in addition to further confirming their therapeutic equivalence (the differences in the VRS score between the test and reference treatments have been evaluated as not statistically significant).

Regarding their safety profile, both products proved to be well tolerated and with an excellent safety profile. In addition, the two products (Test and Reference) are equivalent in terms of safety.

In conclusion, based on the results of the present study, it can be concluded that Verisfield's formulation Lidocaine-Prilocaine (2.5+2.5)% w/w cream is therapeutically equivalent to EMLA/AstraZeneca cream.

Date of the report:	***15/11/2013***