SYNOPSIS

Name of Sponsor: Almirall Hermal GmbH	**Individual Study Table Referring to Dossier Part**	**(For National Authority Use Only)**
Name of Finished Product: Verrumal® Solution	**Volume**	
Name of Active Ingredient: 5 Fluorouracil + Salicylsäure	**Report**	
Title of the clinical study:	Topical treatment of verrucae vulgaris with Verrumal® in organtransplant recipients (OTRs) – prospective, double-blind, placebo-controlled randomized trial	
Name of finished product:	Verrumal® Solution	
Name of active substances:	5-FU 0,5 % Salicylic acid 10,0 % Dimethylsulfoxid 8,0 %	
Study centre:	[redacted] Hospital Department of Dermatology and Allergology [redacted] [redacted] Berlin, Germany	
Investigators:	[redacted]	
Study period (years):	2005 - 2007 Date of first enrolment: 10th August 2005 Date of last completed: 11th June 2007	
Publication (reference):	None.	
Phase of development:	IV	
Indication:	Persistent verrucae vulgares	
Objectives:	The aim was to assess the response of persistent cutaneous warts to Verrumal® Solution in immunosuppressed individuals (OTRs)	
Methodology:	Prospective, randomized, double-blind, placebo-controlled, parallel-group, monocentric clinical study	
Number of patients (planned and analysed):	43 patients screened, 40 patients were enrolled: 30 verum, 10 placebo	

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Study plan:	Screening visit Inclusion visit: day 0 - Baseline Visits under treatment: week 2, week 4, week 8 Follow up visits: month 3 and 6 after end of treatment	
Diagnosis and main criteria for inclusion:	▪ Given written informed consent ▪ Men or women aged 18 or over ▪ Diagnosis of verrucae vulgares with a minimum duration of 3 months in the treatment area ▪ Organ transplant recipients for a minimum of 2 years ▪ Women had to use a reliable method of contraception or were postmenopausal ▪ Existence of a minimum of 5 warts – located on hands and forearms ▪ Patient was willing and able to participate in the study as an outpatient, make frequent visits to the clinic, and comply with all study requirements, including the following: o Clinic visits during the pre-study, treatment, and follow-up period o Application of study medication (Verrumal® Solution, placebo solution) o Pre-treatment curettage for virus typing, blood sample and eyebrow hairs o Post-treatment curettage for virus typing o Pregnancy testing for females of childbearing potential ▪ Negative pregnancy test for females of childbearing potential	
Exclusion Criteria:	▪ Known allergic or hypersensitive reactions to components of the study medication ▪ Diagnosis of subungual or periungal warts in the treatment area ▪ Warts treatment within the previous 3 months before inclusion ▪ Area to be treated exceeds 25 cm^2 ▪ Patient is taking any medication which could interfere with the study drug and could influence interactions; e.g. methotrexate, sulfonylurea, salicylic acid, dihydropyrimidinium-dehydrogenase (DPDH)-inhibitor, brivudin, systemic 5-FU nd any bromine ▪ Renal failure (creatinine > 6mg/dl) ▪ Serious illness within the previous 4 weeks or life-threatening diseases ▪ Pregnancy or nursing (lactation) ▪ Participation in another clinical trial in the month preceding the study	

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	▪ Patient has a severe illness or psychiatric condition on account of which the patient should not participate in the study in the opinion of the investigator ▪ Patient is suffering from active chemical dependency or alcoholism, as assessed by the investigator ▪ Exceeds a maximum of 10 warts in the treatment area	
Duration of treatment:	8 weeks	
Test product, dose and mode of administration, batch number:	Verrumal® Solution (License No: 244.00.00); Batch number: 528KK01 Topical application over 8 weeks, twice daily	
Reference therapy, dose and mode of administration, batch number:	Placebo solution; Batch number: 528KK01 Topical application over 8 weeks, twice daily	
Criteria for evaluation:	Efficacy variables: ▪ The number of lesions ▪ The diameter of lesions ▪ Overall improvement / efficacy assessed by investigator and by patient Safety variables: ▪ Clinical, medical and physical examination ▪ Local skin reactions ▪ Safety laboratory ▪ Overall tolerability of treatment ▪ Adverse events (AEs) Experimental: ▪ Virus typing at screening visit and at first follow-up visit	

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Statistical methods:	The study objective is to show superiority of treatment with Verrumal® Solution to placebo in treatment of persistent cutaneous warts in immunosuppressed individuals, measured by the change in number of lesions from basal values (XB) to values at visit 4 (XE), calculated as XE - XB. The primary variable (study hypothesis) and continuous secondary secondary variables were analysed by means of two-factorial analyses of variance (ANOVA). The error probability of the confirmative analysis of the primary efficacy endpoint is set to $\alpha = 0.05$ for a 2-sided test. The analysis is based on the whole study population. Adverse events were coded using MedDRA. Treatments were coded using the WHO Drug Reference List.	
Primary endpoint:	Change from baseline in the Number of lesions at week 8 (visit 4) (calculated as: Number of lesions at visit 4 (XE) – Number of lesions at baseline (XB) = XE-XB) Primary comparison: Verum versus Placebo	
Secondary endpoints:	- Number of patients with lesions reduction - Diameter of lesions - Overall improvement / efficacy assessed by investigator and by patient - Routine Safety – Laboratory at baseline, week 4 and 8 (creatinine, blood-electrolytes, renal and hepatic values) - AE at each visit - Local skin reactions at each visit - Overall tolerability as rated by investigator and by patient	
Research	- Mode of Action to HPV - HPV-DNA detection, virus load, expression of mRNA, integration analysis of HPV - Expression profiling of tumor suppressor genes	

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Summary – Conclusions:

Overall mean age was 55 years, mean height was 171.6 cm and mean weight was 72.7 kg.

95.0 % of patients (n=38/40) were renal transplanted, one patient (2.5%) was a lung transplant recipient and another patient was both, lung and kidney transplanted. The mean duration since last transplantation was 14.3 ± 6.9 years.

The differences between the treatment groups were marginal and not clinically relevant.

More male than female subjects were included into this study: overall 31 (77.5%) men and 9 (22.5%) women entered the study.

Efficacy results:

The number of lesions was significantly reduced in both groups over the 8 weeks treatment period (verum: 7.0 at visit 1 to 3.8 at visit 4 / placebo: 6.8 at visit 1 to 4.4 at visit 4 / $p<0.0001$). The difference between verum and placebo was not statistically significant ($p=0.3873$).

The percentage of patients showing a reduction of lesions from baseline at visit 4 was for verum: 76.7% and for placebo: 70.0%.

The diameter of lesions from visit 1 to visit 4 was reduced in the verum group by 49.8% and in the placebo group by 39.3%. The difference between verum and placebo was not statistically significant.

A complete healing/ total clearance rate from visit 1 to visit 4 was found for verum of 16.7% and for placebo of 10.0%.

Overall efficacy was stated by the investigators as “clearance” in 6 of 30 patients treated with Verrumal® Solution (20.0 %) and for one patient (n=1/10, 10.0 %) receiving placebo. Lesion improvement (clearance / markedly improved / slightly improved) was seen in 90.0 % and 70.0 % of the verum-treated and placebo-treated patients, respectively. Overall assessment of efficacy by investigator and by patient was both in favour of Verrumal® Solution, but no statistical significance was found.

In summary the primary efficacy analysis of the treatment with Verrumal® Solution versus placebo could not show a significant difference. In terms of number, diameter and complete healing of lesions the treatment with Verrumal® Solution has a significant efficacy, however, verum was not superior to placebo. The overall efficacy assessment as rated by investigator and patient was more positive for patients treated with Verrumal® Solution, but the

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difference to placebo was not statistically significant, either.

There was positive significant correlation between age of lesion and treatment response as well as a weak negative significant correlation between the presence of hyperkeratotic lesions and response to treatment, but no relationship between patient's gender and the response to treatment (spearman rho = 0.19, p = 0.0.0011; rho = -0.11, p = 0.0720).

Safety results:

Verrumal® Solution has a good tolerability in the treatment of persistent warts in immuno-suppressed patients.

For almost all patients of the active treatment group (93.3 %, n=28/30) and all patients of the control group (100 %, n=10/10) investigators stated "good" or "excellent" tolerability ratings.

All patients (96.7 %, n=29/30) treated with Verrumal® Solution showed local skin reactions under treatment, whereas 70.0 % (n=7/10) of patients treated with a placebo had skin reactions.

Conclusion:

The ANOVA analysis showed a highly significant effect of time for the reduction in number of lesions and diameter of lesions ($p < 0.0001$; $p < 0.0001$), but no significant difference for verum versus placebo was found for both parameters ($p = 0.3873$; $p = 0.2024$).

Both treatments showed good efficacy in the treatment of verrucae vulgaris. Although Verrumal® Solution always demonstrated better results no statistical significance versus placebo was found.

Verrumal® Solution proved to be very safe in the treatment of persistent warts in immunosuppressed patients.

Further studies are needed with a higher number of patients to reveal statistically significant results.