2 STUDY SYNOPSIS

Name of Sponsor: Almirall Hermal GmbH	Individual Study Table Referring to Dossier Part	(For National Authority Use Only)
Name of Finished Product: Verrumal®	Volume:	
Name of Active Ingredient: 5-Fluorouracil 0.5% and salicylic acid 10.0%	Report:	

Title of the study:	Study on the efficacy of Verrumal® compared to placebo and Solaraze® in the treatment of actinic keratosis (AK) grade I to II
Coordinating Investigator:	[redacted] Skin Tumour Centre [redacted] [redacted] Berlin, Germany
Study center(s):	38 study centers in Germany.
Publications (references):	None to date
Period of study:	June 05, 2008 to June 09, 2009
Clinical phase:	III
Objectives:	**Primary objective:** The primary objective was to show superiority to placebo and non-inferiority to the comparator Solaraze®, measured by the histological clearance of one pre-defined representative AK lesion 8 weeks post-treatment. **Secondary objectives:** Secondary objectives were the improvement of treated lesions evaluated by standard clinical score (baseline scoring, lesion response), the assessment of tolerability and safety evaluated by physician's global assessment score and the patient's assessment of tolerability and efficacy and patient's compliance.
Methodology (design of study):	This was a randomized, placebo-controlled, double-blind, three-armed, parallel-group, multi-center trial of drug development phase III. Subjects either received Verrumal® or the comparator Solaraze® or placebo in a ratio of 2:2:1. Each subject received treatment with Verrumal®, placebo or Solaraze® for maximally 12 weeks or until the lesions had completely cleared. During the 12-week treatment period, subjects returned to the centers on Days 14, 28, 42, 70 and 84 (end of treatment (EOT)). In addition, they returned on Day 140 (8 weeks after their EOT visit) for final evaluation of safety and efficacy parameters. For long-term follow-up further visits were scheduled 6 and 12 months after the end of treatment; the results of these visits are not included in this report.
Number of subjects:	Approximately 470 subjects (188 subjects receiving Verrumal®, 188 subjects receiving the comparator Solaraze® and 94 subjects receiving placebo with a ratio of 2:2:1) were planned to be included in this study. Four hundred seventy (470) subjects were actually randomized and received treatment with study medication (187 subjects received Verrumal®, 185 subjects received Solaraze® and 98 subjects received placebo). Overall 92.6% of the subjects (92.5% in the Verrumal® group, 91.4% in the Solaraze® group and 94.9% in the placebo group) completed the study as planned. Thirty-five subjects (7.4%) dropped-out prematurely, 14 subjects (7.4%) in the Verrumal® group, 16 subjects

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	(8.7%) in the Solaraze® group and five subjects (5.1%) in the placebo group. All randomized subjects received treatment with study medication and were thus valid for the safety analysis. Overall 14 subjects were excluded from the full analysis set (FAS; 10 subjects in the Verrumal® group and two subjects each in the Solaraze® and placebo group), all because treatment with study medication was equal or less than 12 days. Further 37 subjects were excluded from the per-protocol set (PPS). **Study Populations**

		Treatment group			Overall
		Verrumal®	**Solaraze®**	**Placebo**	
Subjects treated	N	187	185	98	470
Safety set	N (%)	187 (100%)	185 (100%)	98 (100%)	470 (100%)
Full analysis set	N (%)	177 (94.7%)	183 (98.9%)	96 (98.0%)	456 (97.0%)
Per protocol set	N (%)	168 (89.8%)	163 (88.1%)	88 (89.8%)	419 (89.1%)

Diagnosis and main criteria for inclusion:	Female or male subjects aged between 18 and 85 years inclusive and suffering from 4 to 10 AK lesions grade I and II (according to Olsen 1991) in their face and forehead or on their bald scalp. The summarized test area of all single AK lesions was not to cover a total area of more than 25 cm^2 (including a 5 mm to treat surrounding area).
Test product, dose and mode of administration, batch number:	**Test drug:** Verrumal® solution (active ingredients: fluorouracil 0.5% and salicylic acid 10.0% (m/m)), batch number: 809K41 Verrumal® solution was topically applied once daily to the AK lesions. Generally 0.5 g solution covered an overall area up to 25 cm^2. If severe side-effects occurred, the frequency of Verrumal® application could be reduced to three times per week. Throughout the dosing period, subjects were not to miss application on more than one day per week, i.e. one dose of Verrumal®.
Duration of treatment:	Study treatments were applied daily for up to 12 weeks or until the lesions had completely cleared or ulceration of the treated area occurred.
Reference therapy, dose and mode of administration, batch number:	**Placebo:** solution without active ingredients, in color, appearance and consistency not distinguishable from Verrumal®, batch numbers: 811K01 (all subjects on placebo with random numbers < 300), 811K02 (all subjects on placebo with random numbers > 600) **Comparator:** Solaraze® 3% gel (active ingredients: diclofenac sodium 3% (m/m)), batch number: 809K24 Placebo solution were topically applied once daily to the AK lesions. Generally 0.5 g solution covered an overall area up to 25 cm^2. Solaraze® 3 % gel was topically applied twice daily (mornings and evenings) to the AK lesions. Generally 0.5 g gel (pea-sized amount of gel) covered an overall area up to 25 cm^2. If severe side-effects occurred, the frequency of application could be reduced to three times per week (placebo) or to once daily application (Solaraze®). Throughout the dosing period, subject were not to miss application on more than one day per week, i.e. one dose of placebo or two doses of the Solaraze®.

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Criteria of evaluation:	**Efficacy** Primary target variable: Histological status of one predefined target lesion; the histological status 8 weeks post-treatment was categorized as ”cleared” or “not cleared”. Secondary target variables: • The total lesion count at each visit; • The total AK lesion size at each visit; • The lesion response at each visit; • Physician’s global assessment score (PGA); • Physician’s global tolerability score (PGT); • Subject’s overall assessment of efficacy; • Subject’s overall assessment of tolerability. For these variables the changes from baseline for each visit (visit 3 to visit 7) were analyzed. **Safety variables** • Adverse events (AEs); • Changes in the severity scores for skin quality assessment; • Changes in laboratory values; • Changes in physical examination and vital signs.
Study endpoints:	Primary endpoints: The primary endpoints were to show superiority of Verrumal® treatment to placebo and non-inferiority to Solaraze® measured by histological clearance of one target lesion. Secondary endpoints: • Superiority to Solaraze® (for histological clearance), • Improvement of treated lesions (lesion response), • Assessment of tolerability and safety by physician's global assessment scores (PGA, PGT), • Subject’s assessment of tolerability and efficacy and subject’s compliance.
Statistical methods:	**Efficacy** Primary variable: Histological assessment of one pre-defined target lesion The number of subjects, the percentage and its 95% confidence interval within each category "cleared" or "not cleared" were displayed for each treatment group. The primary study hypotheses $H_{0,1}$: The rate of subjects with “cleared” lesions” under placebo-treatment was higher or equal compared to the rate under Verrumal® -treatment, was analyzed with the Chi-Square test at significance level of $\alpha=0.025$ for a 1-sided test. Non-inferiority of Verrumal® compared to Solaraze® was to be concluded when the 97.5% confidence interval of the rate of subjects with “cleared” lesions” under Verrumal® -treatment was larger than the rate of subjects with “cleared” lesions” under Solaraze®-treatment minus 10%. Secondary efficacy variables were exploratively compared between treatment groups.

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Frequencies of subjects for secondary target variables were compared between treatment groups by Chi-Square-tests. Lesion count was compared by Wilcoxon-Mann-Whitney- tests between treatment groups. The scales (PGA, PGT, patient's overall assessment of efficacy and tolerability) were compared between treatment groups by Cochran-Armitage test for trend. The total AK lesion size was compared by T-test between treatment groups.

Safety:

All safety variables were analyzed descriptively. No statistical tests were used.

Summary and conclusions:

The differences between the three treatment groups with regard to the baseline characteristics were marginal and not clinically relevant.

In the FAS the overall mean age was 71.8 years (between 71.6 and 72.3 years for the different treatment groups); most subjects were aged 65 years or older (86.9% to 91.7% in the different treatment groups). More male than female subjects were included into this study: overall 84.7% of the subjects were male and 15.3% were female (safety set). Within the three treatment groups the proportion of male subjects was 84.4% to 85.9%.

In total 2737 lesions were treated, 1091 and 1095 lesions in the Verrumal® and Solaraze® groups, respectively, and 551 lesions in the placebo group; 52.4% of the lesions were located on the face or forehead and 47.6% were located on the bald scalp of the head; 39.6% of the lesions were clinically diagnosed as AK I according to Olsen and 60.4% were diagnosed as AK II. The mean number of lesions per subject prior to treatment was 5.8, 5.9 and 5.6 lesions per subject in the Verrumal®, Solaraze® and placebo group, respectively, ranging from 4 to 10 lesions per subject. The mean total size of the lesions prior to treatment was 355.9 mm^2 in the Verrumal® group, 345.7 mm^2 in the Solaraze® group and 341.4 mm^2 in the placebo group, ranging from 100 mm^2 to 846 mm^2.

The mean amount of Verrumal® applied by the subjects was 16.9 g, subjects randomized to placebo applied 28.5 g and an average of 61.3 g Solaraze® was applied. Differences between the amounts of placebo and Verrumal® can be attributed to the number of subjects, who reduced the dose during the study (52.6% of the subjects in the placebo group and 64.3% in the Verrumal® group) and the time of dose reduction (18.1% of the subjects in the Verrumal® group reduced dose already within the first 3 weeks of treatment, whereas at the same time only 3.1% of the subjects in the placebo group had reduced the dose).

Efficacy:

Histological clearance

At the post-treatment assessment at 8 weeks after the end of treatment AK could no longer be detected in the biopsy in 70.1% of the subjects in the Verrumal® group, in 54.1% of the subjects in the Solaraze® group and in 42.7% of the subjects in the placebo group (FAS).

Biopsy results (FAS)

		Treatment group			Overall
		Placebo N=96	**Solaraze® N=183**	**Verrumal® N=177**	**N=456**
No AK	n (%)	41 (42.7%)	99 (54.1%)	124 (70.1%)	264 (57.9%)
AK still present	n (%)	51 (53.1%)	75 (41.0%)	50 (28.2%)	176 (38.6%)
Missing	n (%)	4 (4.2%)	9 (4.9%)	3 (1.7%)	16 (3.5%)

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Statistical analysis revealed that

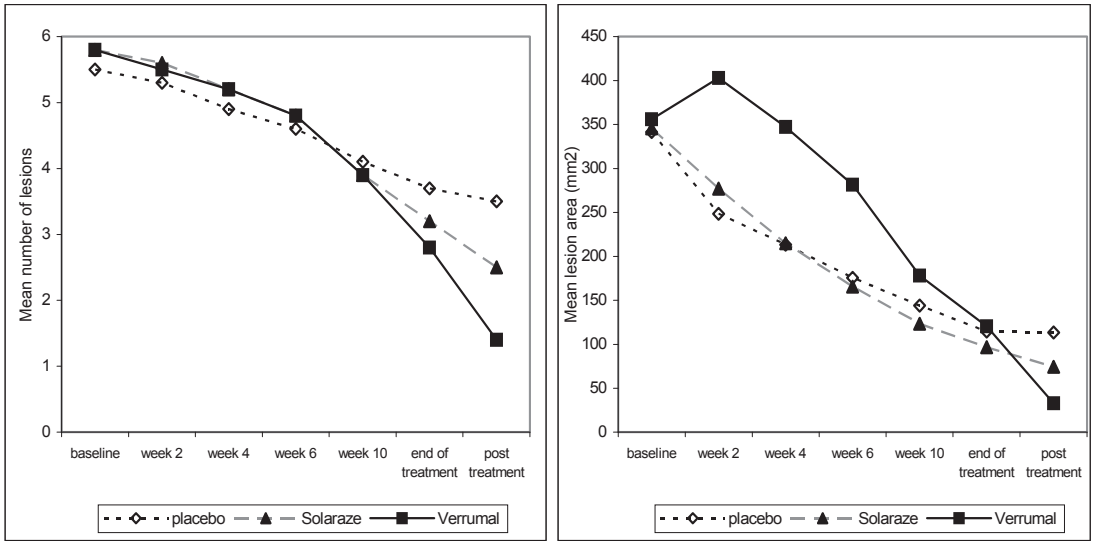
- Verrumal® treatment was superior to placebo treatment (p=0.000019, FAS).
- Treatment with Verrumal® was non-inferior to Solaraze® treatment (p=0.000006, PPS).
- The 97.5% confidence interval for the difference was (-0.242883, -0.011805) indicating, that the difference between the two treatments was statistically significant, i.e. that Verrumal® was superior to Solaraze® (p=0.009182).

Number of lesion and lesion area

Starting from similar baseline data the mean number of lesions per subject reduced to 2.8 lesions in the Verrumal® group compared to 3.7 lesions in the placebo group and 3.2 lesions in the Solaraze® group until the end of treatment (change from baseline: $p < 0.025$ for Verrumal® and Solaraze® compared to placebo). A further decrease to 1.4 lesions in the Verrumal® group compared 3.5 lesions in the placebo group and 2.5 lesions in the Solaraze® group was observed until the post-treatment assessment.

A transient increase in the mean lesion area was observed in week 2 of Verrumal® treatment, which was not observed in the other two treatment groups. Changes from baseline in the mean lesion area until the end of treatment were similar for all three treatment groups. Until the post-treatment visit the mean lesion area decreased remarkably in the Verrumal® group (to 32.7 mm^2), whereas it remained constant in the placebo group (113.5 mm^2) and only slightly decreased in the Solaraze® group (to 74.4 mm^2).

Mean number of lesions per subject and mean total lesion area (FAS)



Lesion response

At the post-treatment visit 74.5% of the lesions were cleared in the Verrumal® group compared to 54.6% in the Solaraze® group and 36.5% in the placebo group. The number of subjects with complete response (all lesions cleared) was again highest in the Verrumal® group (55.4%, $p < 0.001$ for Verrumal® versus both placebo and Solaraze®) compared to 32.0% in the Solaraze® group ($p = 0.0013$ compared to placebo) and 15.1% in the placebo group.

PGA and PGT

By the end of treatment the physicians rated the global outcome as very good or good in 82.3% of

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the subjects in the Verrumal® group (144 subjects), in 65.6% of subjects in the placebo group (61 subjects) and in 74.3% of subjects in the Solaraze® group (130 subjects). A further increase in the number of subjects with very good or good outcome was seen until the post-treatment visit in the Verrumal® group (92.0%, 161 subjects), whereas it remained constant in the Solaraze® group (73.8%, 129 subjects) and decreased in the placebo group (54.9%, 51 subjects, $p < 0.001$ for the comparison of Verrumal® to both other treatments).

Global tolerability was better in the placebo and Solaraze® group compared to the Verrumal® group at week 6 (very good or good tolerability in 89.2% (157 subjects) and 84.1% (79 subjects) of subjects in the Solaraze® and placebo group, respectively, and 68.2% (120 subjects) in the Verrumal® group). Similar tolerability was seen at the end of treatment. Until the post-treatment assessments global tolerability improved in the Verrumal®, but global tolerability was still better in the Solaraze® and placebo group (77.2% (135 subjects) of subjects with good or very good tolerability compared to 87.5% (153 subjects) and 86.0% (80 subjects) in the Solaraze® and placebo group, respectively).

Subject's overall assessment of efficacy and tolerability

Subject's overall assessment of clinical improvement showed no clinically relevant difference between treatments until the end of treatment. At the post-treatment visit clearly more subjects in the Verrumal® group (93.2%) rated the clinical improvement as very good or good compared to the Solaraze® group (81.6%) and the placebo group (66.7%, $p < 0.0001$ for difference between the Verrumal® group and the other two treatment groups).

Subject's overall assessment of tolerability showed a clearly better tolerability of Solaraze® compared to Verrumal®. Especially at 6 weeks after start of treatment inflammation and burning were reported by a high number of subjects in the Verrumal® group (70.3% and 81.3%, respectively, compared to 28.9% and 25.0%, respectively, in the Solaraze® and 22.3% and 57.4%,respectively, in the placebo group). At the end of treatment the number of subjects reporting inflammation decreased in all three treatment groups (50.9%, 21.7% and 22.6% of subjects in the Verrumal®, Solaraze® and placebo group, respectively), whereas burning was still reported by 62.2% of the subjects in the Verrumal® group (compared to 16.6% and 38.7% of the subjects in the Solaraze® and placebo group, respectively). At the post-treatment visit most subjects were free of inflammation and burning. Itching was reported in all three treatment groups by a similar percentage of subjects.

A better skin feeling was rated by the subjects for the Solaraze® treatment compared to placebo and Verrumal®. Most subjects rated the product appearance as very good or good, however, the percentage of subjects was highest in the Solaraze® group compared to the Verrumal® and placebo groups. For most subjects study treatment was easy to apply, however, again the percentage of subjects rating the application as very good or good was highest in the Solaraze® group.

Plasma concentrations of 5-FU and salicylic acid

Plasma concentrations of 5-FU and salicylic acid were determined in the 30 subjects of center 1. No concentrations of 5-FU above the lower limit of quantification (0.05 µg/mL) were detected. In six subjects plasma concentrations of salicylic acid were above the lower limit of quantification (1.0 µg/mL): in three subjects in the Verrumal® group, in one subject in the Solaraze® group and in two subjects in the placebo group (at screening and/or at visits 3/7). All but one subject took acetyl salicylic acid (100 mg) on a regular basis.

Safety:

Overall 403 of 470 subjects (85.7%) reported 1356 AEs during the study, 83 of 98 subjects (84.7%) in the placebo group reported 240 AEs, 142 of 185 subjects (76.8%) in the Solaraze® group reported 431 AEs and 178 of 187 (95.2%) in the Verrumal® group reported 685 AEs.

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Most AEs were of mild to moderate intensity; AEs of severe intensity were experienced by 6 subjects (6.1%, 10 AEs) in the placebo groups and by 27 (14.6%, 56 AEs) and 54 (28.9%, 102 AEs) of subjects in the Solaraze® and Verrumal® group, respectively.

Most AEs were general disorders and administration site conditions, experienced by 74 subjects (75.5%, 176 AEs) in the placebo group, 118 subjects (63.8%, 308 AEs) in the Solaraze® group and 174 (93.0%, 586 AEs) in the Verrumal® group, which were mostly considered as drug related by the investigator. Thus, drug related AEs were reported by 74 subjects (75.5%, 179 AEs) in the placebo group, 118 subjects (63.8%, 327 AEs) in the Solaraze® group and 172 (92.0%, 605 AEs) in the Verrumal® group.

Application site irritation and application site inflammation were the most common administration site disorders, experienced by more subjects in the Verrumal® group (86.1% and 73.3%, respectively) compared to the Solaraze® group (38.4% of the subjects for both events) and the placebo group (61.2% and 35.7%, respectively). Application site pruritus was experienced by a similar percentage of subjects in the three treatment groups (44.9% in the Verrumal® group, 40.8% in the placebo group and 38.9% in the Solaraze® group).

Summary of TEAEs (administration site disorders) (Safety set)

Preferred term	**Placebo**		**Solaraze®**		**Verrumal®**	
	relation to study drug		**relation to study drug**		**relation to study drug**	
	not related	**related**	**not related**	**related**	**not related**	**related**
	x (y, z%)	**x (y, z%)**	**x (y, z%)**	**x (y, z%)**	**x (y, z%)**	**x (y, z%)**
Total	4 (3, 3.1%)	170 (74, 75.5%)	4 (4, 2.2%)	301 (116, 62.7%)	6 (6, 3.2%)	580 (172, 92.0%)
Application site bleeding	-	4 (3, 3.1%)	-	1 (1, 0.5%)	-	2 (2, 1.1%)
Application site dermatitis	-	-	-	-	-	1 (1, 0.5%)
Application site discharge	-	-	-	1 (1, 0.5%)	-	-
Application site eczema	-	-	-	2 (2, 1.1%)	-	1 (1, 0.5%)
Application site erosion	-	1 (1, 1.0%)	-	5 (5, 2.7%)	-	15 (13, 7.0%)
Application site erythema	-	3 (3, 3.1%)	-	18 (15, 8.1%)	1 (1, 0.5%)	23 (21, 11.2%)
Application site exfoliation	-	-	-	-	-	1 (1, 0.5%)
Application site inflammation	1 (1, 1.0%)	42 (35, 35.7%)	1 (1, 0.5%)	85 (71, 38.4%)	3 (2, 1.1%)	170 (137, 73.3%)
Application site irritation	-	68 (60, 61.2%)	-	83 (71, 38.4%)	2 (1, 0.5%)	209 (161, 86.1%)
Application site oedema	-	-	-	2 (2, 1.1%)	-	1 (1, 0.5%)
Application site pain	1 (1, 1.0%)	8 (8, 8.2%)	-	16 (15, 8.1%)	-	50 (47, 25.1%)
Application site pruritus	1 (1, 1.0%)	43 (40, 40.8%)	2 (1, 0.5%)	85 (72, 38.9%)	-	103 (84, 44.9%)
Application site scab	-	1 (1, 1.0%)	-	-	-	2 (2, 1.1%)
Application site scar	-	-	-	2 (1, 0.5%)	-	-
Application site ulcer	-	-	-	-	-	2 (1, 0.5%)
Application site vesicles	-	-	-	1 (1, 0.5%)	-	-
Inflammation	1 (1, 1.0%)	-	1 (1, 0.5%)	-	-	-

x (y, z%): x = number of AEs
y = number of subjects with particular AE
z = percentage of subjects with particular AE who received respective treatment

Most local TEAEs were of mild to moderate intensity. Overall, there were five local TEAEs of severe intensity in the placebo group, 44 local TEAEs in the Solaraze® group and 94 local TEAEs in the

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Verrumal® group. Application site irritation and inflammation of severe intensity were reported by more subjects in the Verrumal® group (40 and 29 subjects, respectively) than in the Solaraze® (11 and 12 subjects, respectively) and in the placebo groups (three and one subjects, respectively). Application site pruritus of severe intensity occurred more often in the Solaraze® group (13 subjects, compared to nine subjects in the Verrumal® and no subject in the placebo group).

Differences in the onset of local TEAEs between the treatment groups were seen for application site irritation and inflammation, which started in a higher percentage of subjects within the first 4 weeks of treatment with Verrumal® compared to the Solaraze® or placebo groups.

Seven subjects in the Verrumal® group, nine subjects in the Solaraze® group and one subject in the placebo group stopped treatment due to local TEAEs.

Overall 15 subjects experienced a SAE, four subjects (4.1%) in the placebo group (in two subjects before start of treatment), nine subjects (4.9%) in the Solaraze® group and two subjects (1.1%) in the Verrumal® group. None of the SAEs was considered to be related to the study medication. Three subjects died during the study, all three belonged to the Solaraze® group. The most frequently reported SAEs were neoplasms, followed by cardiac disorders, gastrointestinal disorders and nervous disorders.

Cosmetic outcome was at least satisfactory in about 80% of the subjects. At the post-treatment visit 44.9% of the subjects in the Verrumal® group had a very good or good cosmetic outcome compared to 42.7% and 38.7% in the Solaraze® and placebo group, respectively.

Laboratory data and vital signs measurements showed no clinically relevant treatment-related differences.

Conclusion

- Topical treatment with Verrumal® was highly effective. Verrumal® treatment showed superiority to placebo treatment and non-inferiority to the Solaraze® treatment, when measuring the histological clearance of one pre-defined representative AK lesion 8 weeks post-treatment.
- Verrumal® treatment was even superior to Solaraze® treatment.
- Secondary efficacy endpoints, like total lesion count, total AK lesion size, lesion response, PGA and subject's overall assessment of efficacy confirmed the results of the primary endpoint. For all these endpoints treatment with Verrumal® proved to be better than treatment with placebo and Solaraze® at 8 weeks post-treatment.
- Overall assessments of tolerability showed that Verrumal® was well tolerated although tolerability was lower than for Solaraze® or placebo. Subject's assessment revealed a high incidence of burning and inflammation after Verrumal® treatment
- Application site disorders were the main adverse events occurring more frequently after Verrumal® treatment compared to the Solaraze® or placebo treatment; however they were mainly of mild to moderate intensity and were accepted by the subjects.