2 STUDY SYNOPSIS

Name of Sponsor: Almirall Hermal GmbH **Name of Finished Product**: **Name of Active Ingredient**: LAS 41005	Individual Study Table Referring to Dossier Part Volume: Report:	(For National Authority Use Only)
Title of the study:	A prospective comparator controlled randomized exploratory study on the efficacy of LAS 41005 compared to cryotherapy in subjects with hyperkeratotic actinic keratosis	
Coordinating Investigator:	[redacted] Klinik für Dermatologie, Venerologie und Allergologie des Universitätsklinikum [redacted] [redacted] Germany	
Study center(s):	4 study centers in Germany.	
Publications (references):	None to date	
Period of study:	April 13, 2011 to August 20, 2012	
Clinical phase:	II	
Objectives:	The aim was to evaluate the efficacy and safety of LAS 41005 compared to cryotherapy in subjects with moderate to severe hyperkeratotic actinic keratosis (AK, confirmed by punch biopsies).	
Methodology (design of study):	This was an exploratory, open, randomized, prospective, two-armed phase II study, observer blinded. Subjects either received LAS 41005 or cryotherapy in a ratio of 1:1. Subject randomized to LAS 41005 received LAS 41005 for 6 weeks. Subjects randomized to cryotherapy received one treatment with cryotherapy on the first study day. Subjects could receive a second treatment, if necessary, 3 weeks after the first cryotherapy. Visit schedule for both treatment groups: Visit 1 – Screening visit Visit 2 – Day 1 - Baseline Visit 3 – Day 21 Visit 4 – Day 42 – End of treatment (EOT) Visit 5 – Day 98 – Post treatment visit (PT) Visit 6 – Follow-up visit after 6 months after EOT	
Number of subjects:	Sixty (60) subjects were planned to complete the study (30 subjects receiving LAS 41005, 30 subjects receiving cryotherapy). Considering a drop-out rate of 15%, 69 subjects were planned to be included. Sixty-seven (67) male and female subjects entered the study. One subject withdrew the consent prior to start of treatment; all other randomized subjects received treatment with study medication and were valid for the safety analysis. They all provided post-dose efficacy data and were therefore included in the full analysis set (FAS). Overall 9 subjects were excluded from the per protocol set (PPS) because they had no biopsy results at the post-treatment visit and/or stopped or interrupted treatment.	

Name of Sponsor: Almirall Hermal GmbH	Individual Study Table Referring to Dossier Part	(For National Authority Use Only)
Name of Finished Product:	Volume:	
Name of Active Ingredient: LAS 41005	Report:	

	Study populations Percentages based on number of subjects randomized in the respective group All 33 subjects in the LAS 41005 and 31 subjects in the cryotherapy group provided 6-month follow-up data.
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 II and III (according to Olsen et al. 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:** LAS 41005 (active ingredients: 5-fluorouracil 0.5%, salicylic acid 10%), batch number: CHB035K272 LAS 41005 was applied to each target lesion and a surrounding area of approximately 5 mm to treat surrounding sub-clinical parts of the AK lesions. In case of adverse events the number of application days per week could be reduced to 3 days
Duration of treatment:	Study treatments were applied daily for up to 6 weeks or until the lesions had completely cleared or ulceration of the treated area occurred.
Reference therapy, dose and mode of administration, batch number:	Cryotherapy (liquid nitrogen) One cryotherapy was performed on Day 1 of the trial; a further cryotherapy could be performed at 3 weeks after the first cryotherapy, if necessary.
Criteria of evaluation:	**Efficacy** <u>Primary target variable:</u> Histological status of one predefined target lesion. <u>Secondary target variables:</u> • Total lesion count at each visit; • Total AK lesion size at each visit; • Lesion response at each visit; • Physician's global assessment score (PGA); • Subject's overall assessment of efficacy; • Cosmetic outcome. **Safety variables** • Adverse events (AEs) (local skin reactions had only to be reported as AE if they were of severe intensity); • Physician's global tolerability score (PGT); • Subject's overall assessment of tolerability. • Physical examination and vital signs • Skin quality assessment

		LAS 41005 n (%)	Cryotherapy n (%)	Overall n (%)
Subjects randomized	N	34	33	67
Safety set	N (%)	33 (97.1%)	33 (100%)	66 (98.5%)
Full analysis set	N (%)	33 (97.1%)	33 (100%)	66 (98.5%)
Per protocol set	N (%)	26 (76.5%)	31 (93.9%)	57 (85.1%)

Name of Sponsor: Almirall Hermal GmbH	Individual Study Table Referring to Dossier Part Volume:	(For National Authority Use Only)
Name of Finished Product:		
Name of Active Ingredient: LAS 41005	Report:	

Study endpoints:

Primary endpoints:

Histological clearance at 8 weeks after end of treatment with LAS 41005, respectively 14 weeks after first cryotherapy.

Secondary endpoints:

- Lesion response (100% clearance, 75% clearance);
- Lesion size;
- Lesion count;
- Assessment of tolerability and safety by physician's global assessment scores (PGA, PGT);
- Subject's global assessment of efficacy and tolerability;
- Assessment of cosmetic outcome;
- Adverse Events (AEs) / Serious Adverse Events (SAEs).

Statistical methods:

Efficacy

For the primary efficacy variable, histological clearance on Day 98, the number and percentage of subjects histologically cleared and not cleared in each group was presented. Analysis was performed by deriving a two-sided 95% confidence interval (CI) of the difference in the histological clearance rate of LAS 41005 and cryotherapy treatment. In addition, a logistic regression model was developed with histological clearance as dependent variable, and treatment received and total number of lesions at baseline as independent regression variables.

Variables based on lesion count and lesion size were summarized descriptively. Odds ratios for complete and partial clearance, derived from a logistic regression model, were provided together with a 95% CI. An analysis of co-variance (ANCOVA) was performed with treatment as factor and total sum of AK lesions or lesion area at baseline as covariate.

All other efficacy variables were summarized using descriptive statistics.

Safety:

All safety variables were analyzed descriptively.

Summary and conclusions:

Overall mean age was 70.9 years; most subjects were aged 65 years or older (77.3%). Mean height was 174.2 cm and mean weight was 81.7 kg. The differences between the treatment groups were marginal and not clinically or statistically relevant.

More male than female subjects were included into this study: overall 58 (87.9%) men and only 8 (12.1%) women entered the study.

Efficacy:

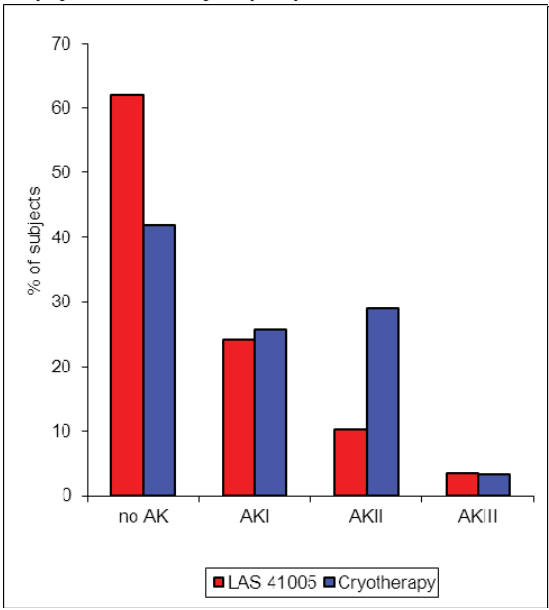
At the post-treatment assessment at 8 weeks after the end of treatment AK could no longer be detected in the biopsy in 18 subjects (62.1%) in the LAS 41005 group and in 13 subjects (41.9%) in the cryotherapy group (FAS). The difference between the 2 treatments was 20.13% with a 95% CI of [-4.64, 44.90]. The global logistic regression model was not statistically significant (p-value = 0.185). The results for PPS were similar.

The number of subjects with complete clearance at the post-treatment visit was higher in the LAS 41005 group (11 subjects [33.3%]) than in the cryotherapy group (8 subjects [25.0%], difference 8.33% with 95% CI of [-13.66, 30.33]), and further increased in the LAS 41005 group until the end of the 6-month follow-up period (15 subjects [45.5%]) compared to again 8 subjects (25.8%) in the cryotherapy group, difference 19.65% with 95% CI of [-3.28, 42.58]). A partial clearance (at least 75% reduction of the number of AK lesion) was observed in more subjects after treatment with

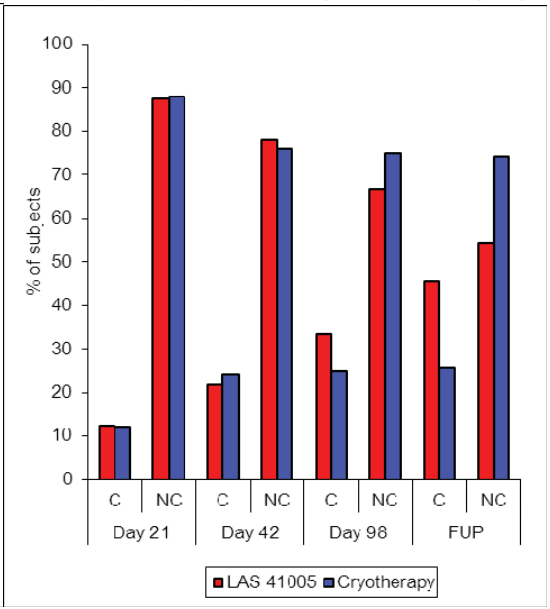
Name of Sponsor:	Individual Study Table	(For National Authority Use Only)
Almirall Hermal GmbH	Referring to Dossier Part	
Name of Finished Product:	Volume:	
Name of Active Ingredient: LAS 41005	Report:	

cryotherapy (20 subjects, 62.5%) compared to 17 subjects (51.5%) after LAS 41005 treatment on Day 98 (difference -11.0% with 95% CI of [-34.90, 12.93]), however, at the end of the follow-up period the number of subjects with partial clearance was higher in the LAS 41005 group (23 subjects [69.7%] compared to the cryotherapy group (17 subjects [54.8%], difference 14.86% with 95% CI of [-8.65, 38.37]).

Biopsy results on Day 98 (FAS)

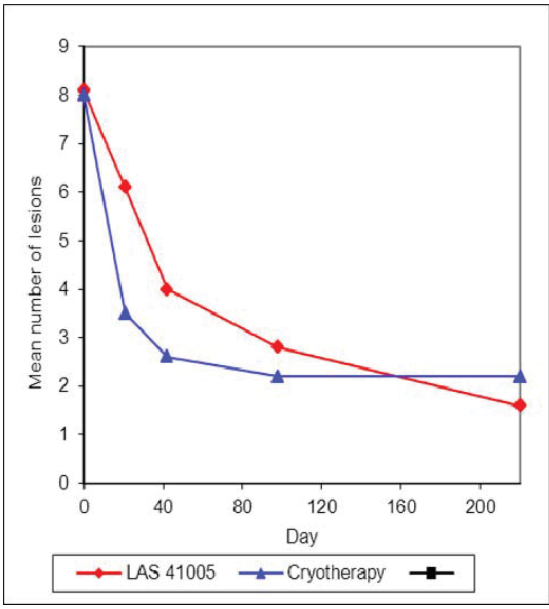


Percentage of subjects with complete clearance (FAS)

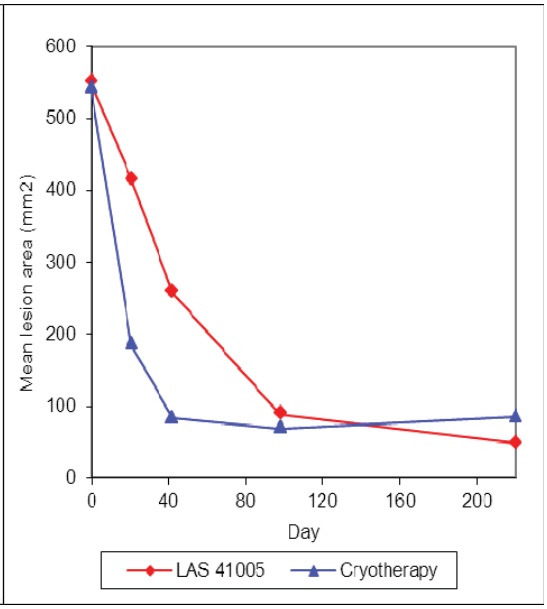


C = complete clearance, NC = not cleared

Mean number of lesions



Mean lesion area



6-month follow-up are displayed as Day 220

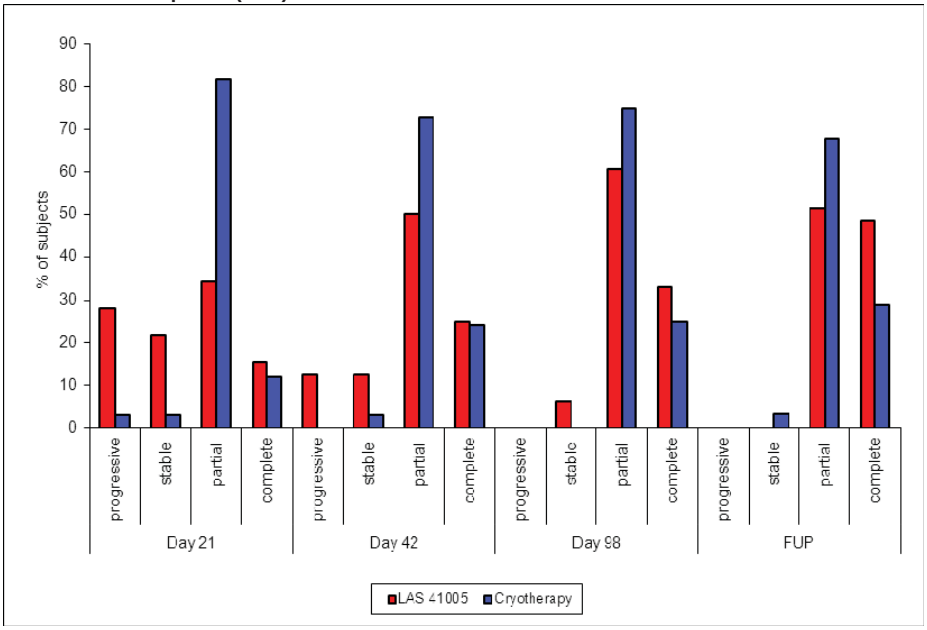
Name of Sponsor: Almirall Hermal GmbH	Individual Study Table Referring to Dossier Part	(For National Authority Use Only)
Name of Finished Product:	Volume:	
Name of Active Ingredient: LAS 41005	Report:	

Starting from similar baseline data (mean number of lesions per subject of 8.1 in the LAS 412005 group and of 8.0 in the cryotherapy group) the mean number of lesions per subject decreased by 4.0 (LAS 41005) and 5.4 lesions (cryotherapy) until the end of the treatment period (Day 42). At the post-treatment visit (Day 98) the mean number of lesions per subject decreased by 5.2 (LAS 41005) and 5.7 lesions (cryotherapy group) compared to baseline. Until the end of the 6-month follow-up period the mean number of lesions per subject further decreased in the LAS 41005 group (by 6.4 lesions compared to baseline) and remained unchanged in the cryotherapy group (still a decrease of 5.7 lesions compared to baseline). No statistically significant differences between the treatment groups were observed (LS-mean for the difference between cryotherapy and LAS 41005 was -0.606 with 95% CI for the difference of [-1.855, 0.644] on Day 98 and 0.613 with 95% CI for the difference of [-0.449, 1.675] at follow-up).

Mean total lesion area was similar for both treatment groups at baseline (550.9 mm^2 in the LAS 41005 group and 542.4 mm^2 in the cryotherapy group). Mean lesion area decreased faster in the cryotherapy group, however, until the post-treatment visit the mean lesion area decreased by a similar extent in both treatment groups (change from baseline of -461.8 mm^2 in the LAS 41005 and of -471.6 mm^2 in the cryotherapy group). Until the end of the 6-month follow-up period mean lesion area further decreased in the LAS 41005 group (change from baseline of -502.4 mm^2) and showed no considerable changes in the cryotherapy group (change from baseline of -451.6 mm^2). The difference between the treatment groups was not statistically significant (LS-mean for the difference between cryotherapy and LAS 41005 of -18.050 mm^2 95% CI for the difference [-73.403; 37.303]). When considering only lesions clinically graded as AKII, similar results were observed.

At the post-treatment visit the overall percentage of subjects with a clinical response (partial + complete response) was 93.9% of subjects in the LAS 41005 group and 100% in the cryotherapy group. At the 6-month follow-up all subjects in the LAS 41005 showed a clinical response and all but 1 subject in the cryotherapy group (96.8%).

Overall lesion response (FAS)



By the end of treatment the percentage of subjects for whom the physicians rated the global outcome as very good or good in 66.7% of the subject in the LAS 41005 group (22 subjects) and in

Name of Sponsor: Almirall Hermal GmbH	Individual Study Table Referring to Dossier Part	(For National Authority Use Only)
Name of Finished Product:	Volume:	
Name of Active Ingredient: LAS 41005	Report:	

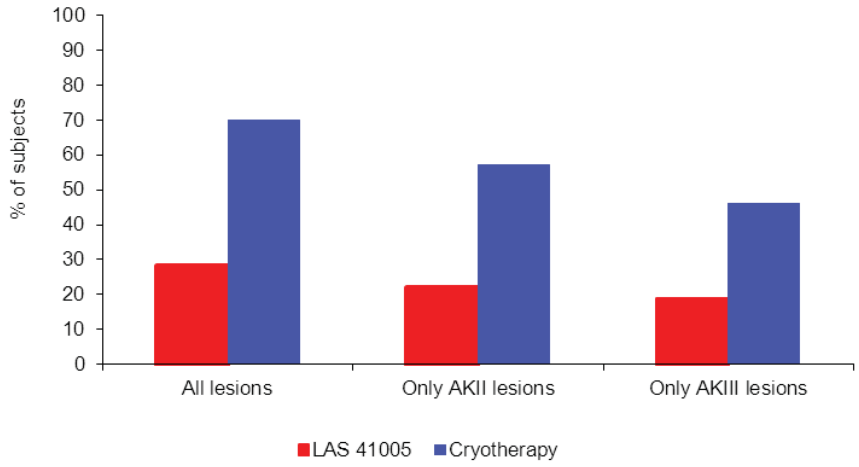
81.8% of subjects in the cryotherapy group (27 subjects). A further increase in the number of subjects with very good or good outcome was seen in the LAS 41005 group (84.9%, 28 subjects), whereas it remained constant in the cryotherapy group (84.4%, 27 subjects). At the 6-month follow-up similar results were seen (84.9%, 28 subjects in the LAS 41005 group and 83.9%, 26 subjects in the cryotherapy group with very good or good outcome).

At the end of the treatment period 69.7% of subjects in the LAS 41005 group (23 subjects) and 81.8% of subjects in the cryotherapy group (27 subjects) rated the clinical improvement as very good or good. A further increase in the number of subjects rating the clinical improvement as very or good was observed in the LAS 41005 group until the post-treatment visit (81.8%, 27 subjects), whereas no further increase was observed in the cryotherapy group (78.2%, 25 subjects).

Until Day 98 the number of subjects with very good or good cosmetic outcome was slightly higher in the LAS 41005 group (28 subjects [84.9%] when judged by the investigator and by the subject) compared to the cryotherapy group (24 subjects [75.0%] when judged by the investigator and 26 subjects [81.3%] when judged by the subject). At the end of the 6-month follow-up the number of subjects with very good or good cosmetic outcome remained similar: 27 subjects (81.8%) when assessed by the investigator and 29 subjects (87.8%) when assessed by the subject in the LAS 41005 group and 22 subjects (70.9%) and 25 subjects (80.7%), respectively, in the cryotherapy group.

Until the end of the 6-month follow-up period the number of subjects with recurrences was lower in the LAS 41005 group compared to the cryotherapy group: 13 of 172 cleared lesions in 9 subjects (27.3%) in LAS 41005 group and 38 of 178 in 21 subjects (67.7%) in the cryotherapy group were recurrent). The difference between the 2 treatments was -41.88% with a 95% CI of [-64.49, -19.26].

Recurrences during the follow-up



Regarding only the subjects with complete clearance on Day 98, again the number of recurrences was lower in the LAS 41005 group (3 of 11 subjects in the LAS 41005 group (27.3%) showed 3 of 90 recurrent lesions and 4 of 8 subjects in the cyrotherapy group (50.0%) showed 9 of 65 recurrent lesions at the 6-month follow-up).

Name of Sponsor: Almirall Hermal GmbH	Individual Study Table Referring to Dossier Part	(For National Authority Use Only)
Name of Finished Product:	Volume:	
Name of Active Ingredient: LAS 41005	Report:	

Safety:

Overall 21 of 66 subjects (31.8%) experienced 35 TEAEs during the study, 13 subjects (39.4%) in the LAS 41005 group reported 23 TEAEs and 8 subjects (24.2%) in the cryotherapy group reported 12 TEAEs.

Eight subjects (24.2%, 13 TEAEs) treated with LAS 41005 and by 2 subjects (6.1%, 2 TEAEs) treated with cryotherapy reported TEAEs considered drug-related by the investigator.

Most TEAEs were of mild to moderate intensity. Severe TEAEs were reported for 6 subjects (18.2%, 10 events) treated with LAS 41005 and for 1 subject (3.0%, 1 event) treated with cryotherapy. TEAEs of severe intensity were mainly application site disorders.

The most frequently reported TEAEs were administration site disorder (8 TEAEs experienced by 7 subjects [21.2%] after treatment with LAS 41005 and 1 TEAE experienced by 1 subject [3.0%] in the cryotherapy group) and skin and subcutaneous tissue disorders (5 TEAEs in 4 subjects [12.1%] in the LAS 41005 group and 4 TEAEs in 4 subjects [12.1%] in the cryotherapy group) (please note that only in case the investigator considered a local skin reaction severe, this had to be recorded as an AE).

Summary of TEAEs considered drug-related* by the investigator (Safety set)

SOC	Preferred term	LAS 41005 N=33 x / y (z%)	Cryotherapy N=33 x / y (z%)
Total		13 / 8 (24.2%)	2 / 2 (6.1%)
General disorders and administration site conditions	At least one	7 / 6 (18.2%)	-
	Application site discoloration	1 / 1 (3.0%)	-
	Application site erythema	2 / 2 (6.1%)	-
	Application site inflammation	1 / 1 (3.0%)	-
	Application site pain	1 / 1 (3.0%)	-
	Inflammation	1 / 1 (3.0%)	-
	Pain	1 / 1 (3.0%)	-
Nervous system disorders	At least one	3 / 3 (9.1%)	-
	Burning sensation	3 / 3 (9.1%)	-
Skin and subcutaneous tissue disorders	At least one	3 / 3 (9.1%)	2 / 2 (6.1%)
	Blister		1 / 1 (3.0%)
	Erythema	1 / 1 (3.0%)	-
	Pruritus	1 / 1 (3.0%)	-
	Scab	1 / 1 (3.0%)	1 / 1 (3.0%)

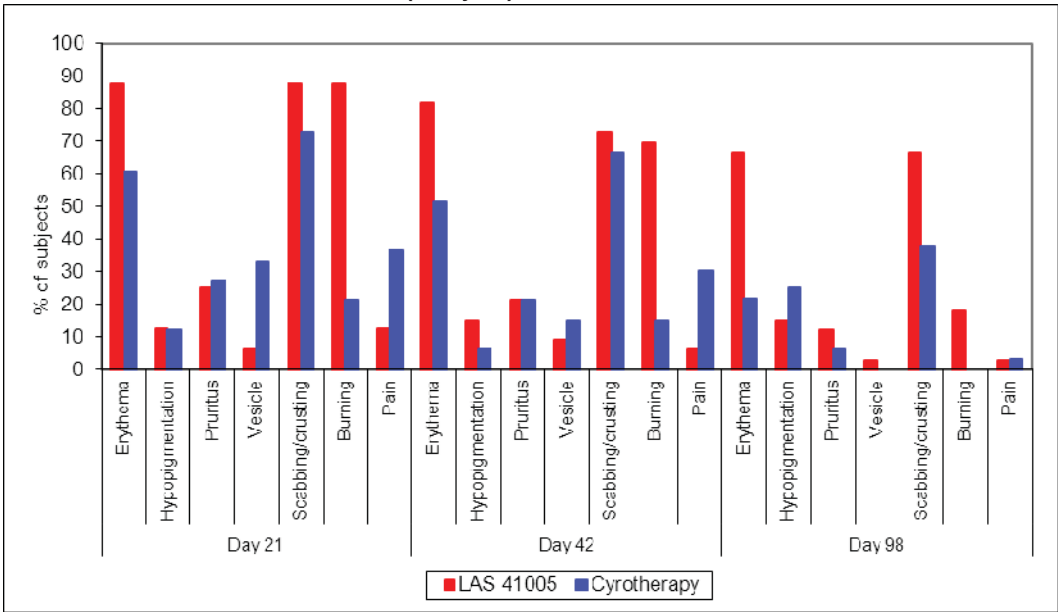
x / y (z%): x = number of AEs
y = number of subjects with particular AE
z = percentage of subjects with particular AE who received respective treatment

* relationship probable or possible

The most common local skin reactions were erythema, scabbing/crusting and burning, mainly of mild to moderate intensity. Erythema occurred more often after treatment with LAS 41005 than after cryotherapy and was observed for a longer duration in subjects treated with LAS 41005. The incidence of scabbing/crusting was similar for both treatment groups. Burning was mainly observed during the treatment with LAS 41005 and disappeared until Day 98 in most subjects. During the 6-month follow-up the number of subjects with local skin reaction was similar in both treatment groups except for a still slightly higher incidence of erythema in the LAS 41005 group and a slightly higher incidence of hypopigmentation in the cryotherapy group.

Name of Sponsor: Almirall Hermal GmbH	Individual Study Table Referring to Dossier Part	(For National Authority Use Only)
Name of Finished Product:	Volume:	
Name of Active Ingredient: LAS 41005	Report:	

Incidence of the main local skin reactions (Safety set)



Only skin reactions which occurred in ≥25% of the subjects in any treatment group on any day

Three subjects stopped treatment with LAS 41005 prematurely and further 2 subjects interrupted dosing.

One subject in the LAS 41005 group experienced an SAE which was considered unlikely related to study treatment.

The proportion of subjects for whom the physicians rated the global tolerability as very good or good was higher in the cryotherapy group compared to the LAS 41005 group; however the difference between the groups was small on Day 98 (81.9% of subjects in the LAS 41005 group and 90.7% in the cryotherapy group. At the 6-month follow-up visit the tolerability was similar in both treatment groups (very good or good tolerability in for 87.9% of subjects in LAS 41005 group and of 90.3% in the cryotherapy group).

The subject's assessment gave similar results. Generally more subjects in the cryotherapy group judged the overall tolerability as very good or good than in the LAS 41005 group. On Day 98, 72.7% of subjects in the LAS 41005 group and 90.6% of subjects in the cryotherapy group judged to tolerability as very good or good.

Overall, skin quality improved in both treatment groups; a mild advantage was observed for LAS 41005 with respect to skin surface, hyperpigmentation and hypopigmentation.

Conclusion

- T
he proportion of subjects with histological clearance of one pre-defined representative AK lesion 8 weeks post-treatment was higher after LAS 41005 treatment (62.1%) than after cryotherapy (41.9%, difference of 20.13% with a 95% CI of [-4.64, 44.90].
- T
he proportion of subjects with complete clearance at the post-treatment visit was again higher in the LAS 41005 group (33.3%) than in the cryotherapy group (25.0%, difference of 8.33% with 95% CI of [-13.66, 30.33]). At the end of the 6-month follow-up the proportion of subjects with complete clearance further increased in the LAS 41005 group (45.5%) and

Name of Sponsor: Almirall Hermal GmbH	Individual Study Table Referring to Dossier Part	(For National Authority Use Only)
Name of Finished Product:	Volume:	
Name of Active Ingredient: LAS 41005	Report:	

remained similar in the cryotherapy group (25.8%, difference of 19.65% with 95% CI of [-3.28, 42.58]).

- Further secondary efficacy endpoints, like total lesion count, total AK lesion size, lesion response, PGA and subject's overall assessment of efficacy supported the previous results.
- The recurrence rate of cleared lesions at the 6-month follow-up visit was clearly lower in the LAS 41005 group compared to the cryotherapy group. The difference between the 2 treatments was -41.88% with a 95% CI of [-64.49, -19.26].
- Overall assessments of tolerability showed that LAS 41005 was well tolerated although tolerability was lower than for cryotherapy. Subject's assessment revealed a high incidence of erythema and burning after LAS 41005 treatment (81.8% and 69.7% of subjects on Day 42, respectively, compared to 51.6% and 15.2% in the cryotherapy group). For scabbing/crusting the differences between the treatments until the end of treatment were lower (72.7% and 66.7%, respectively, on Day 42).
- Adverse events related to the skin were the main adverse events occurring more frequently after LAS 41005 treatment compared to the cryotherapy treatment (24.2% of subjects in the LAS 41005 group and 6.1% of the subjects in the cryotherapy group).