Exclusion criteria

Patients were excluded if they had prior treatment with IngMeb within the selected treatment area; treatment areas within 5 cm of an incompletely healed wound, a suspected basal cell carcinoma, or a suspected squamous cell carcinoma; presence of atypical lesions (hypertrophic, hyperkeratotic or cutaneous horns) within the treatment area and/or AK lesions that did respond to cryotherapy on two previous occasions; history or evidence of skin condition, or use of therapeutic or cosmetic products, that could interfere with the evaluation of the intervention.

Analysis of primary and secondary endpoints

To analyze primary and secondary endpoints, a multiple imputation technique using negative binomial regression model with treatment group, AK counts at the previous visit, and analysis sites as covariates was employed to account for the few missing counts (2%) at Week 8. Log baseline AK count was used as offset. AKCLEAR 100 and AKCLEAR 75 at Week 8 were analyzed by a Cochran-Mantel-Haenszel test, adjusting for analysis site. A log transformation was applied to the estimated relative risks in order to apply Rubin's pooling method.[1] Reduction in AK count from baseline to Week 8 was analyzed using a negative binomial regression including log baseline AK count as offset and treatment group and analysis site as factors. Observed values were also tabulated.

Reference:

1. Rubin DB. Multiple imputation for nonresponse in surveys: John Wiley & Sons, 2004.

Supplementary Table 1. Classification of neoplasms benign, malignant, and unspecified

	After central review by pathologist		
	Keratoacanthoma	**SCC**	**Unknown – no central review**
AE reported by investigator			
Keratoacanthoma	3	0	0
SCC	11	0	0
SCC *in situ*	0	1	0
Intra-epidermal carcinoma	0	0	1
Total	**14**	**1**	**1**

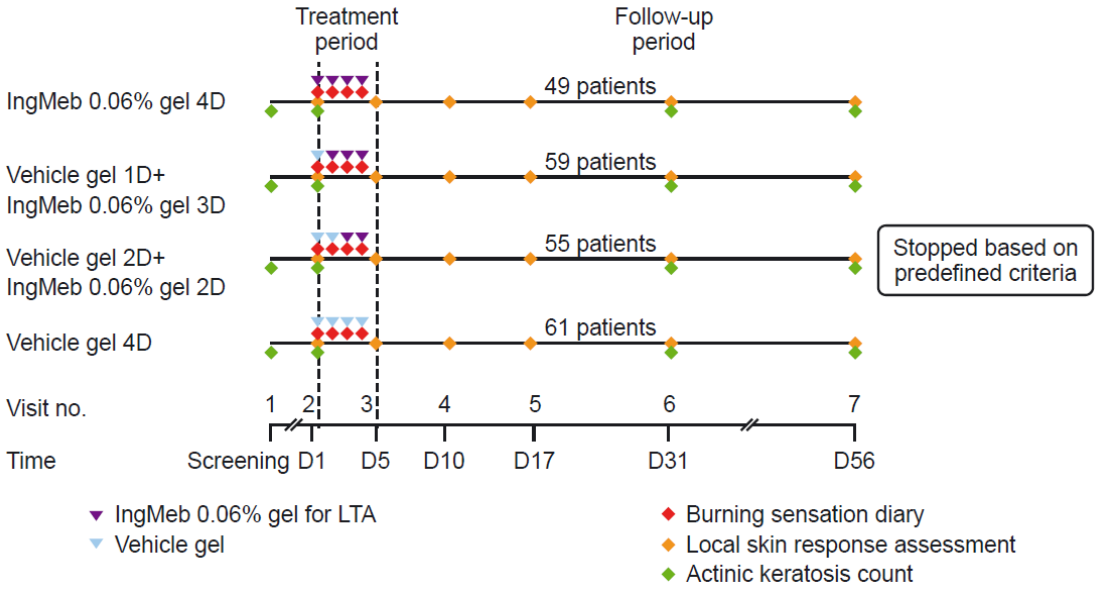
AE, adverse event; SCC, squamous cell carcinoma.

Supplementary Table 2. TSQM-derived scores at end of treatment

	IngMeb 0.06% gel			
	2D (n=55)	**3D (n=59)**	**4D (n=49)**	**Vehicle (n=61)**
Effectiveness score, mean (SD)	68.4 (21.8)	67.8 (24.4)	72.3 (21.1)	37.4 (27.7)
– Number	55	58	48	56
– Difference vs vehicle[a]	31.0	30.4	N/A	–
– (95% CI)	(21.7–40.3)	(21.2–39.6)		
– P-value	p<0.001	p<0.001		
Side effects, mean (SD)	87.3 (18.8)	88.3 (23.2)	84.9 (22.8)	99.9 (0.8)
– Number	55	58	48	58
– Difference vs vehicle[a]	-12.5	-11.5	N/A	–
– (95% CI)	(-18.9– -6.1)	(-17.8– -5.2)		
– P-value	p<0.001	p<0.001		
Global satisfaction, mean (SD)	64.9 (23.7)	68.5 (25.2)	63.5 (24.8)	36.0 (27.7)
– Number	55	58	48	57
– Difference vs vehicle[b]	29.1	32.7	N/A	–
– (95% CI)	(19.5–38.6)	(23.2–42.1)		
– P-value	p<0.001	p<0.001		
Convenience, mean (SD)	79.9 (14.8)	79.1 (17.0)	77.7 (14.1)	78.7 (15.3)
– Number	55	58	48	58
– Difference vs vehicle[a]	1.3	0.6	N/A	–
– (95% CI)	(-4.5–7.1)	(-5.1–6.3)		
– P-value	p=0.66	p=0.84		

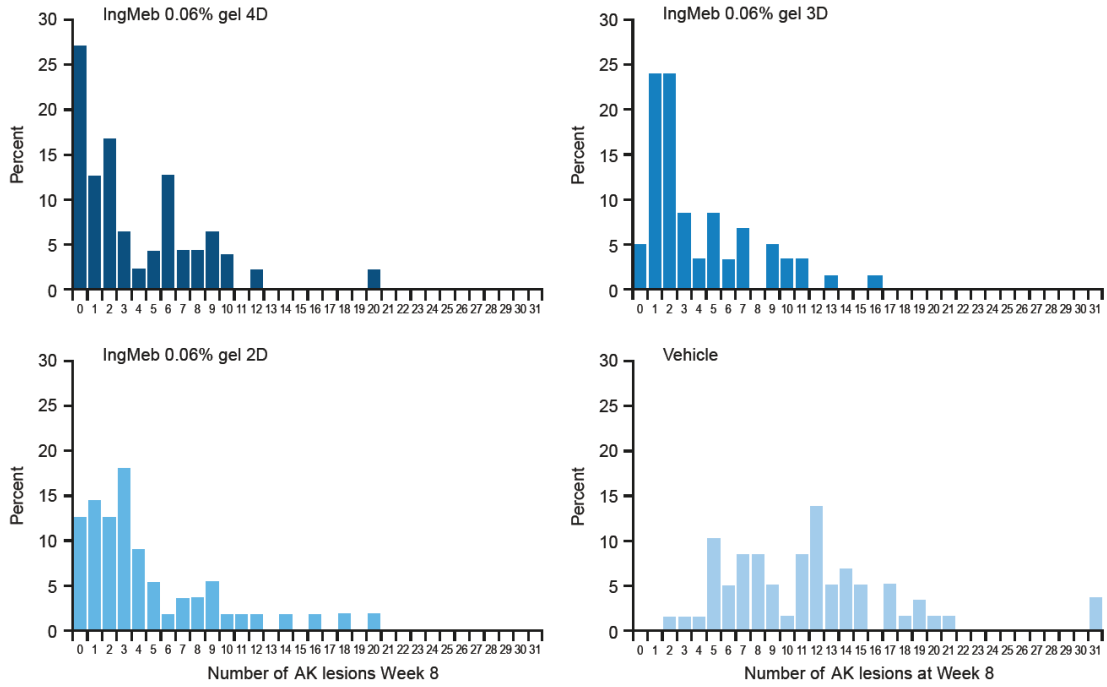
AK, actinic keratosis; CI, confidence intervals; IngMeb, ingenol mebutate; N/A, not available; SD, standard deviation; TSQM, Treatment Satisfaction Questionnaire for Medication.

[a]Least Squares Means difference: From ANOVA with factors: treatment group and analysis site.



IngMeb, ingenol mebutate; LTA, large treatment area

Supplementary Figure 1. Trial design



2D, 2-day group; 3D, 3-day group; 4D, 4-day group; AK, actinic keratosis; IngMeb, ingenol mebutate.

Supplementary Figure 2. AK count at Week 8