Efficacy and safety of ingenol mebutate gel in field treatment of actinic keratosis on full face, balding scalp or approximately 250 cm^2 on the chest: a Phase III, randomized, controlled trial

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Background

- Ingenol mebutate (IngMeb; Picato®) is indicated for the topical treatment of actinic keratosis (AK) in areas of skin up to 25 cm^2[1]
- Two or three consecutive days of treatment with IngMeb provides clinically relevant clearance of AK lesions on the face/scalp (0.015% gel) and trunk/extremities (0.05% gel) when compared with vehicle gel;[2] in addition, treatment effects of IngMeb gel are maintained long term[3]
- However, some patients may require treatment of AK over areas of skin larger than 25 cm^2

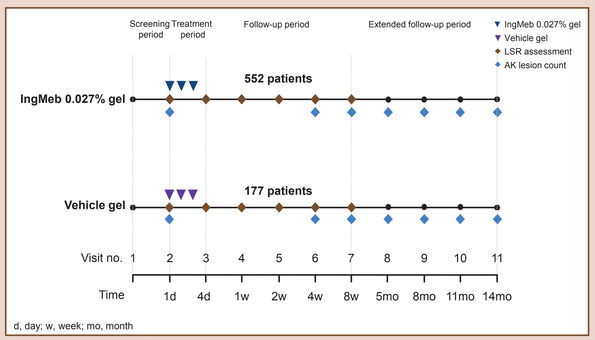
Study objective

- To compare the efficacy and safety of IngMeb 0.027% gel with vehicle gel, as a field treatment in patients with AK, when applied once daily for three consecutive days on the full face, balding scalp or ~250 cm^2 on the chest (clinical trial identifier: NCT02361216)

Methods

- Phase III, randomized, parallel-group, double-blind, vehicle-controlled, eight-week trial in patients with AK (**Figure 1**)
- Patients were eligible if they had 5–20 clinically typical, visible and discrete AK lesions within a selected treatment area of sun-damaged skin on either the full face, full balding scalp (>25 cm^2–250 cm^2) or a contiguous area of (~250 cm^2) on the chest

Figure 1. Trial design



Study endpoints

Primary

- Complete clearance (AKCLEAR 100), defined as a 100% reduction from baseline in the number of clinically visible AK lesions, at Week 8

Secondary

- Partial clearance (AKCLEAR 75), defined as ≥75% reduction from baseline in the number of clinically visible AK lesions, at Weeks 4 and 8
- Percent reduction in AK lesion count from baseline at Week 8

Safety

- Local skin responses (LSRs) and adverse events (AEs), assessed by investigators on Days 1 and 4, and Weeks 1, 2, 4, and 8, respectively

Physician- and patient-reported outcomes

- Global photo-damage outcome assessment by investigator at Week 8
- Patient Treatment Satisfaction Questionnaire for Medication (TSQM) v.1.4, and cosmetic outcome at Week 8

Results

Patient population

- In total 729 patients were randomized to receive IngMeb 0.027% gel (n=552) or vehicle gel (n=177). The median age was 67.5, most patients were male (73.4%), all were white and 95.6% of patients had Fitzpatrick skin type I–III (**Table 1**). Median AK count at baseline was 12 (range 5–56)

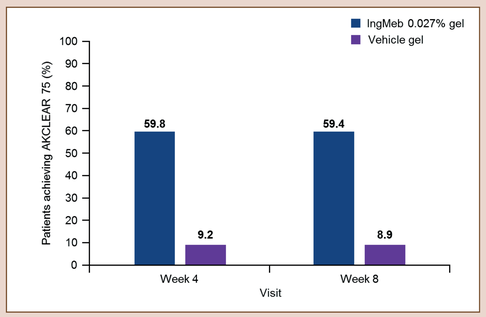
Table 1. Baseline demographics and disease characteristics

		All randomized (N = 729)	
		Median	**(Range)**
Age (years)		67.5	(38-91)
		N	**%**
Sex	Male	535	73.4%
	Female	194	26.6%
Race	White	729	100.0%
Ethnicity	Not hispanic or latino	726	99.6%
	Hispanic or latino	3	0.4%
Skin type	I Always burns easily, never tans	138	18.9%
	II Always burns easily, tans minimally	359	49.2%
	III Burns moderately, tans gradually (light brown)	200	27.4%
	IV Burns minimally, always tans well (moderate brown)	31	4.3%
	V Rarely burns, tans profusely (dark brown)	1	0.1%

Efficacy

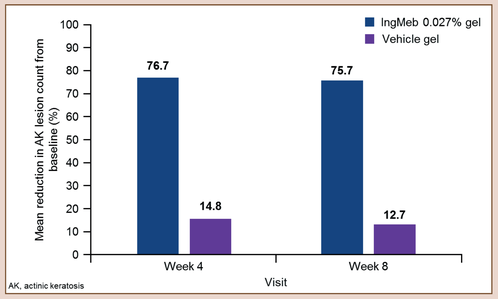
- AKCLEAR 100 (non-site-specific score) at Week 8 was 21.4% (95% CI, 18.0–24.9) for IngMeb 0.027% gel vs 3.4% (95% CI, 0.7–6.1) for vehicle gel (p<0.001). Efficacy at Week 8 differed according to anatomical site:
  - For IngMeb, AKCLEAR 100 was 23.8% (95% CI, 19.7–27.8) for the face/chest (n=435) and 12.5% (95% CI, 6.4–18.6) for the scalp (n=114); respective values in the vehicle group were 3.5% (95% CI, 0.5–6.5; n=144) and 3.1% (95% CI, 0.0–9.2; n=32)
- AKCLEAR 75 (non-site-specific score) at Week 4 was 59.8% (95% CI, 55.7–63.9) for IngMeb 0.027% gel vs 9.2% (95% CI, 4.8–13.5) for vehicle (p<0.001, **Figure 2**)
- At Week 8, AKCLEAR 75 was 59.4% (95% CI, 55.2–63.5) for IngMeb 0.027% gel vs 8.9% (95% CI, 4.6–13.2) for vehicle gel (p<0.001); both values were similar to those observed at Week 4 (**Figure 2**)

Figure 2. AKCLEAR 75 by visit



  - For IngMeb, AKCLEAR 75 was 63.4% (95% CI, 58.8–67.9) for the face/chest (n=435) and 44.1% (95% CI, 35.0–53.3) for the scalp (n=114) at Week 8; respective values in the vehicle group were 9.5% (95% CI,4.6–14.4; n=144) and 6.3% (95% CI, 0.0–14.7; n=32). The breakdown by anatomical location at Week 4 was similar to these Week 8 values
- Reduction in AK lesion count from baseline at Week 8 with IngMeb was 75.7% (95% CI, 73.9–77.3) vs 12.7% (95% CI, 3.0–21.4) with vehicle. A similar effect was observed at Week 4 (**Figure 3**)

Figure 3. Reduction in AK lesion count by visit

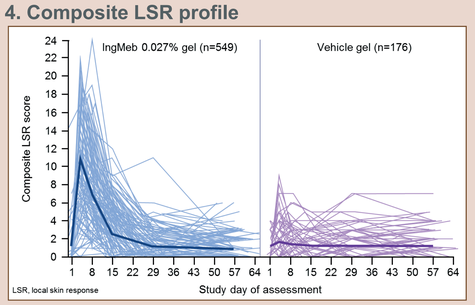


  - For IngMeb, reduction in AK lesion count from baseline at Week 8 was 76.8% (95% CI, 74.7–78.6) for the face/chest (n=435) and 64.3% (95% CI, 59.1–68.8) for the scalp (n=114); respective values in the vehicle group were 15.5% (95% CI, 3.4–26.1; n=144) and 8.2% (95% CI, -14.9–26.6; n=32)

Safety

- Mean composite LSR scores peaked at Day 4 (IngMeb 0.027% gel, 10.8; vehicle, 1.6), rapidly declined and returned to minimal levels by Week 4 (**Figure 4**)
- The lower efficacy of IngMeb observed on the scalp vs face/chest corresponded with lower LSR scores in this area
  - Mean LSR scores for face, chest and scalp groups were 11.7, 9.5 and 8.8, respectively

Figure 4. Composite LSR profile



- Treatment-related AEs (TRAEs) were experienced by 73.8% and 9.1% of patients in the IngMeb and vehicle groups, respectively. Serious AEs occurred in 1.5% vs 1.1% of patients receiving IngMeb or vehicle, respectively; none were treatment related
- The most frequently reported AEs (occurring in ≥2% patients receiving IngMeb 0.027% gel) included application-site pain and application-site pruritus (**Table 2**)

Table 2. Most frequent AEs

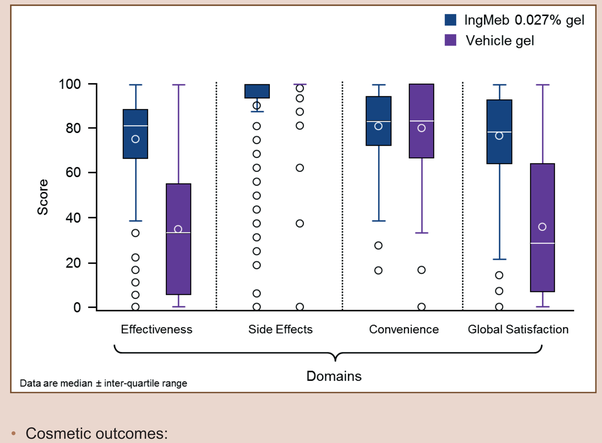
	IngMeb 0.027% (n=549)		Vehicle (n=176)	
General disorders and administration-site conditions				
Application-site pain	350	63.8%	4	2.3%
Application-site pruritus	202	36.8%	7	4.0%
Application-site discomfort	28	5.1%	2	1.1%
Application-site paresthesia	14	2.6%	2	1.1%
Nervous system disorders				
Headache	22	4.0%	4	2.3%
Eye disorders				
Eyelid edema	14	2.6%	0	0.0%

AEs were classified according to MedDRA version 15.1

Physician- and patient-reported outcomes

- Investigators reported that 80% of patients receiving IngMeb experienced minor, moderate or marked improvements in the global photo-damage outcome at Week 8, vs 18% in the vehicle group
- TSQM global satisfaction score, driven by patients' perceptions of Effectiveness, was significantly higher for IngMeb vs vehicle (41.0-point difference; p<0.001, **Figure 5**). No differences were reported for the Side Effects or Convenience domains

Figure 5. TSQM scores



- Cosmetic outcomes:
  - Overall feel: 'much improved' or 'somewhat improved' reported by 92% patients receiving IngMeb vs 18% for vehicle
  - Overall appearance: 'much improved' or 'somewhat improved' reported by 94% patients receiving IngMeb vs 19% for vehicle

Limitations

- Since LSRs were observed during the study, with early onset and rapid resolution, those receiving active treatment could potentially be identified

Conclusions

- IngMeb 0.027% gel was superior to vehicle as a field treatment on full face, balding scalp or ~250 cm^2 on the chest in patients with AK, although it was less efficacious for the treatment of AK on the scalp
- AKCLEAR 75 and 100, and percent reduction in lesion count were similar at Weeks 4 and 8, suggesting a maximal treatment effect of IngMeb by Week 4
- The safety profile of IngMeb, for both LSRs and AEs, was as expected
- IngMeb was also associated with higher levels of patient treatment satisfaction and cosmetic outcomes compared with vehicle

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