Efficacy and Safety of Ingenol Mebutate in Patients With Actinic Keratosis on Face and Scalp: Subgroup Analysis of Two Vehicle-Controlled Trials According to Age (<65 and ≥65 Years)

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Introduction

Background

- Actinic keratosis (AK) is a common skin disease typically diagnosed clinically by the presence of thickened, cornified, scaly patches on sun-exposed skin
- Although the frequency of the disease is highest in older individuals, AKs are also observed in those who are younger[1-4]
  - In the RCTs for AK therapies overall, the average age of participants has been >60 y, although eligibility criteria include age ≥18 y[5-9]
- The mean age of patients in the RCTs of 3-day, ingenol mebutate treatment of the face and scalp was approximately 65 y[9]
- The effect of age on the efficacy and safety of AK treatment has not been reported and merits investigation

Objective

- A subanalysis of pooled data from Phase 3 studies of ingenol mebutate gel 0.015% used for AKs on the face and scalp was conducted to assess the effect of age on the efficacy and safety of this treatment[9]

Methods

- An age-based subgroup analysis included pooled data from the 2 vehicle-controlled trials of ingenol mebutate gel 0.015% for the treatment of AKs on the face and scalp
  - ClinicalTrials.gov Identifier: NCT00915551 and NCT00916006
- Patients were classified into 1 of 2 subgroups based on age, <65 y or ≥65 y
- In this post hoc analysis, complete and partial clearance rates were analyzed for each subgroup, with corresponding confidence intervals (CIs) derived using the exact binomial method; *P*-value was based on the chi-square test
- For each of the age-based subgroups, the following end points were analyzed descriptively:
  - Percent reduction from baseline in lesion count
  - Mean scores for local skin response (LSR)
  - Number of adverse events (AEs)

Results

Baseline Characteristics

- The 2 face and scalp studies included a total of 547 Caucasian patients (**Table 1**)
  - 284 (51.9%) patients were <65 y, and 263 (48.1%) patients were ≥65 y
  - Patients ranged in age from 34 y to 89 y
  - In the active treatment cohort, the difference in the average age between the 2 subgroups was approximately 18 y
- Demographic and baseline characteristics were similar between the ingenol mebutate and vehicle cohorts for both age categories

Table1: Demographics and Baseline Characteristics

		Ingenol Mebutate Gel 0.015% (N=277)		Vehicle Gel (N=270)	
		<65 y (n=144)	≥65 y (n=133)	<65 y (n=140)	≥65 y (n=130)
Age	**Mean (SD), y**	**55.7 (6.2)**	**73.4 (6.3)**	**56.0 (5.8)**	**72.7 (5.7)**
	Median (range), y	**56.0 (34-64)**	**72.0 (65-88)**	**57.0 (40-64)**	**72.0 (65-89)**
		n (%)			
Country	Australia	14 (9.7)	7 (5.3)	11 (7.9)	9 (6.9)
	USA	130 (90.3)	126 (94.7)	129 (92.1)	121 (93.1)
Sex	Female	29 (20.1)	15 (11.3)	19 (13.6)	19 (14.6)
	Male	115 (79.9)	118 (88.7)	121 (86.4)	111 (85.4)
Ethnicity	Caucasian Hispanic	0 (0.0)	1 (0.8)	3 (2.1)	0 (0.0)
	Caucasian Non-Hispanic	144 (100.0)	132 (99.2)	137 (97.9)	130 (100.0)
Treatment area	Face	116 (80.6)	104 (78.2)	110 (78.6)	110 (84.6)
	Scalp	28 (19.4)	29 (21.8)	30 (21.4)	20 (15.4)

AK Clearance

- Rates of complete and partial clearance were numerically higher in patients <65 y than in those ≥65 y, but the difference was not significant (**Figure 1**) (**Table 2**)
- Percent reduction from baseline in lesion count was numerically higher in patients <65 y than in those ≥65 y (**Figure 2**)

Figure 1: Age-Based Subanalysis of AK Clearance Rates

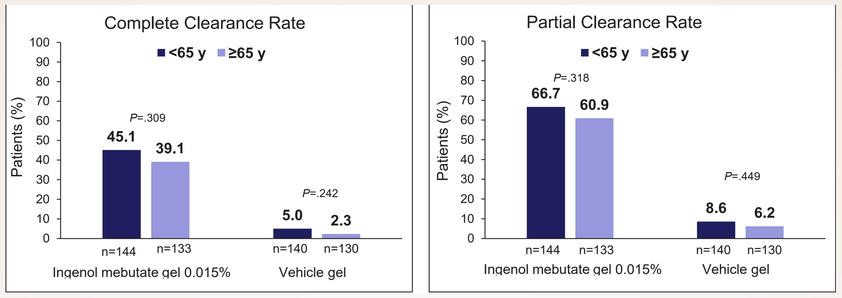


Table 2: Age-Based Subanalysis of Complete and Partial Clearance Rates, With Variance

Rate of Complete Clearance

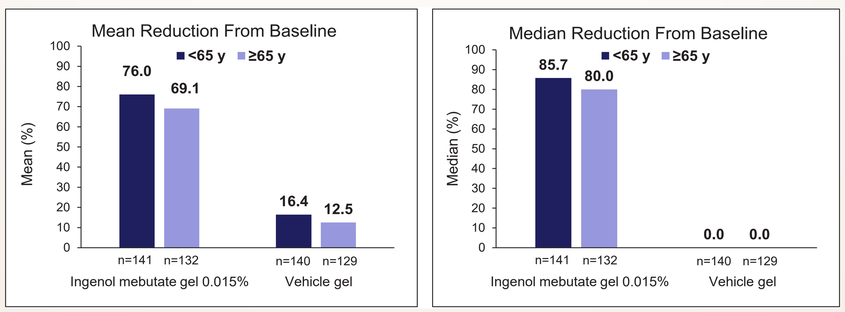
	Ingenol Mebutate Gel 0.015% (n=277)				Vehicle Gel (n=270)				
	Patients (n)	**Rate**; 95% CI (%)	OR; 95% CI	*P*		Patients (n)	**Rate**; 95% CI (%)	OR; 95% CI	*P*
<65 y (n=144)	65	**45.1**; 37.0, 53.3	1.28; 0.79, 2.07	.309	<65 y (n=140)	7	**5.0**; 1.4, 8.6	2.23; 0.56, 8.81	.242
≥65 y (n=133)	52	**39.1**; 30.8, 47.4			≥65 y (n=130)	3	**2.3**; 0.0, 4.9		

Rate of Partial Clearance

	Ingenol Mebutate Gel 0.015% (n=277)				Vehicle Gel (n=270)				
	Patients (n)	**Rate**; 95% CI (%)	OR; 95% CI	*P*		Patients (n)	**Rate**; 95% CI (%)	OR; 95% CI	*P*
<65 y (n=144)	96	**66.7**; 59.0, 74.4	1.28; 0.79, 2.10	.318	<65 y (n=140)	12	**8.6**; 3.9, 13.2	1.43; 0.57, 3.62	.449
≥65 y (n=133)	81	**60.9**; 52.6, 69.2			≥65 y (n=130)	8	**6.2**; 2.0, 10.3		

CI=confidence interval; OR=odds ratio.

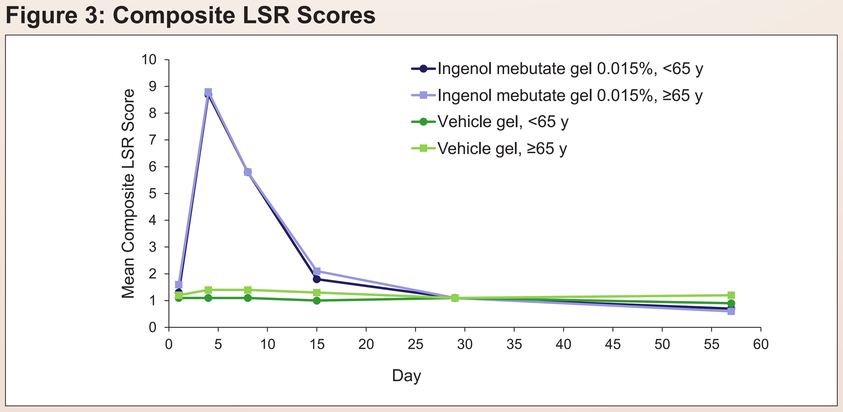
Figure 2: Age-Based Subanalysis of Reduction in AK Count From Baseline



Tolerability

- The intensity and the time course of development and resolution of LSRs in the active treatment and vehicle cohorts were the same in patients <65 y and ≥65 y (**Figure 3**)
  - Assessments occurred on days 1, 4, 8, 15, 29, and 57

Figure 3: Composite LSR Scores



Adverse Events

- In the ingenol mebutate treatment group, the proportion of patients who had AEs was lower in those <65 y (31.8%) than in those ≥65 y (42.3%) (**Table 3**)
  - Among the most frequently reported AEs, rates of application-site pain, pruritus, and irritation were lower in the younger subgroup
- The rate of serious AEs was low in all cohorts, between 1% and 2% in all ingenol mebutate and vehicle groups

Table 3: Any AE, Any Serious AE, and Any Type of AE Occurring at ≥2.0% in Any Ingenol Mebutate Subgroup

	Ingenol Mebutate Gel 0.015% (n=274)				Vehicle Gel (n=271)			
	<65 y (n=132)		≥65 y (n=142)		<65 y (n=130)		≥65 y (n=141)	
	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
Any AE	42 (31.8)	76	60 (42.3)	118	28 (21.5)	55	32 (22.7)	52
Any serious AE	3 (2.3)	6	3 (2.3)	4	3 (2.1)	4	2 (1.4)	2
Type of AE								
Application-site pain	14 (10.6)	19	24 (16.9)	31	1 (0.8)	2	0 (0.0)	0
Application-site pruritus	7 (5.3)	7	15 (10.6)	15	1 (0.8)	1	2 (1.4)	2
Application-site irritation	1 (0.8)	1	4 (2.8)	4	0 (0.0)	0	0 (0.0)	0
Application-site infection	3 (2.3)	3	4 (2.8)	4	0 (0.0)	0	0 (0.0)	0
Periorbital edema	4 (3.0)	5	3 (2.1)	3	0 (0.0)	0	0 (0.0)	0

Conclusions

- There were no significant differences in rates of AK clearance between younger and older patients treated with ingenol mebutate gel 0.015% based on this post hoc analysis of Phase 3 studies of the face and scalp
  - Complete clearance rate: 45.1% (<65 y) vs 39.1% (≥65 y)
  - Partial clearance rate: 66.7% (<65 y) vs 60.9% (≥65 y)
- Reduction from baseline in AK count was also similar for the 2 subgroups
  - Mean reduction: 76.0% (<65 y) vs 69.1% (≥65 y)
  - Median reduction: 85.7% (<65 y) vs 80.0% (≥65 y)
- No differences between younger and older patients were observed in the severity and time course of resolution of LSRs
- The frequency of AEs was numerically lower in those <65 y (31.8%) than in those ≥65 y (42.3%)
- Ingenol mebutate gel 0.015% is an effective and safe treatment option for patients with AKs on the face and scalp, regardless of age

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Acknowledgments

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