Is there a clinically relevant risk of hyperkalemia with topical clascoterone treatment?

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INTRODUCTION

- Acne vulgaris (AV) is a common, inflammatory skin disease primarily affecting adolescents and young adults[1,2]
  - — Androgens play a key role in driving acne pathogenesis via binding to androgen receptors (AR)[1]
- Chronic treatment with steroidal antiandrogens can produce systemic adverse effects, including hyperkalemia,[3] a plasma potassium level exceeding the upper limit of normal (ie, >5.0 mmol/L)
- Clascoterone cream 1% is a novel topical AR inhibitor[4] approved to treat AV in patients ≥12 years of age[5]

OBJECTIVE

- To assess the clinical relevance of hyperkalemia in patients treated with topical clascoterone in the clascoterone clinical development program

METHODS

- Data analyzed included Phase 1 studies in healthy adults, pharmacokinetic and maximal use (MUSE) trials in patients with moderate-to-severe AV, and Phase 2 studies in patients with AV (**Table 1**)
  - — One study used a clascoterone 7.5% solution formulation not approved by the Food and Drug Administration (FDA) for treatment of AV
  - — All other studies evaluated clascoterone cream ≤1%

Table 1. Description of clinical studies included in the FDA multidisciplinary review of hyperkalemia

Phase/design	Treatment duration	Participants	Dose[a]	Participants, n	
				Clascoterone	Vehicle
Phase 1 single ascending dose	Single dose	Healthy adult males, 18–65 years	1 mL 2 mL 4 mL Vehicle	6 6 6 -	- - - 6
Phase 1 multiple dose	14 days, QD	Healthy adults, 18–65 years	4 mL 8 mL	12 12	- -
Phase 1 ECG study	BID for 3 days, QD on Day 4	Healthy adults, 18–40 years	7.5% solution 3 mL Vehicle	24 -	- 8
Phase 1 pharmacokinetic study	6 weeks, QD	Adults with moderate-to-severe facial/truncal acne vulgaris	6 g	8	-
Phase 2 maximum dose	2 weeks, BID	Adults/adolescents with moderate-to-severe facial/truncal acne vulgaris	6 g[b]	20 adults 22 adolescents	-
Phase 2 maximum dose	2 weeks, BID	Children with moderate-to-severe facial/truncal acne vulgaris	2 g	27	-
Phase 2 single dose	8 weeks, QD	Male patients (18–45 years) with facial acne vulgaris	Clascoterone 1% Retin-A® 0.05% cream[c] Vehicle	30 - -	- - 15
Phase 2 dose escalating	12 weeks, QD/BID	Patients ≥12 years old with mild-to-severe facial acne vulgaris (IGA Grade 2–4)	0.1% BID 0.5% BID 1% QD/BID Vehicle QD/BID	72 76 70/70 -	- - - 75

[a]Clascoterone cream 1% unless otherwise specified.
[b]Patients who were <18 years of age and had a body surface area ≤1.6 m^2 applied 4 g.
[c]Thirty-two patients applied Retin-A® 0.05% cream.
Adults defined as ≥18 years of age; adolescents defined as 12–17 years of age; children defined as 9–11 years of age.
BID, twice daily; ECG, electrocardiogram; FDA, Food and Drug Administration; IGA, Investigator's Global Assessment; QD, once daily.

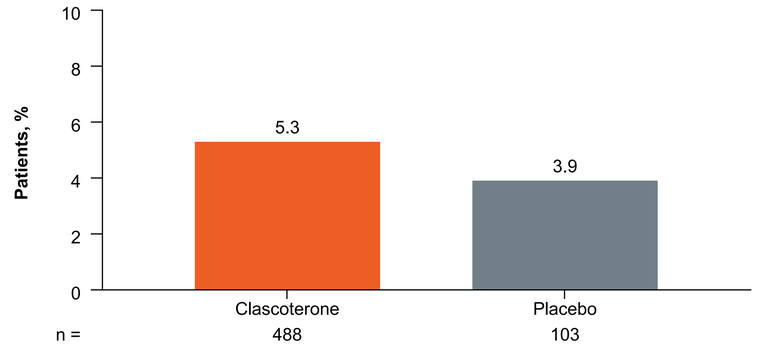
- The recommended dosage for clascoterone cream 1% in the FDA-approved product labeling is approximately 1 g twice daily[5]
- In MUSE studies, patients applied clascoterone cream diffusely (entire face, shoulders, upper chest, and upper back)
  - — Adult (≥18 years of age) and adolescent (12–17 years of age) patients applied 6 g of clascoterone cream twice daily, except adolescents with a body surface area ≤1.6 m^2, who applied 4 g
  - — Children (9–11 years of age) applied 2 g twice daily
- The percentage of patients with a shift from low/normal/missing to elevated potassium was calculated among patients with a baseline and ≥1 postbaseline value; hemolyzed samples were excluded
  - — The baseline value was defined as the value recorded at the last visit on or before the first dose of study drug
- Least squares (LS) mean and difference values were based on an analysis of covariance, with treatment, baseline value, and age included in the model

RESULTS

Clinical laboratory evaluations of hyperkalemia

- Overall, 26/488 (5.3%) clascoterone-treated and 4/103 (3.9%) vehicle-treated patients exhibited a shift from low/normal/missing to elevated potassium (**Figure 1**)

Figure 1. Overall percentage of patients with a shift from normal to high potassium



Data shown as % unless otherwise noted.
Hemolyzed samples were excluded from analysis.

- — The LS mean maximum percent change from baseline was 0.10% and 0.06% in the clascoterone and vehicle groups, respectively, with a difference of 0.03% (95% confidence interval, –2.20% to 2.27%; **Table 2**)

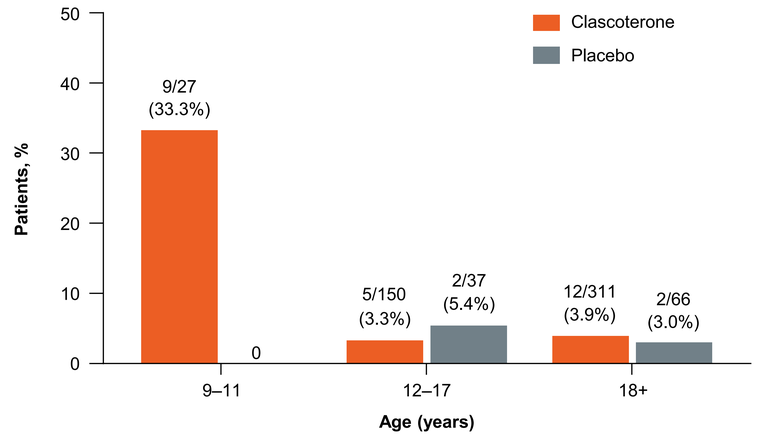
Table 2. Maximum percent change from baseline in potassium levels

	Clascoterone (n = 495)	Vehicle (n = 103)
Baseline (mmol/L)		
Mean (SD)	4.22 (0.41)	4.23 (0.42)
Range (min–max)	3.1–6.3	3.4–6.1
Maximum percent change from baseline		
LS mean[1]	0.10%	0.06%
Difference (95% CI)	0.03% (−2.20% to 2.27%)	

[1]LS mean and difference based on ANCOVA with treatment, baseline value, and age in the model.
ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; max, maximum; min, minimum; SD, standard deviation.

- The highest percentage of shifts to elevated potassium levels (9/27 patients; 33%) was noted in children 9−11 years of age in a MUSE study (**Figure 2**)

Figure 2. Percentage of patients with a shift from normal to high potassium by age



Data shown as % unless otherwise noted.
Hemolyzed samples were excluded from analysis.
Results in patients aged 9–11 years are based on data from a maximal use study.

Exposure-response analysis

- Plasma concentrations of clascoterone and the metabolite cortexolone were generally low in pediatric patients with abnormal potassium values (**Table 3**)
- An exposure-response analysis found no clear correlation between plasma concentrations of clascoterone and cases of hyperkalemia

Table 3. Plasma concentrations of clascoterone and cortexolone in pediatric patients who had a shift in potassium from normal to high

Patient #	Clascoterone		Cortexolone	
	Screening	Day 14	Screening	Day 14
1	BQL	0.378	BQL	BQL
2	BQL	0.545	1.100	1.510
3	BQL	0.844	BQL	BQL
4	BQL	0.358	BQL	BQL
5	BQL	BQL	1.020	BQL
6	BQL	0.256	0.689	BQL
7	BQL	2.550	BQL	0.868
8	BQL	0.918	0.660	0.917
9	BQL	0.986	BQL	0.972

Data shown as ng/mL unless otherwise noted.
The lower limit of quantitation was 0.25 ng/mL for clascoterone and 0.5 ng/mL for cortexolone.
BQL, below the lower limit of quantitation.

Clinical relevance of hyperkalemia in clascoterone clinical studies

- None of the episodes of hyperkalemia were reported as adverse events or resulted in study discontinuation
- Baseline or subsequent laboratory monitoring was not required in the Phase 3 studies or recommended in the FDA-approved prescribing information[5]

CONCLUSION

- Hyperkalemia was observed as an occasional laboratory finding in both clascoterone- and vehicle-treated patients, but no exposure-response correlation was found; there were no adverse events or study discontinuations related to hyperkalemia
- The frequency of hyperkalemia was highest in patients treated with clascoterone <12 years of age, for whom clascoterone is not FDA approved

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DISCLOSURES

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