Q301 (Zileuton) Cream Is Superior to Vehicle in Improving Atopic Dermatitis: Results From a Phase 2a Trial

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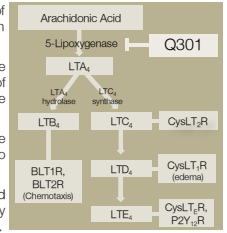
Introduction

- Leukotriene B4 (LTB4) plays a significant role in the progression of Atopic Dermatitis (AD)[1, 2, 3, 4]. LTB4 levels are high in AD lesions and an injection of LTB4 produces neutrophil infiltration on histology.
- LTB4 is shown to be involved in immune cell recruitment to the disease site as well as in the mediation of pruritus[3, 5]. Therefore, the control of LTB4 levels at the site of the disease appears to be an effective strategy for controlling AD.
- Zileuton is an inhibitor of 5-lipoxygenase, an enzyme that catalyzes the conversion of arachidonic acid to leukotrienes, which contributes to atopic inflammation.
- Q301 Cream is a topical formulation of zileuton, the oral drug approved in treating asthma, has been developed to treat AD by directly delivering drug to the affected skin while minimizing systemic exposure.

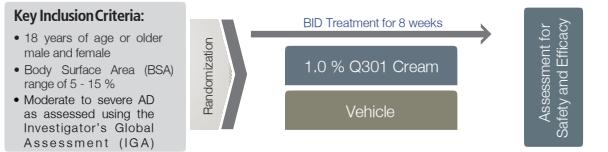


Methods

Study Design

- This was a Phase 2a, randomized, double-blind, vehicle-controlled, parallel-group comparison study (NCT02426359) in male or female patients 18 years of age or older with moderate to severe AD.
- Following a 2-week screening period, patients were randomized to receive 1.0 % Q301 Cream or Vehicle.
- Study drug was self-administered by patients twice daily for 8 consecutive weeks period.
- After randomization at Week 0, patients were evaluated for safety and efficacy at their respective trial sites at Week 2, 4, 6 and 8, and then at Week 10 for safety follow-up (Figure 1).

Figure 1. Study Design



Week -2 - 0	Week 0 – 8 (Visit at Week 0, 2, 4, 6, and 8)	Visit at Week 10
Screening & Randomization	Treatment Period	Safety follow-up

Assessments

Primary Endpoint

- Percentage of patients achieving an IGA score of 0 (clear) or 1 (almost clear) at Week 8.

Secondary Endpoints

- Percent change from Baseline to Week 8 in the Visual Analog Scale (VAS) score for pruritus
- Percent change from Baseline to Week 8 in Eczema Area and Severity Index (EASI) score
- Percent change from Baseline to Week 8 in Scoring Atopic Dermatitis (SCORAD) score
- Percent change from Baseline to Week 8 in the Dermatology Life Quality Index (DLQI)

Safety Endpoints

- Clinical laboratory parameters (hematology, serum chemistry including liver function tests, and urinalysis), 12-lead electrocardiogram (ECG), physical examinations, vital signs, adverse events (AEs) including symptoms of hepatotoxicity and neuropsychiatric events, prior and concomitant medications, local tolerability assessment, and compliance assessment by reviewing the patient's diary.

Statistical Analysis

- Categorical variables were summarized as the number and percentage of patients, and the difference in proportions with 95 % confidence interval (for primary endpoint only).
- Continuous variables were summarized with the mean, standard deviation, median, 25th and 75th percentiles, minimum value, and maximum value.
- 57 patients were randomized, 52 (ITT) were treated, and 38 (66.7 %) completed the study (Figure 2).
- The demographic and Baseline characteristics in the 1.0 % Q301 Cream group and the Vehicle group were similar (Table 1).

Figure 2. Patient Disposition

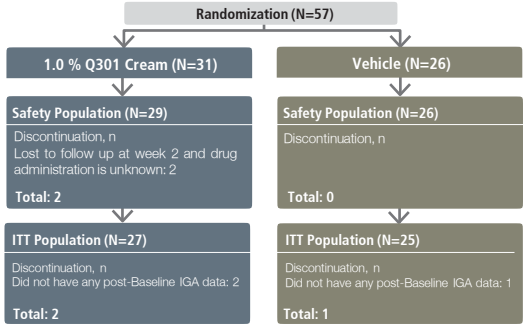


Table 1. Demographic and Baseline Characteristics (Randomized Set)

Characteristics		1.0 % Q301 Cream (N=31)	Vehicle (N=26)	Overall (N=57)
Age, years, Mean (SD)		42.4 (13.78)	44.4 (18.87)	43.3 (16.18)
Gender, n (%)	Female	21 (67.7)	15 (57.7)	36 (63.2)
	Male	10 (32.3)	11 (42.3)	21 (36.8)
Race, n (%)	Black or African American	11 (35.5)	11 (42.3)	22 (38.6)
	White	20 (64.5)	14 (53.8)	34 (59.6)
	Other	0 (0.0)	1 (3.8)	1 (1.8)
% BSA, Mean (SD)		8.1 (3.64)	9.0 (3.34)	8.5 (3.50)
IGA, Mean (SD)		3.2 (0.43)	3.2 (0.43)	3.2 (0.42)

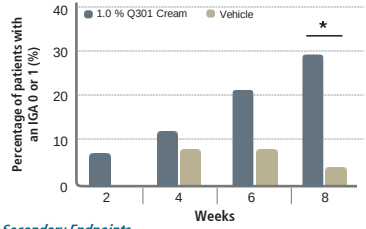
Efficacy

Primary Endpoint

- In the ITT population, 1.0 % Q301 Cream showed a significantly greater percentage of patients who had an IGA score of 0 or 1 (clear or almost clear) at Week 8 as compared to Vehicle (29.6 % vs. 4.0 %; $p = 0.02$) (Figure 3).
- 1.0 % Q301 Cream showed continuous improvement from Week 2 to Week 8 (Figure 3).

Results

Figure 3. Summary of Percentage of Patients with an IGA Score of 0 or 1 (ITT Population)



Visits	1.0 % Q301 Cream (N=27)	Vehicle (N=25)
Week 2	7.4 %	0 %
Week 4	11.1 %	8.0 %
Week 6	22.2 %	8.0 %
Week 8	29.6 %	4.0 %

* $p = 0.02$ (based on the Fisher's Exact test)

Secondary Endpoints

- In the ITT Population, the secondary efficacy endpoints except DLQI demonstrated a non-significant numerically greater decrease in the mean percent change from Baseline to Week 8 although these parameters were not controlled in the inclusion criteria.

Table 2. Summary of Percentage Change from Baseline for Secondary Endpoints (ITT Population)

Secondary Endpoints	Statistics	1.0 % Q301 Cream (N=27)	Vehicle (N=25)
EASI90	% of patients with EASI90 at Week 8	22	4
VAS	% Change from Baseline to Week 8 Mean (SD)	-36.4 (66.78)	-16.6 (79.72)
EASI		-47.9 (44.67)	-39.5 (39.35)
SCORAD		-32.4 (35.43)	-26.2 (32.81)
DLQI		-31.3 (66.88)	-33.2 (55.29)

Safety Endpoints

- Six of 29 (20.7 %) 1.0 % Q301 Cream treated patients experienced a total of 10 treatment-emergent adverse events (TEAEs), while 10 of 26 (38.5 %) Vehicle treated patients experienced a total of 17 TEAEs.
- The most common TEAEs was application site pruritus in the 1.0 % Q301 Cream group (3/29, 10.3 %) and cough and application site erythema in the Vehicle group (2/26, 7.7 % for each). All other TEAEs occurred only once. The majority of TEAEs were mild or moderate in intensity.
- No significant abnormalities in laboratory assessments, vital signs, or ECGs were observed.

Conclusions

- 1.0 % Q301 Cream showed a significantly greater percentage of patients who had an IGA score of 0 or 1 (clear or almost clear) at Week 8 as compared to Vehicle (29.6 % vs. 4.0 %; $p = 0.02$).
- 1.0 % Q301 Cream showed numerically greater improvement in secondary endpoints including VAS, EASI, and SCORAD.
- Q301 Cream appears to be a promising topical non-corticosteroidal anti-inflammatory drug for decreasing the signs and symptoms of AD. No evidence of any systemic toxicity was observed.
- Ongoing Phase 2b (NCT03571620) study will evaluate the safety and efficacy of Q301 Cream in adolescents and adults.

References
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