GBR 830 INDUCES PROGRESSIVE AND SUSTAINED IMPROVEMENTS IN ATOPIC DERMATITIS SKIN BIOMARKERS AND CLINICAL PARAMETERS

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ABSTRACT

GBR 830 is a first-in-class, humanized, monoclonal IgG1 antibody specific for inhibiting OX40, a costimulatory receptor on activated T cells. This proof-of-concept study (NCT02683928) investigated the effects of GBR 830 on atopic dermatitis (AD) biomarkers and generated the first clinical evidence of biological activity. Adults with BSA ≥10%, EASI ≥12, SCORAD ≥20, IGA ≥3, and history of inadequate response to topical treatments were randomized 3:1 to GBR 830 (10 mg/kg IV, at baseline [BL] and Day 29) or placebo (PBO). 63% (39/62) of AD subjects had ≥1 TEAE; TEAEs were similarly distributed between the GBR 830 and PBO groups. 40 subjects had evaluable skin biopsies at BL, 39 at Day 29 (GBR 830=28, PBO=11), and 29 at Day 71 (GBR 830=22, PBO=7). Significant reductions from BL ($p<0.001$) were found with GBR 830 (but not PBO) in treatment-specific biomarkers ($OX40^+$ T cells, $OX40L^+$ dendritic cells). The GBR 830 group also had significant reductions from BL ($p<0.001$) in hyperplasia measures (epidermal thickness, keratin 16 mRNA and protein expression, and Ki67 cell counts). Significant reductions from BL with GBR 830 ($p<0.01$) were seen in AD biomarkers, including Th2 chemokines (CCL17, CCL11, TSLPR), Th1/IFN markers (IFN gamma, CXCL10), and Th17/Th22-associated products (IL-23p19, S100A9/S100A12). Clinically, a greater proportion of GBR 830-treated patients achieved EASI 50 (≥50% score reduction from BL) vs PBO at Day 29 (43.6% vs 20.0%; $p=0.11$) and Day 71 (76.9% vs 37.5%; $p=0.04$). In summary, GBR 830 was well-tolerated, induced significant, progressive, and long-lasting changes in lesional biopsies up to Day 71.

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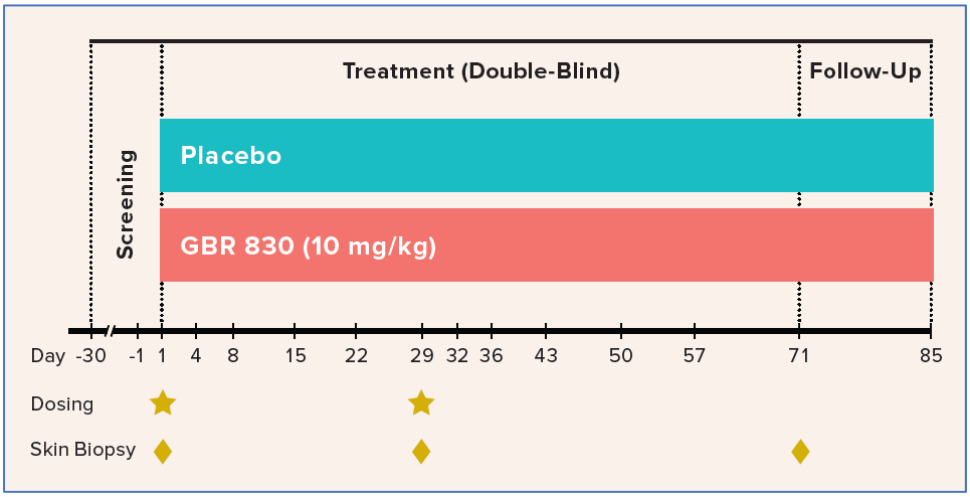
KEY FINDINGS

STUDY DESIGN

- Randomized, double-blind, placebo-controlled, repeated-dose study conducted across 17 centers in North America in adults (≥18 years) with moderate-to-severe AD for >1 year
- Subjects randomized 3:1 to GBR 830 or placebo; 2 repeated doses (each 10 mg/kg) were administered intravenously on Days 1 and 29 (**Figure 1**)

Figure 1. Study Design



RESULTS

Subjects

- Intent-to-treat (ITT) population: included 62 subjects who were randomized and received ≥1 partial or full dose of study drug (GBR 830, n=46; placebo, n=16)
- Biological Activity Set (BAS): included 40 subjects, all ITT subjects who had ≥1 post-baseline skin biopsy and received both doses of study drug (GBR 830, n=29, placebo, n=11)
- Demographic and baseline characteristics were generally similar between treatment groups in the ITT/safety and BAS populations (**Table 1**)

Table 1. Baseline Characteristics

	ITT		BAS	
	GBR 830 (n = 46)	Placebo (n = 16)	GBR 830 (n = 29)	Placebo (n = 11)
Demographics				
Age, years				
Mean ± SD	36.2 ± 13.4	40.4 ± 15.1	34.1 ± 12.2	40.7 ± 14.7
Median (min, max)	34 (18, 66)	41 (19, 59)	33 (18, 61)	42 (19, 59)
Sex, n (%)				
Male	21 (45.7)	11 (68.8)	16 (55.2)	8 (72.7)
Female	25 (54.3)	5 (31.2)	13 (44.8)	3 (27.3)
Race, n (%)				
Asian	5 (10.9)	2 (12.5)	4 (13.8)	2 (18.2)
Black or African American	9 (19.6)	3 (18.7)	5 (17.2)	1 (9.1)
White	31 (67.4)	11 (68.8)	19 (65.5)	8 (72.7)
Other	1 (2.2)	0	1 (3.4)	0
Body mass index, mean ± SD, kg/m^2	26.1 ± 4.1	26.2 ± 3.7	25.7 ± 3.7	26.1 ± 3.9
Baseline Disease Characteristics				
BSA affected, mean ± SD, %	38.6 ± 23.4	39.3 ± 21.5	38.6 ± 24.0	38.4 ± 21.6
EASI				
Mean ± SD	25.1 ± 12.3	23.3 ± 9.4	25.4 ± 13.7	22.2 ± 9.6
Median (min, max)	21.0 (12.4, 65.0)	19.9 (14.1, 47.5)	20.1 (12.7, 65.0)	18.9 (14.1, 47.5)
Epidermal thickness (lesional), µm				
Mean ± SD	NA	NA	140.6 ± 57.6	125.0 ± 47.0
Median (min, max)	NA	NA	130.2 (58.4, 287.4)	136.9 (60.8, 187.1)
Epidermal thickness (non-lesional), µm				
Mean ± SD	NA	NA	63.3 ± 25.2	59.0 ± 21.5
Median (min, max)	NA	NA	56.8 (29.5, 155.6)	54.2 (33.1, 96.0)

BAS, Biological Activity Set; BSA, body surface area; EASI, Eczema Area and Severity Index; ITT, intent-to-treat; NA, not applicable; SD, standard deviation.

KEY FINDINGS

Adverse Events (Safety Population)

- TEAEs occurred with similar incidence between treatment groups (**Table 2**); most were mild or moderate in intensity

Table 2. Adverse Events

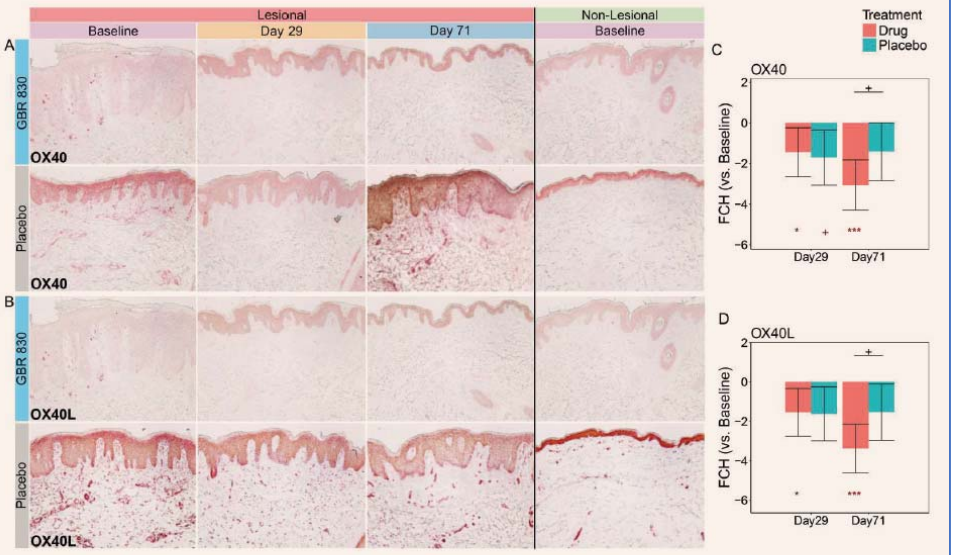
Adverse Events, n (%)	GBR 830 (n = 46)	Placebo (n = 16)
Deaths	0	0
Any TEAE	29 (63.0)	10 (63.0)
Any serious AE	1 (2.2)[a]	0
Discontinuation due to AEs	2 (4.3)	1 (6.3)
Common TEAEs[b]		
Headache	6 (13.0)	4 (25.0)
Dermatitis atopic	6 (13.0)	2 (12.5)
Nasopharyngitis	4 (8.7)	2 (12.5)
Upper respiratory tract infection	4 (8.7)	2 (12.5)
Post-procedural infection	4 (8.7)	0
Myalgia	3 (6.5)	0

[a]Subject had coronary artery occlusion (not related to study treatment).
[b]Reported in ≥5% of subjects in the GBR 830 group.
AE, adverse event; TEAE, treatment-emergent adverse event.

Biomarker Signatures (BAS Population)

- Significant decreases from baseline in OX40$^+$ T cell and OX40L$^+$ DC cellular staining in lesional skin were found with GBR 830 treatment at Day 29 ($p<0.05$) and Day 71 ($p<0.001$) (**Figure 2**)
  - Drug versus placebo trended on significance at Day 71 for both markers

Figure 2. OX40 Target Expression From Representative GBR 830- and Placebo-Treated Subjects

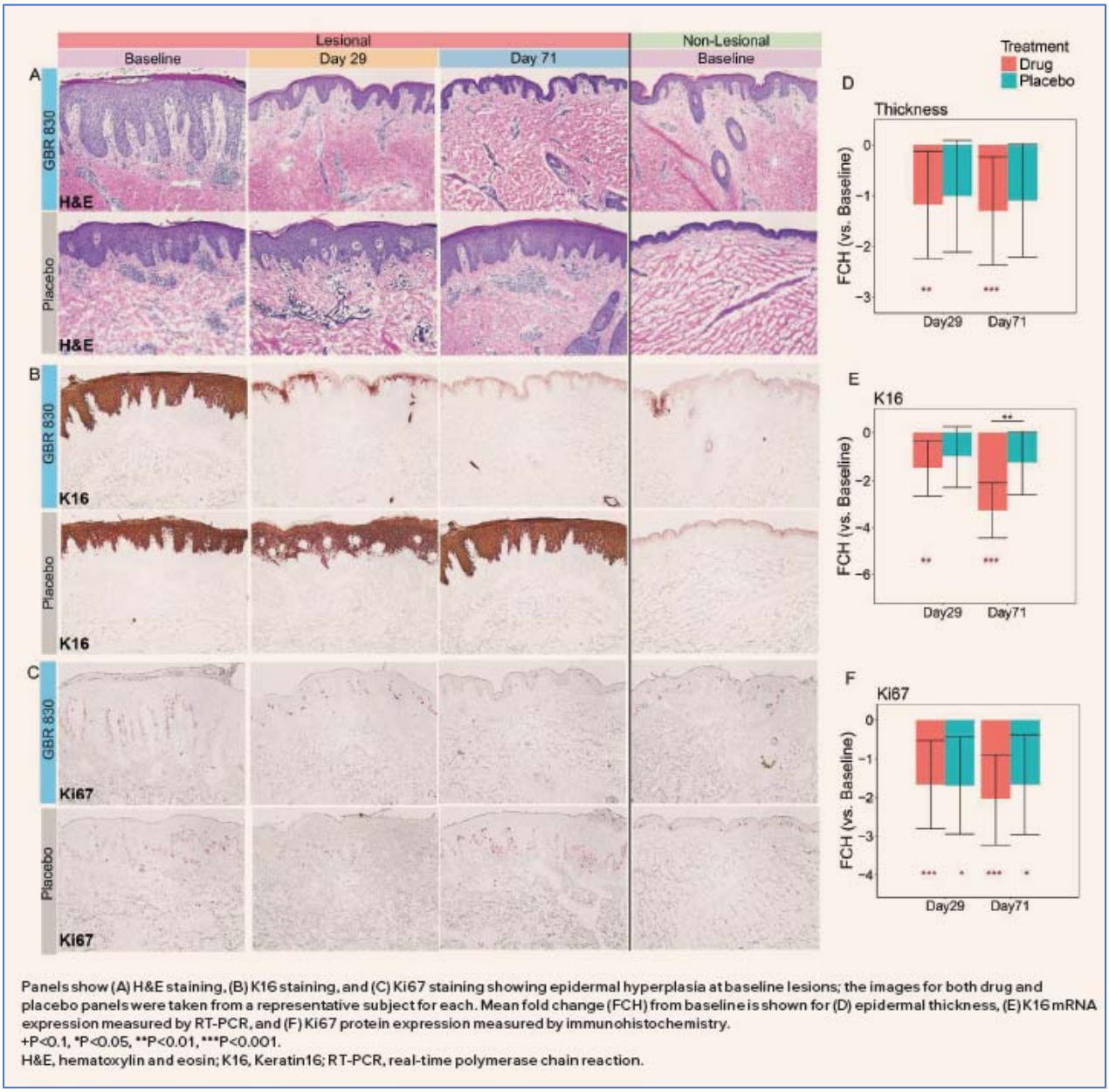


Immunohistochemistry staining of OX40 (A) and OX40L (B) at baseline and after treatment (Day 29 and Day 71); protein expression is shown in red staining and the images in each line were taken from the same subject. Mean fold change (FCH) from baseline in OX40 expression (C) and OX40L expression (D). +P<0.1, *P<0.05, **P<0.01, ***P<0.001.

KEY FINDINGS

- GBR 830-treated subjects had significant reductions from baseline in epidermal thickness (**Figure 3A, 3D**), K16 mRNA expression (**Figure 3B, 3E**), and Ki67+ cells at Days 29 and 71 (**Figure 3C, 3F**)
  - Changes from baseline with placebo were not significant (thickness, K16) or less pronounced (Ki67+)

Figure 3. Epidermal Proliferation at Baseline and After Treatment

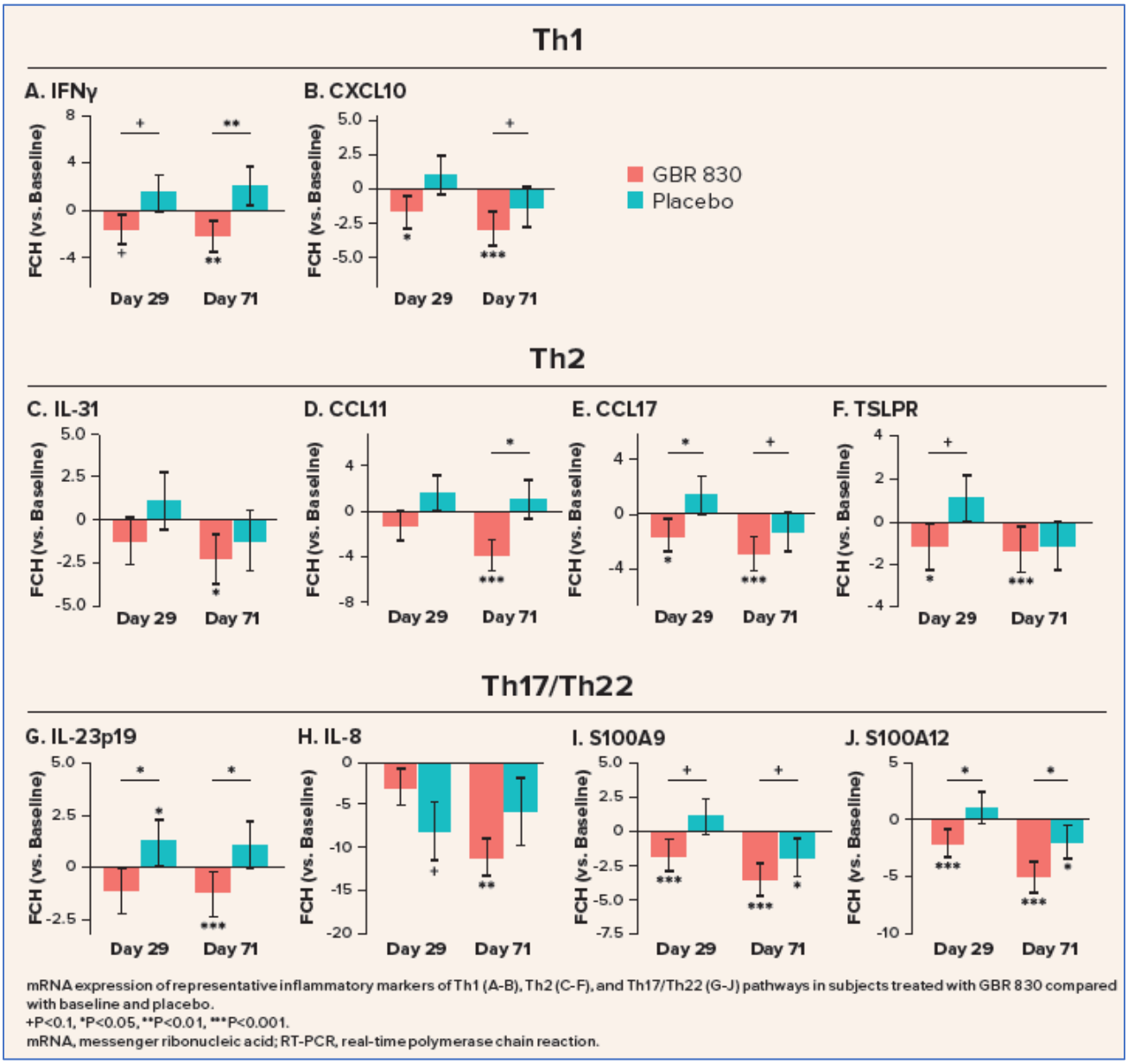


Panels show (A) H&E staining, (B) K16 staining, and (C) Ki67 staining showing epidermal hyperplasia at baseline lesions; the images for both drug and placebo panels were taken from a representative subject for each. Mean fold change (FCH) from baseline is shown for (D) epidermal thickness, (E) K16 mRNA expression measured by RT-PCR, and (F) Ki67 protein expression measured by immunohistochemistry.
+P<0.1, *P<0.05, **P<0.01, ***P<0.001.
H&E, hematoxylin and eosin; K16, Keratin16; RT-PCR, real-time polymerase chain reaction.

KEY FINDINGS

- GBR 830-treated subjects had significant reductions in most mRNA biomarkers of disease activity compared with baseline and placebo (**Figure 4**)

Figure 4. Changes in Quantitative RT-PCR mRNA Expression Following Treatment



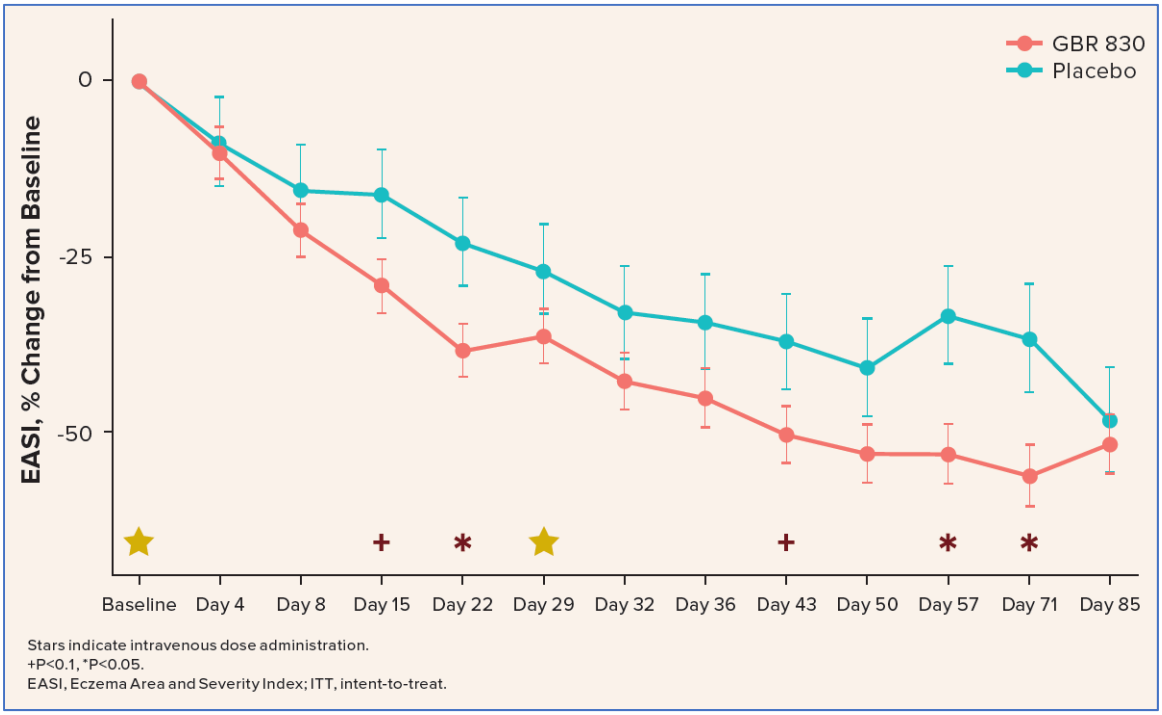
mRNA expression of representative inflammatory markers of Th1 (A-B), Th2 (C-F), and Th17/Th22 (G-J) pathways in subjects treated with GBR 830 compared with baseline and placebo.
+P<0.1, *P<0.05, **P<0.01, ***P<0.001.
mRNA, messenger ribonucleic acid; RT-PCR, real-time polymerase chain reaction.

KEY FINDINGS

Clinical Efficacy (ITT Population)

- A greater proportion of GBR 830-treated subjects achieved EASI 50 versus placebo at Day 29 (43.6% vs 20.0%; p=0.2) and Day 71 (76.9% vs 37.5%; p=0.02) (**Figure 5**)
- A positive association was seen between improvements in clinical assessments and changes in tissue AD biomarkers

Figure 5. Percentage Change in EASI from Baseline Through Day 85



Stars indicate intravenous dose administration.
+P<0.1, *P<0.05.
EASI, Eczema Area and Severity Index; ITT, intent-to-treat.

CONCLUSIONS

- GBR 830 was safe and well tolerated, with a similar TEAE profile to placebo
- GBR 830 inhibits the OX40/OX40L pathway, as shown through reduced expression of OX40/OX40L in lesional skin
- Treatment with GBR 830 resulted in reductions in epidermal hyperplasia, proliferation, and mRNA biomarkers for disease activity, indicating an effect on both the acute and chronic stages of AD
- Although the study was not powered for statistical testing, subjects treated with GBR 830 had improvements in AD scores that were consistent with biomarker results
- Results of this proof-of-concept study indicate that GBR 830 may be an effective treatment for AD