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

EMMA GUTTMAN-YASSKY[1]; ANA B. PAVEL[1]; YERIEL ESTRADA[1]; LISA ZHOU[1]; YACINE SALHI[2]; GIRISH GUDI[2]; VINU CA[3]; JULIE MACOIN[4]; JONATHAN BACK[4]; GERHARD WOLFF[2]

[1]ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI, NEW YORK, NY, USA; [2]GLENMARK PHARMACEUTICALS INC., USA; [3]GLENMARK PHARMACEUTICALS LTD., INDIA; [4]GLENMARK PHARMACEUTICALS SA, SWITZERLAND

SYNOPSIS/OBJECTIVE

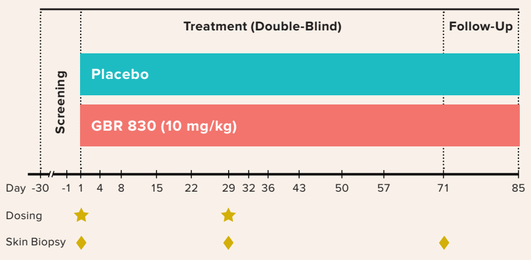
- GBR 830 is an investigational, first-in-class, humanized, monoclonal IgG1 antibody specific for inhibiting OX40, a costimulatory receptor on activated T cells[1]
- By blocking binding of OX40 to its ligand OX40L, GBR 830 reduces longevity and efficacy of effector and memory T cells[1]
- OX40 inhibition is suggested to have a potential therapeutic role in T cell-mediated diseases, including atopic dermatitis (AD), one of the most common inflammatory skin disorders that affects up to 10% of adults[2]
- This phase 2a proof-of-concept study in patients with moderate-to-severe AD (NCT02683928) was conducted to investigate the safety of GBR 830, evaluate its effects on AD biomarkers, and generate the first clinical evidence of its biological activity

METHODS

Study Design

- Randomized, double-blind, placebo-controlled, repeated-dose study conducted in 17 North American centers
- Three phases: screening (up to 30 days), treatment (Day 1 [baseline] and 29), follow-up (through Day 85) (**Figure 1**)
- Treatment: randomization 3:1 to GBR 830 or placebo; 2 repeated doses (each 10 mg/kg, administered intravenously) on Days 1 and 29
- Skin punch biopsies: obtained from lesional skin on Days 1, 29, and 71

Figure 1. Study Design



Subjects

- Key inclusion criteria:
  - Adult subjects (≥18 years) with moderate-to-severe AD for >1 year
  - Affected body surface area (BSA) ≥10%
  - Eczema Area and Severity Index (EASI) score ≥12
  - Scoring of Atopic Dermatitis (SCORAD) ≥20
  - Investigator's global assessment (IGA) score ≥3 (5-point scale)
  - History of inadequate response to topical therapies
- Key exclusion criteria:
  - Live vaccination within 12 weeks before randomization
  - History of serious infection, including latent or active tuberculosis
  - Prior treatment with systemic corticosteroids, topical steroids, phototherapy, and/or biologics

Study Endpoints

- Co-primary: treatment-emergent adverse events (TEAEs; frequency, severity); change from baseline in epidermal hyperplasia and active AD mRNA expression biomarker signatures measured from lesional skin biopsies
- Key secondary: EASI 50 response (≥50% improvement from baseline) on Day 29 and Day 71

Statistical Analyses

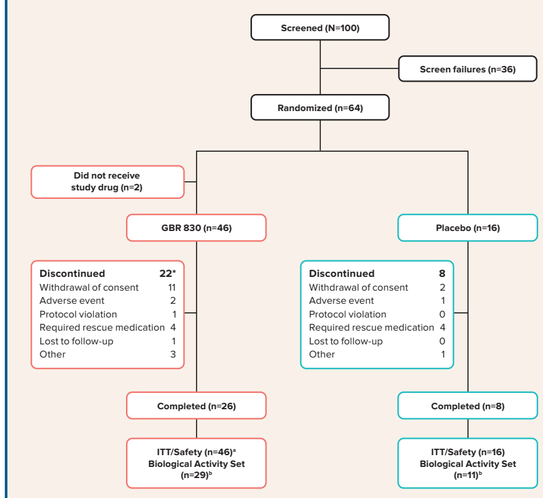
- Intent-to-treat (ITT) population: all subjects who were randomized and received ≥1 partial or full dose of study drug
- Safety population: all subjects who took ≥1 partial or full dose of study drug
- Biological Activity Set (BAS): all ITT subjects who had ≥1 post-baseline skin biopsy and received both doses of study drug
- EASI 50 response was analyzed descriptively at Day 29 and Day 71
- Immunohistochemistry and RT-PCR data was log2-transformed prior to analysis using a linear mixed effect model with Time, Tissue, and Treatment as fixed factors and a random intercept for each subject

RESULTS

Subjects

- ITT/safety population included 62 subjects: GBR 830, n=46; placebo, n=16 (**Figure 2**)
- BAS population included 40 subjects: GBR 830, n=29; placebo, n=11

Figure 2. Subject Disposition



*Includes subjects who did not receive GBR 830 (n=2).
[a]Excludes subjects from the randomized population (GBR 830, n=2) who did not receive ≥1 partial or full dose of study drug.
[b]Excludes subjects from the ITT population (GBR 830, n=17; placebo, n=5) who did not receive both doses of study drug and have ≥1 post-baseline skin biopsy (Day 29 or Day 71).
ITT, intent-to-treat.

- 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/m²	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.

Adverse Events (Safety Population)

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

Table 2. Treatment-Emergent Adverse Events (Safety Population)

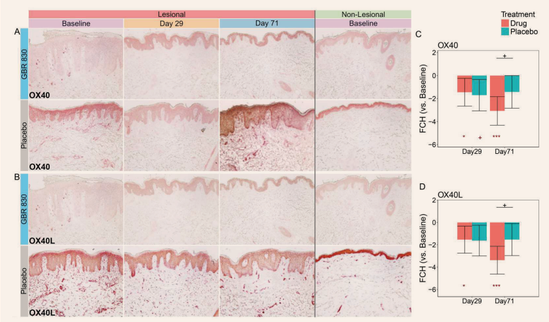
Adverse Events, n (%)	GBR 830 (n = 46)	Placebo (n = 16)
Deaths	0	0
Any TEAE	29 (63.0)	10 (63.0)
Any serious AE	1 (2.2)[a]	0
Discontinuation due to AEs	2 (4.3)	1 (6.3)
Common TEAEs[b]		
Headache	6 (13.0)	4 (25.0)
Dermatitis atopic	6 (13.0)	2 (12.5)
Nasopharyngitis	4 (8.7)	2 (12.5)
Upper respiratory tract 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 3**)
  - Drug versus placebo trended on significance at Day 71 for both markers

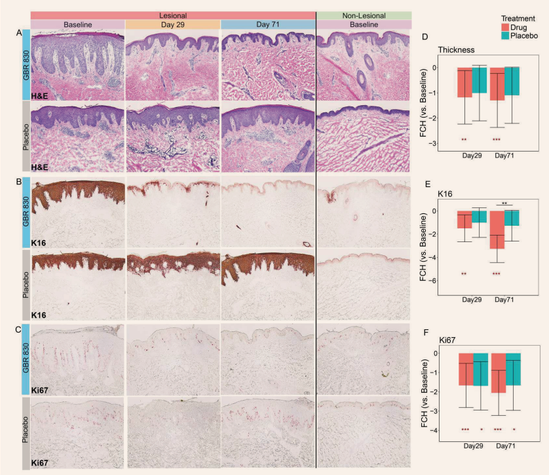
Figure 3. OX40 Target Expression From Representative GBR 830- and Placebo-Treated Subjects



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.

- GBR 830-treated subjects had significant reductions from baseline in epidermal thickness (**Figure 4A, 4D**), K16 mRNA expression (**Figure 4B, 4E**), and Ki67⁺ cells at Days 29 and 71 (**Figure 4C, 4F**)
  - Changes from baseline with placebo were not significant (thickness, K16) or less pronounced (Ki67⁺)

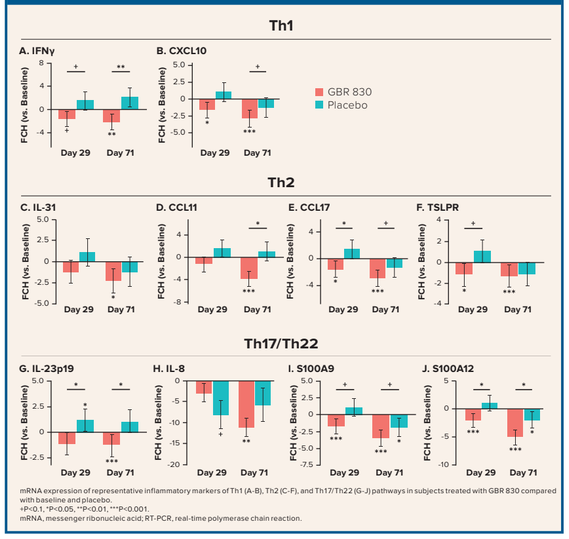
Figure 4. Epidermal Proliferation at Baseline and After Treatment



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.

- GBR 830-treated subjects had significant reductions in most mRNA biomarkers of disease activity compared with baseline and placebo (**Figure 5**)

Figure 5. Changes in Quantitative RT-PCR mRNA Expression Following Treatment

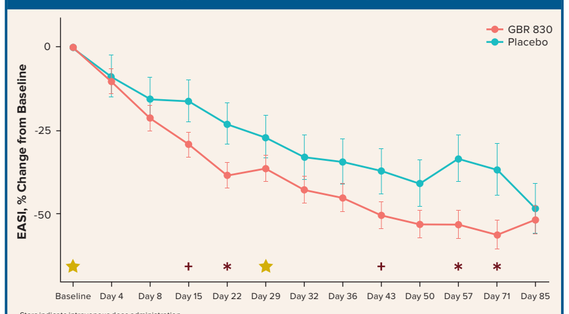


mRNA expression of representative inflammatory markers of Th1 (A-B), Th2 (C-F), and Th17/Th22 (G-J) pathways in subjects treated with GBR 830 compared with baseline and placebo.
+P<0.1, *P<0.05, **P<0.01, ***P<0.001.
mRNA, messenger ribonucleic acid; RT-PCR, real-time polymerase chain reaction.

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)
- GBR 830-treated subjects demonstrated greater percentage change in EASI from baseline through Day 85 compared with placebo (**Figure 6**)
- A positive association was seen between improvements in clinical assessments and changes in tissue AD biomarkers

Figure 6. Percentage Change in EASI from Baseline Through Day 85 (ITT Population)



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

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DISCLOSURES

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