RESULTS FROM A PHASE 2A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, EXPLORATORY, MULTICENTER STUDY OF GBR 830 IN ADULT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

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ABSTRACT

Background

GBR 830 is an investigational, first-in-class, humanized, monoclonal IgG1 antibody specific for inhibiting OX40, a costimulatory receptor on activated T cells. By blocking the binding of OX40 to its ligand OX40L, GBR 830 reduces longevity and efficacy of effector and memory T cells. This mechanism gives GBR 830 the potential to treat T cell-mediated autoimmune diseases, including atopic dermatitis (AD).

Objectives

To investigate the effects of GBR 830 on AD biomarkers and generate the first clinical evidence of its biological activity.

Methods

In this study (NCT02683928), 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 and Day 29) or placebo. Forty subjects had evaluable skin biopsies at baseline, 39 at Day 29 (GBR 830=28; placebo=11), and 29 at Day 71 (GBR 830=22; placebo=7). Primary endpoints were treatment-emergent adverse events (TEAEs) and change from baseline in gene expression signatures of key Th2, Th22, Th17, and Th1 immune pathway biomarkers from skin biopsies. Secondary endpoints included EASI 50 and EASI 75 response (≥50% or ≥75% score reduction from baseline, respectively) and IGA response (score of 0 [clear] or 1 [almost clear]).

Results

Demographics and baseline disease characteristics were generally similar between treatment groups. Approximately one-half of subjects in both groups completed the study. 63% (39/62) of AD subjects had ≥1 TEAE; headache was the most common TEAE (GBR 830=13%; placebo=25%). A greater proportion of subjects achieved an EASI response with GBR 830 vs placebo: EASI 50 (Day 29: 43.6% vs 20.0%; Day 71: 76.9% vs 37.5% [p=0.04]); EASI 75 (Day 29: 12.8% vs 6.7%; Day 71: 42.3% vs 25.0%). The proportion of subjects with IGA response was also greater with GBR 830 vs placebo (Day 29: 5.1% vs 0%; Day 71: 23.1% vs 12.5%). A decline in epidermal hyperplasia measures and mRNA expression of key Th2, Th22, and Th1 skin biomarkers was observed in the GBR 830 group throughout the study period. A positive association was seen between improvements in clinical assessments and changes in tissue AD biomarkers.

Conclusions

GBR 830 was generally well tolerated in adults with moderate-to-severe AD. Clinically meaningful and sustained improvement of AD symptoms were found following GBR 830 treatment through Day 71, with consistency between molecular and clinical responses.

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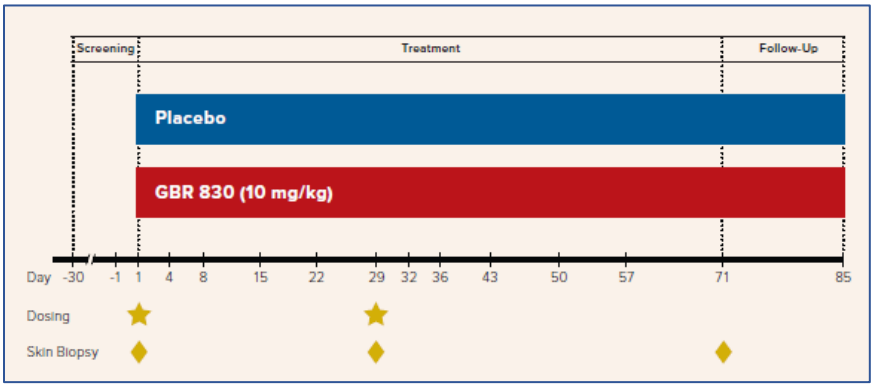
KEY FINDINGS

STUDY DESIGN

- Randomized, double-blind, placebo-controlled, repeated-dose study conducted in 17 centers in North America **(Figure 1)**
- Included adults with moderate-to-severe atopic dermatitis (AD) for >1 year
- Subjects randomized 3:1 to GBR 830 or placebo and received 2 repeated doses (each 10 mg/kg, administered intravenously) on Days 1 and 29 with a follow-up phase of 56 days

Figure 1. Study Design



RESULTS

Subjects

- Intent-to-treat (ITT) population: all 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): 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 **(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, no. (%)				
Male	21 (45.7)	11 (68.8)	16 (55)	8 (73)
Female	25 (54.3)	5 (31.2)	13 (45)	3 (27)
Race, no. (%)				
Asian	5 (10.9)	2 (12.5)	4 (14)	2 (18)
Black or African American	9 (19.6)	3 (18.7)	5 (17)	1 (9)
White	31 (67.4)	11 (68.8)	19 (66)	8 (73)
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)

BAS, Biological Activity Set; BSA, body surface area; EASI, Eczema Area and Severity Index; ITT, Intent-to-treat; SD, standard deviation.

KEY FINDINGS

Adverse Events

- TEAEs occurred with similar incidence between treatment groups **(Table 2)**
- The most commonly reported TEAE was headache, with no clinically meaningful difference between GBR 830 and placebo

Table 2. Treatment-Emergent Adverse Events

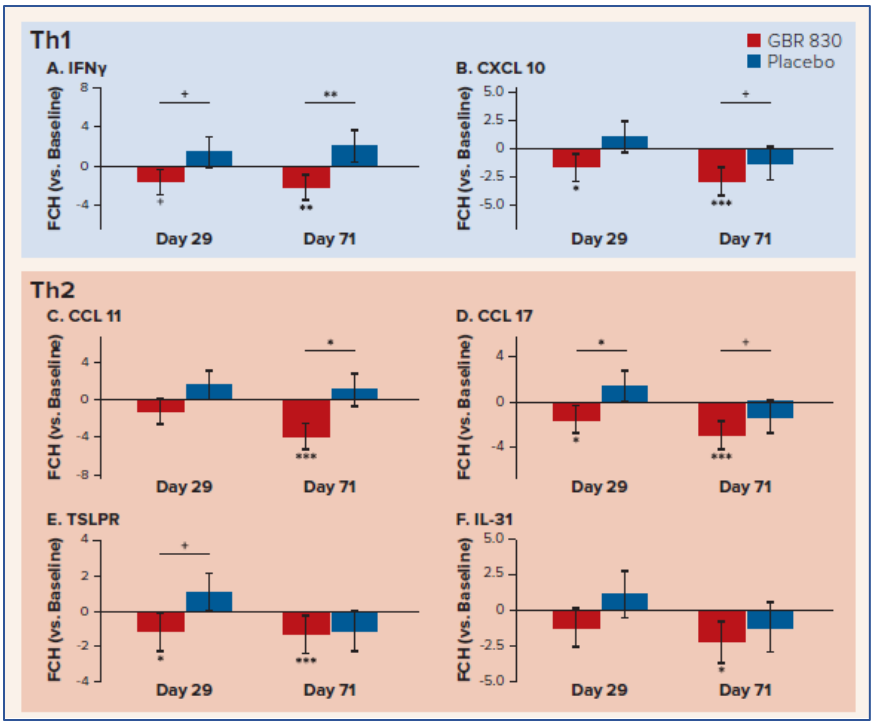
Adverse Events, n (%)	GBR 830 (n = 46)	Placebo (n = 16)
Deaths	0	0
Any TEAE	29 (63.0)	10 (63.0)
Any serious AE	1 (2.2)[a]	0
Discontinuation due to AEs	2 (4.3)	1 (6.3)
Common TEAEs[b]		
Headache	6 (13.0)	4 (25.0)
Dermatitis atopic	6 (13.0)	2 (12.5)
Nasopharyngitis	4 (8.7)	2 (12.5)
Upper respiratory tract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

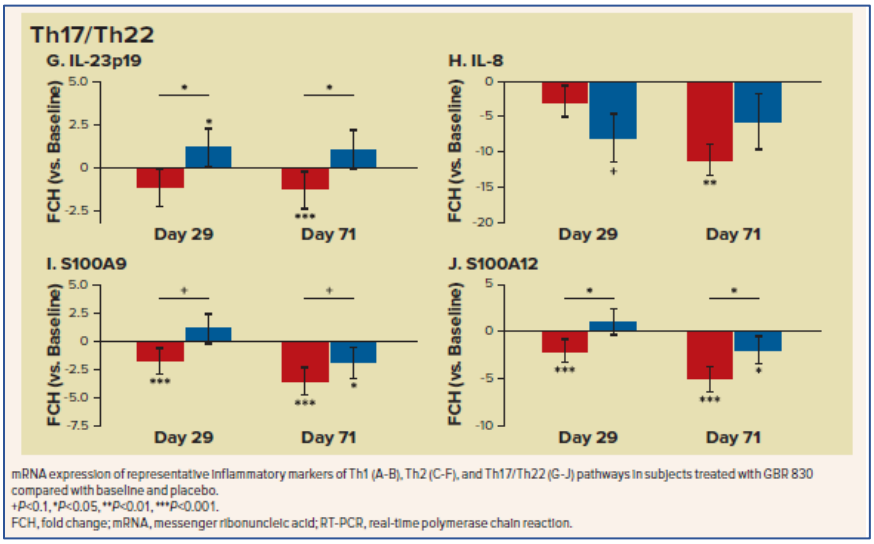
Biomarker Signatures

- GBR 830-treated patients had significant reductions in mRNA biomarkers of disease activity compared with baseline and placebo **(Figure 2)**

Figure 2. Changes in Quantitative RT-PCR mRNA Expressions Following Treatment



KEY FINDINGS



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.
FCH, fold change; mRNA, messenger ribonucleic acid; RT-PCR, real-time polymerase chain reaction.

Clinical Efficacy

- At Days 29 and 71 in the ITT and BAS populations, a greater proportion of subjects achieved an EASI or IGA response with GBR 830 versus placebo **(Table 3)**

Table 3. Clinical Outcomes

	ITT		BAS	
Response, n/N (%)	GBR 830	Placebo	GBR 830	Placebo
EASI 50 (≥50% score reduction from baseline)				
Day 29	17/39 (43.6)	3/15 (20.0)	15/29 (51.7)	3/11 (27.3)
Day 71	20/26 (76.9)	3/8 (37.5)	18/24 (75.0)	3/7 (42.9)
EASI 75 (≥75% score reduction from baseline)				
Day 29	5/39 (12.8)	1/15 (6.7)	4/29 (13.8)	1/11 (9.1)
Day 71	11/26(42.3)	2/8 (25.0)	10/24 (41.7)	2/7 (28.6)
IGA response (score of 0 or 1)				
Day 29	2/39 (5.1)	0	2/29 (6.9)	0
Day 71	6/26 (23.1)	1/8 (12.5)	6/24 (25.0)	1/7 (14.3)

BAS, Biological Activity Set; EASI, Eczema Area and Severity Index; IGA, Investigator's global assessment (5-point scale); ITT, Intent-to-treat; n, number of subjects who met response criterion; N, number of subjects with non-missing values at the study visit.

CONCLUSIONS

- GBR 830 was safe and well tolerated, with a similar TEAE profile to placebo
- Treatment with GBR 830 resulted in a reduction in 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 demonstrated sustained and clinically meaningful improvement in AD symptoms that were consistent with the biomarker results
- Results of this proof-of-concept study suggest that GBR 830 may be an effective treatment for AD