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

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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.

By blocking binding of OX40 to its ligand OX40L, GBR 830 reduces longevity and efficacy of effector and memory T cells.

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.

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 Day 29), follow-up (through Day 85) (Figure 1).

Treatment: randomization 3:1 to GBR 830 or placebo; 2 repeated doses (each 10 mg/kg). Subjects received study drug intravenously on Days 1 and 29.

Skin punch biopsies: obtained from lesional skin on Days 1, 29, and 71.

RESULTS

Subjects

ITT Tolerability 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.

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

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

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)

<table>
<thead>
<tr>
<th>Event</th>
<th>GBR 830 (n=29)</th>
<th>Placebo (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any TEAEs</td>
<td>29 (100%)</td>
<td>10 (90.9%)</td>
</tr>
<tr>
<td>Discontinuation due to TEAEs</td>
<td>2 (7.1%)</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>Common TEAEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>headache</td>
<td>6 (21.4%)</td>
<td>4 (36.4%)</td>
</tr>
<tr>
<td>dermatitis atopic</td>
<td>4 (13.8%)</td>
<td>3 (27.3%)</td>
</tr>
<tr>
<td>skin infection</td>
<td>1 (3.4%)</td>
<td>0</td>
</tr>
<tr>
<td>nasopharyngitis</td>
<td>4 (13.8%)</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>upper respiratory tract infection</td>
<td>4 (13.8%)</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (13.8%)</td>
<td>0</td>
</tr>
<tr>
<td>hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypothyroid</td>
<td>3 (10.3%)</td>
<td>0</td>
</tr>
</tbody>
</table>

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).

GBR 830-treated subjects had significant reductions in most 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 placebo (Figure 4).

GBR 830-treated subjects had significant reductions from baseline in epidermal thickness (Figure 4A, 4D); K16 mRNA expression (Figure 4B, 4E), and K67+ cells at Days 29 and 71 (Figure 4C, 4F).

Th1/Th2

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

Clinical Efficacy (ITT Population)

A greater proportion of GBR 830-treated subjects achieved EASI 50 versus placebo at Day 26 (43.6% vs 20.0%; p=0.02) 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)

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.

REFERENCES

4. Prescott Medical Communications Group, Chicago, IL.

DISCLOSURES

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