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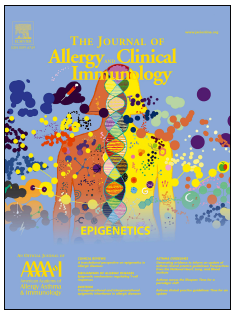


GBR 830, an anti-OX40, improves skin gene-signatures and clinical scores in atopic dermatitis

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# GBR 830, an anti-OX40, improves skin gene-signatures and clinical scores in atopic dermatitis

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**On behalf of the GBR 830 in AD study team*

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ABSTRACT

Background

GBR 830 is a humanized, monoclonal antibody against OX40, a co-stimulatory receptor on activated T-cells. OX40 inhibition may have a therapeutic role in T-cell-mediated diseases, including atopic dermatitis (AD).

Objective

This exploratory phase 2a study investigated safety, efficacy, and tissue effects of GBR 830 in AD.

Methods

Moderate-to-severe AD subjects (affected body-surface area ≥10%, Eczema Area and Severity Index [EASI] ≥12, inadequate response to topical treatments) were randomized 3:1 to intravenous GBR 830 10 mg/kg or placebo on Day 1/baseline and Day 29. Biopsies were collected (n=40) at Days 1, 29, and 71. Primary endpoints included treatment-emergent adverse events (TEAEs) and changes from baseline in biomarkers (epidermal hyperplasia/cytokines) at Days 29 and 71.

Results

GBR 830 was well-tolerated, with equal TEAE distribution (GBR 830, 63.0% [29/46]; placebo, 63.0% [10/16]). One serious TEAE in the GBR 830 group was deemed unrelated to study drug. At Day 71, the proportion of intent-to-treat subjects achieving ≥50% improvement in EASI was higher with GBR 830 (76.9% [20/26]) versus placebo (37.5% [3/8]). GBR 830 induced significant, progressive reductions in Th1 (IFNγ/CXCL10), Th2 (IL-31/CCL11/CCL17), and Th17/Th22 (IL-23p19/IL-8/S100A12) mRNA in lesional skin. Significant, progressive reductions until Day 71 in the drug-group were seen in OX40+ T-cells and OX40L+ dendritic

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cells ($p<0.001$). Hyperplasia measures (thickness/K16/Ki67) showed higher reductions with GBR 830 ($p<0.001$).

Conclusions

Two doses of GBR 830, 4-weeks apart, were well-tolerated and induced significant, progressive tissue and clinical changes until Day 71 (42 days after last dose), highlighting the potential of OX40-targeting in AD.

## CLINICAL IMPLICATIONS

Inhibition of the co-stimulatory OX40 molecule appears to have improvements on lesional skin pathology and clinical disease activity parameters in patients with moderate-to-severe atopic dermatitis, suggesting its therapeutic potential in this disease.

## CAPSULE SUMMARY

This proof-of-concept study with GBR 830, an OX40 antagonist, has generated the first evidence of the potential pathogenic role of OX40 in AD and of the emerging therapeutic potential of anti-OX40 targeting strategies in moderate-to-severe AD.

## KEY WORDS

Atopic dermatitis, inflammation, hyperplasia, OX40, co-stimulation, trial, Th1, Th2, Th17/Th22, biomarkers.

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Abbreviations:

AD = atopic dermatitis

DC = dendritic cells

AE = adverse event

BAS = Biological Activity Set

BSA = body surface area

DLQI = Dermatology Life Quality Index

EASI = Eczema Area and Severity Index

FCH = fold change

IGA = investigator's global assessment

IL = interleukin

ITT = intent-to-treat

mRNA = messenger ribonucleic acid

NRS = Pruritus Numerical Rating Scale

RT-PCR = real-time polymerase chain reaction

SCORAD = SCORing Atopic Dermatitis

TEAE = treatment-emergent adverse event

Th = T-helper cell

TNFR = tumor necrosis factor receptor

TSLP = thymic stromal lymphopoietin

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## INTRODUCTION

Atopic dermatitis (AD) is one of the most common inflammatory skin disorders with a similar prevalence in children, adolescents, and young adults.[1] Conventional treatment and management options for patients with moderate-to-severe disease, who constitute approximately 20% of the overall AD patient population, include topical corticosteroids and calcineurin inhibitors, phototherapy, systemic immune-suppressants, topical and systemic antihistamines and antibiotics to treat superinfections, emollients, and avoidance of certain triggers.[2-7] Most patients can be managed by conventional intervention, but for those who require systemic immunosuppressive therapies, many of the available treatments have limited efficacy or harbor significant long-term toxicity, and are therefore not appropriate for continuous use.[6-11] Moreover, most are intended for symptomatic relief and are not designed to target specific pathways underlying disease biology.[12, 13]

Emerging, narrow-targeting agents blocking specific cytokines/cytokine receptors have shown significant clinical benefit in AD, paving the way for safer therapeutic approaches.[14-20] Dupilumab, a specific Th2 antagonist recently approved by the Food and Drug Administration for AD, provided evidence for the pathogenic role of Th2 inflammation in AD.[14, 15] In phase 3 trials of AD, treatment response with biweekly or once-weekly dupilumab was 36-38%, based on the primary endpoint defined as an Investigator's Global Assessment (IGA) score of 0 or 1 (clear or almost clear).[15] Although statistically significant versus placebo, these results did not reach the levels of response found in psoriasis, where more than 50% of patients achieve Psoriasis Area Severity Index 100 with novel therapies.[21] Furthermore, to maintain clinical benefit, dupilumab necessitates administration every two weeks.[14, 15] Thus, a large unmet need

still exists for therapeutics that can provide better and/or more durable therapeutic responses in moderate-to-severe AD patients.

OX40 (CD134), a co-stimulatory molecule of the tumor necrosis factor receptor/tumor necrosis factor superfamily (TNFR/TNFSF), is predominantly expressed on T-cells, including effector cells and Foxp3$^{+}$ regulatory T-cells (Tregs),[22] 24 to 72 hours following activation. Its ligand, OX40L (CD252), is expressed on activated antigen presenting cells (APCs), including dendritic cells (DCs) and endothelial cells. OX40-OX40L engagement is key to potentiate T-cell responses triggered through the T-cell receptor (TCR), including: (I) expansion of effector T-cells and prolongation of their survival by suppressing apoptosis; (II) promoting and sustaining CD4+ T-cell memory; (III) facilitating adhesion and migration; and (IV) enhancing T-cell effector functions, such as cytokine production.[23, 24]

In autoimmunity, upregulation of OX40-OX40L plays a critical multi-functional role in disruption of T-cell tolerance by increasing cell survival and suppressing apoptosis, increasing cell proliferation, and amplifying cytokine production.[23-25] The OX40-OX40L interaction bridges Th2 and Th1 pathways by inducing interferon gamma secretion and causing otherwise harmless autoreactive T-cells to acquire effector T-cell function.[26, 27] In this context, stimulation of OX40 on the Foxp3+ Tregs impaired their suppressor functions.[28-30]

In AD, OX40L+ DCs are highly increased compared with psoriatic and normal skin, with greater expression of OX40 in AD lesions.[31-34] Moreover, OX40 is usually upregulated at sites of inflammation, especially on infiltrating lymphocytes and on peripheral circulating lymphocytes.

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GBR 830 is an investigational, first-in-class, humanized monoclonal IgG1 antibody specific for inhibiting OX40 to treat autoimmune and chronic inflammatory disorders (Fig 1). In previous healthy volunteer studies, GBR 830 was well tolerated after single and multiple dose-escalating intravenous (IV) administration of up to 20 mg/kg and 40 mg/kg, respectively.[35] In this first-in-patient, proof-of-concept study, we show that two IV administrations of GBR 830 10 mg/kg 4 weeks apart to adult subjects with moderate-to severe AD, were safe and well tolerated. Moreover, analysis of lesional skin showed a decline in messenger ribonucleic acid (mRNA) of Th1, Th2, and Th17/22 biomarkers for disease activity and epidermal pathology indicating an effect of GBR 830 on both acute and chronic stages of AD.

## METHODS

### Study design

This was a phase 2a, randomized, double-blind, placebo-controlled, repeated dose study (NCT02683928), conducted in 17 centers in US/Canada from March 2016 to June 2017 to evaluate safety and biological activity of GBR 830 in adult subjects with moderate-to-severe AD. The study protocol and informed consent were approved by local institutional review boards. The study was conducted in accordance with Good Clinical Practice[36] and the Declaration of Helsinki[37] and all subjects provided written informed consent prior to entering the study. The study consisted of a screening phase (up to 30 days) followed by treatment (Day 1 [baseline] and Day 29) and follow-up (through Day 85).

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*Participants*

Adult subjects (≥18 years) with moderate-to-severe AD who met the following criteria were included in the study: physician diagnosis of moderate-to-severe atopic dermatitis for >1 year; affected body surface area (BSA) ≥10%; Eczema Area and Severity Index (EASI[38]) score ≥12; Scoring of Atopic Dermatitis (SCORAD[39]) ≥20; investigator's global assessment (IGA[40]) score ≥3 (5-point scale); and history of inadequate response, defined as a failure to achieve and/or maintain remission, or low disease activity to a stable regimen (>1 month) of class ≥3 strength topical corticosteroids or calcineurin inhibitors, or patients for whom topical treatments are otherwise inadvisable (e.g., because of important side effects or safety risks). Exclusion criteria are detailed in the Online Repository.

Randomization, treatment, and blinding

Eligible subjects were randomized 3:1 to receive intravenous GBR 830 (10 mg/kg) or corresponding placebo using a computer-generated scheme reviewed and approved by an independent statistician. Subjects received two intravenous infusions of GBR 830 or placebo on Days 1 and 29 (Fig 2). Subjects were closely monitored at the sites for 6 hours after the first infusion and for 3 hours after the Day 29 dose. Study drugs were identical in appearance.

Study endpoints

Primary endpoints included treatment-emergent adverse events (TEAEs) and change from baseline in epidermal hyperplasia and in the active AD mRNA expression signature, measured from lesional skin biopsies. Secondary endpoints included: percent improvement from baseline in SCORAD, IGA, BSA, EASI score; EASI50 and EASI75 responses, defined as ≥50% and

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≥75% score improvements from baseline, respectively; and IGA scores of 0 or 1. Pruritus Numerical Rating Scale (NRS) and Dermatology Life Quality Index (DLQI) changes from baseline to each visit were also assessed. Safety assessments included vital signs, physical examinations, laboratory evaluations, and electrocardiograms.

Statistical analyses

This study was not powered to detect differences between treatment groups. Clinical efficacy was analyzed in the intent-to-treat (ITT) population, defined as all randomized subjects who received ≥1 partial or full study treatment dose. Biomarker analyses of disease activity obtained from skin biopsies were based on the Biological Activity Set (BAS) population, which consisted of ITT subjects who received both doses of study drug and provided one baseline and ≥1 post-baseline skin biopsy. The safety population included all subjects with ≥1 partial or full study treatment dose. The number of samples at different time points for each population is detailed in Table E1. Percent changes in the severity scores (SCORAD) of the ITT subjects were estimated over time using a mixed model repeated measure (MMRM) approach, with Time and Treatment as fixed factors and a random intercept for each subject. Additional information about exclusion criteria and sample size calculation are provided in the Online Repository.

Statistical differences were calculated for post- versus pre-treatment (baseline) differences in lesional skin within each treatment arm, as well for pre- and post- GBR 830 versus placebo treatment (drug effect). Fold-changes from baseline are represented as bar graphs. Significance for both types of analyses is indicated by the following symbols: +$P$<0.1 (trend), *$P$<0.05, **$P$<0.01, ***$P$<0.001.

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219 Biomarker analysis of skin biopsies

220 Baseline biopsies (Day 1) were obtained prior to the first dose, then bisected for
221 immunohistochemistry and gene expression studies. Immunohistochemistry staining was
222 performed on frozen sections using purified mouse anti-human monoclonal antibodies (Table E2
223 in Online Repository).[41, 42] Epidermal thickness and cell counts were quantified with ImageJ
224 V1.42 (National Institutes of Health, Bethesda, MD). RNA was extracted and quantitative real-
225 time polymerase chain reaction (RT-PCR)[41] was used to assess mRNA expression (primers are
226 listed in Table E3). Immunohistochemistry and RT-PCR data in the BAS population were log2-
227 transformed prior to statistical analysis. To account for missing data points between baseline and
228 end of treatment, data was analyzed using a linear mixed effect model with Time, Tissue, and
229 Treatment as fixed factors and a random intercept for each subject. Hypothesis testing was
230 conducted with contrasts under the general framework for linear models in the R *nlme* package.
231 Results are presented as fold changes (FCHs) between post-treatment biopsy timepoints (Day 29
232 and 71) and baseline (Day 1). See the Online Repository for additional details.

233

234 RESULTS

235 Demographics and baseline characteristics

236 A total of 64 eligible AD subjects were randomized in a 3:1 ratio to receive either GBR 830
237 or corresponding placebo. Two subjects assigned to GBR 830 withdrew informed consent prior
238 to dosing. Therefore, only 62 subjects received treatment: GBR 830, n=46; placebo, n=16
239 (ITT; Fig 2). 40 AD subjects in the ITT population completed treatment and provided at least
240 2 biopsies: one at Day 1 before treatment (baseline) and at least another one after treatment

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(Day 29 or 71). Those 40 subjects who received two treatments and provided a biopsy (before and once after treatment) formed the Biological Activity Set (BAS: GBR 830, n=29; placebo, n=11). Demographic characteristics were generally similar between treatment groups in both the ITT and the BAS population (Table I). Analysis of baseline disease characteristics showed similarity between placebo and GBR 830 subjects for EASI, SCORAD, and NRS. GBR 830 subjects had higher baseline DLQI and IGA scores relative to placebo subjects (Table I).

Safety

Safety and tolerability were assessed in all subjects who received at least one dose of treatment (ITT, n=62). 62.9% of subjects experienced at least 1 TEAE, with similar incidence between treatment groups during the whole study period up to day 85 (Table II). The most commonly reported TEAE was headache, with no clinically meaningful differences between GBR 830 (13.0%) and placebo (25.0%). Four subjects in the GBR 830 group had a TEAE of post-procedural infection, which included 1 subject with infection after tooth extraction and 3 subjects with a secondary infection at the biopsy site. Most TEAEs were mild or moderate in intensity. The average time to TEAE onset was 7.5 days after treatment initiation and the average TEAE duration was 12.5 days.

Two subjects (3.2% overall) had a severe TEAE: 1 (6.3%) in the placebo group with supraventricular tachycardia, and 1 (2.2%) in the GBR 830 group with a coronary artery occlusion that was also considered serious. This event was not judged by the Investigator as related to study treatment due to multiple pre-existing risk factors (see case report in the Online Repository for more details). Three subjects (4.8% overall) experienced a moderate TEAE which

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resulted in withdrawal of the study drug and subsequent discontinuation from the study: 1 (6.3%) in the placebo placebo group for swelling of the face, and 2 (4.3%) in the GBR 830 group for probable tooth abscess and disease worsening. Eight subjects (12.9% overall) experienced a TEAE that were considered related to study drug: 4 (25.0%) in the placebo group, and 4 (8.7%) in the GBR 830 group.

No deaths occurred. No clinically meaningful differences in laboratory values, vital signs, physical examinations, and electrocardiograms were noted, and data were similar between treatment groups. These data suggest that IV administration of GBR 830 four weeks apart was safe and well tolerated in this proof-of-concept study.

Biomarker analyses

*GBR 830 hits target and reduces OX40 and OX40L in lesional skin*

Changes with GBR 830 in the direct target OX40, and its corresponding ligand OX40L, were assessed in pre- and post-treatment lesional skin. As seen with representative GBR 830 and placebo subject images (Fig 3, A and B), significant decreases from baseline in $OX40^+$ T-cell and $OX40L^+$ DC cellular staining in lesional skin were only found with GBR 830 treatment at Day 29 ($p<0.05$) and Day 71 ($p<0.001$), with drug versus placebo trending on significance at Day 71 for both markers (Fig 3, C and D). These data suggest that GBR 830 successfully hits its target and inhibits the OX40-OX40L pathway.

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*GBR 830 reduces measures of epidermal hyperplasia and proliferation*

Changes in epidermal hyperplasia were measured via epidermal thickness of hematoxylin and eosin (H&E) sections (Fig 4, A and D) and immunohistochemistry for two measures of epidermal proliferation, keratin 16 (K16; Fig 4B) and Ki67 (Fig 4, C and F). K16 mRNA expression was evaluated using RT-PCR (Fig 4E). Representative subject images are shown in Fig 4, A-C. Subjects treated with GBR 830 demonstrated significant reductions from baseline in epidermal thickness at Day 29 ($p<0.01$) and Day 71 ($p<0.001$), with no significant changes in placebo-treated subjects (Fig 4D). K16 mRNA expression was significantly reduced from baseline at Days 29 and 71 ($p<0.01$ for both) in GBR 830-treated subjects only (Fig 4E), with a significant difference between GBR 830 and placebo at Day 71 ($p<0.01$). Larger, more significant reductions in $Ki67^+$ cells were seen in GBR 830-treated group, as compared to placebo at both Day 29 and Day 71 ($p<0.001$ in drug and $p<0.05$ in placebo; Fig 4F). Overall, the significant changes in measures of epidermal hyperplasia with drug suggest that GBR 830 has beneficial effects on ameliorating the AD-associated epidermal pathology.

*OX40 blockade modulates expression of polar immune mediators*

Expression of a selected number of immune genes previously linked with disease pathogenesis and/or upregulated in AD were measured via RT-PCR (Fig 5, Fig E1).[8, 9, 43-47] The Th1 axis genes were significantly modulated only by GBR 830, which induced downregulation of IFNγ at Day 29 (trend toward significance) and 71 ($p<0.01$ versus baseline), while upregulations were seen in placebo (Fig 5A; $p<0.01$ at Day 71 for drug versus placebo). GBR 830 also significantly modulated the IFNγ-induced chemokine CXCL10 at Days 29 and 71 ($p<0.05$ and $p<0.001$ versus

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baseline, respectively), with results approaching significance for GBR 830 compared to placebo at Day 71 (Fig 5B).

Additionally, GBR 830 induced progressive, significant downregulation at both days (with $p<0.001$ at Day 71) of several key Th2 markers including IL-31 and Th2-attracting chemokines, (CCL11, CCL17, and TSLPR; Fig 5C-F), with significance achieved versus placebo ($p<0.05$) in CCL11 at Day 71 (Fig 5D) and in CCL17 at Day 29 (Fig 5E), with a trend toward significance versus placebo in CCL17 at Day 71 (Fig 5E). In fact, upregulations in these markers were seen with placebo at Day 29 and in CCL11 also at Day 71, with smaller and non-significant reductions in placebo-arm in IL-31 and CCL17 at Day 71. GBR 830 also induced significant downregulations of Th17/Th22-related genes, including IL-23p19, IL-8, and S100As (Fig 5G-J). GBR 830 induced significant, progressive down-regulations towards Day 71 of these markers, with significance versus baseline ($p<0.001$) at both days for the IL-17/IL-22-regulated S100A9/S100A12[45, 48] and at Day 71 for IL-23p19 and IL-8, with significance or trending towards significance versus placebo at both timepoints for all markers but IL-8 (Fig 5G-J). Of note, primary Th2 cytokines (IL-4 and IL-13) and Th17/Th22 cytokines (IL-17 and IL-22) were not significantly modulated with GBR 830 compared with placebo (Fig E1). Overall, significant and progressive differences were found between GBR 830 and placebo treatments in several Th1 (IFN), Th2 (CCL11, CCL17), and Th17/Th22 measures (S100A12).

*Clinical efficacy*

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The clinical effects of GBR 830 were assessed in all subjects who received treatment (ITT population). Changes in disease activity over time (SCORAD, IGA, BSA, DLQI, NRS, and EASI) were analyzed by descriptive assessment during the treatment period of Day 1 up to Day 71. During this time, two doses of GBR 830 or corresponding placebo were given on Day 1 and Day 29. As compared to baseline, there was a gradual and continuous improvement in EASI score starting at Day 4 (Fig 6A), including for subjects with severe disease at baseline, defined as having SCORAD >50 (Fig 6B). Interestingly, beginning with Day 15 there was a continuous and consistent separation between placebo and GBR 830, showing a greater decline in EASI score for GBR 830-treated subjects compared to placebo-treated subjects (Fig 6A). This greater decline in EASI score first reached a maximum 22 days after the first dose ($p<0.05$), with a second maximum starting at Day 57 and maintained until Day 71 ($p<0.05$), the last treatment period day of taking skin biopsies. At Day 71, the percentage change from baseline indicated greater mean improvement with GBR 830 relative to placebo (56% and 38%, respectively). EASI scores between GBR 830 and placebo showed even greater separation through Day 71 in severe subjects (SCORAD >50) (Fig 6B). Subjects with the greatest improvement in EASI had the greatest improvement in IGA (data not shown).

Consistent with the improvement over time in EASI and SCORAD, categorical measurements of IGA showed greater improvement in GBR 830-treated subjects compared to placebo (Table E4). The number of subjects with IGA response (score of 0 or 1) at Day 71 was 6/26 (23.1%) for GBR 830 compared to 1/8 (12.5%) for placebo. Notably, the proportion of subjects with severe/very severe IGA at baseline was higher in the GBR 830 group (20/46; 43.5%) compared to placebo (5/16; 31.2%). This finding is in line with the observation that EASI improvement

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in subjects with severe disease at baseline (SCORAD >50) may benefit more compared to the ITT population.

Higher proportions of GBR 830-treated subjects achieved EASI50 and EASI75 over time as compared to placebo (Online Repository, Tables E4 and E5). At Day 71 (final skin biopsy assessment visit), ITT response rates for GBR 830 (EASI50, 76.9% [20/26]; EASI75, 42.3% [11/26]) were higher than placebo response rates (EASI50, 37.5% [3/8]; EASI75, 25.0% [2/8]). All 5 subjects who achieved EASI75 at Day 29 maintained their improvement until Day 71.

Changes in SCORAD, BSA, and pruritis NRS showed small numerical improvement with very high variability, making these data difficult to interpret in the ITT population. This variability was slightly lower in the BAS population. However, comparison of the efficacy endpoints between ITT and BAS population showed similarity in outcome measures between both populations (Online Repository, Tables E4 and E5).

## DISCUSSION

This proof-of-concept study is the first clinical trial targeting a co-stimulatory molecule of immune regulation to treat moderate-to-severe AD patients. The current report also provides the first evidence for the pathogenic role of the OX40 pathway in AD. The administration of two IV doses of the anti-OX40 antibody GBR 830, 4 weeks apart, induced significant and progressive improvements in clinical severity scores and in the cutaneous molecular AD signature lasting until Day 71.

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While progressive clinical improvements were observed with GBR 830, the study was not powered to detect clinical efficacy, but rather was designed primarily as a safety and mechanistic biomarker study. Two IV doses of GBR 830, administered 4 weeks apart, were well tolerated and showed an acceptable safety profile, with no clinically meaningful differences as compared to placebo. Rates of post-procedural infections were low, and consistent with published reports of infection rates following diagnostic skin biopsies.[49, 50] These short-term findings support further research that includes longer trial durations and larger patient populations in order to establish safety and tolerability for long-term usage in moderate-to-severe AD. Further, population PK-based simulations suggest that subcutaneous (SC) injections of GBR 830—600 mg loading dose followed by biweekly 300 mg maintenance doses—would achieve and maintain steady-state concentrations with similar trough concentrations as those achieved in this proof-of-concept study, which would be expected to elicit clinical benefit in AD patients. To this end, a randomized placebo-controlled 16-week phase 2b study with different SC dosing regimens was recently initiated (NCT03568162).

The similar distribution of TEAEs between GBR 830 and placebo in our study is in line with other early clinical development studies that have examined the inhibition of the OX40-OX40L axis (or its main inducer TSLP) in autoimmune and chronic inflammatory diseases such as asthma and psoriasis.[51-53] In this respect, OX40 is a potential target of interest for immunology and oncology, with ongoing research exploring both agonistic and antagonistic anti-OX40 antibodies.[54-59] In a first in-patient study receiving a single cycle with an agonistic anti-human OX40 monoclonal antibody, anti-OX40 treatment was well tolerated and the maximum tolerated dose was not reached.[54]

Inhibition of the OX40 pathway with GBR 830 has led to significant and progressive decreases in $OX40^+$ T-cells as well as to changes in $OX40L^+$ DCs that mark the "atopic DCs" in lesional skin.[31, 60] This indicates that GBR 830 modulates the OX40-OX40L interaction, which is critical to the TSLP-mediated Th2 inflammation in atopic diseases.[9, 32, 61] In addition to the modulation of key Th2 measures (IL-31, CCL11, CCL17, and TSLPR), OX40 antagonism also inhibited other immune pathways, which are also upregulated in AD, including Th1 (IFNγ, CXCL10) and Th17/Th22 (IL-23p19, IL-8, S100As).[5, 6, 62, 63] This effect may have particular value in AD, addressing the plasticity and diversity of disease endotypes.[63] Furthermore, several subtypes, such as intrinsic, Asian, pediatric, and $filaggrin^+$ AD subcategories were shown to have differential upregulations in Th17/Th22 or Th1 axes.[32-34, 64] Thus, Th1 and Th17/22 modulation in addition to Th2 may provide broader and/or more sustained therapeutic benefit. Interestingly, GBR 830 did not have significant impact on mRNA expressions of the key Th2 cytokines (IL-4, IL-13), similar to dupilumab,[16] and also did not show differential effects compared to placebo on the IL-22 and IL-17 cytokines. The observed clinical improvement was accompanied by significant improvements persisting up to Day 71 in hyperplasia measures (K16, Ki67, epidermal thickness) in lesional skin of GBR 830-treated AD subjects, consistent with previous studies showing that clinical reversal by effective therapeutic intervention is also associated with improvement in the pathological epidermal hyperplasia characterizing active AD lesions.[16, 65, 66] To evaluate the possible suppression of immune pathways, longer-term studies that examine changes in inflammatory cell parameters and cytokines in blood are needed, particularly with respect to treatment effects on Tregs. Since OX40L is present on Tregs, the OX40L-OX40 pathway may have additional immunoregulatory effects.[28, 30]

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The results of this study demonstrate for the first time in a clinical setting that targeting OX40 leads to downregulation of members of both the Th1 and Th2 dysregulated pathways and that these effects are associated with clinical improvement. Involvement of OX40-OX40L interaction has been demonstrated in several inflammatory conditions associated with atopy (ie, asthma, allergic rhinitis, and allergic conjunctivitis).[67, 68] In preclinical in vivo mouse and non-human primate models of skin inflammation and asthma, blockade of OX40L significantly reduced the extent of Th2-mediated inflammation.[61] Anti-OX40L antibodies also blocked TSLP-induced inflammation in the skin, as measured by decreased ear swelling responses and decreased cytokine mRNA expression levels (IL-4, IL-5, IL-13).[61] In addition, inhibition of OX40-mediated signaling was also shown to reduce inflammation and ameliorate the severity of autoimmunity in pre-clinical models of multiple sclerosis (experimental autoimmune encephalomyelitis), asthma, and arthritis.[69-71] In other inflammatory diseases such as ulcerative colitis, OX40-OX40L has also been demonstrated to be increased[72] and is now subject to clinical testing (NCT02985593, NCT02647866).

Per the primary objectives of this study, the safety and biomarker results suggest that larger clinical trials of GBR 830 are warranted. However, the efficacy results are considered preliminary and should be interpreted accordingly. Efficacy analyses were limited by the 3:1 (drug:placebo) randomization design and the planned sample size of approximately 40 subjects, which was largely based on the practical consideration of collecting multiple biopsy samples for each participant. The sample size was considered large to provide adequate descriptive analyses, but any observed significance for GBR 830 versus placebo needs further confirmation in larger

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clinical trials. Nevertheless, some parameters which show opposing trends for placebo and GBR 830 (e.g., Th1/IFNγ, Th17/IL-23p19, and Th2/CCL11 markers; significant improvements versus baseline in the active arm only) suggest that this novel drug will have demonstrable clinical effects in future studies.

One factor to consider when interpreting clinical results is the potential for placebo effect. Placebo effects have been seen with drugs proven to be clinically and/or mechanistically effective in AD, including dupilumab and IL-22 antagonism.[10, 14-17, 73, 74] Nevertheless, the magnitude of clinical response is higher with drug (when efficacious) compared to placebo. The placebo effect in AD studies may be due to multiple possible causes, including natural fluctuation in disease course and the use of emollients. In the current study, it is important to note that only 2 doses of GBR 830 were administered. Based on the available data, the placebo effect in this study seems to have been largely driven by dropouts in the placebo group. The potential of these dropouts to enhance placebo effects was amplified by the small sample size and the 3:1 randomization for drug to placebo.

In sum, targeting key switches of immune regulation, such as OX40, which regulates aberrant immune responses, may provide a novel therapeutic strategy for AD. Two doses of 4-weeks apart intravenous GBR 830 were safe, well-tolerated, and induced significant and progressive clinical improvements, paralleled by molecular and cellular effects until Day 71 (more than 42 days post treatment). GBR 830 may potentially provide a novel therapeutic paradigm for patients with moderate-to-severe AD.[5, 46] This first report that both the clinical and tissue disease pathology can be improved in an inflammatory human disease via OX40-targeting, coupled with

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466 the preclinical data of amelioration of inflammation through OX40-OX40L inhibition, has
467 extended implications far beyond the skin, to other atopic or autoimmune conditions.

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681 GBR 830 Study Team

682 The members of the GBR 830 in AD study team are William Abramovits, Afsaneh Alavi,
683 Neal Bathia, Suzanne Bruce, Seth Forman, Emma Guttman-Yassky, Michael Hassman,
684 Craig Leonardi, Charles Lynde, Catherine Maari, Adnan Nasir, Kim Papp, Howard Sofen,
685 Jeffrey Travers, and Stephen Tyring.

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686 FIGURE LEGENDS

687

688 Figure 1. GBR 830 inhibition of OX40-OX40L binding

689 Binding of the OX40L to the OX40 receptor on T cells potentiates inflammatory responses,
690 chronicity, and loss of tolerance. Inhibition of OX40L/OX40 binding by GBR 830 attenuates
691 these effects.

692

693 Figure 2. Study design and subject disposition

694 *Includes subjects who did not receive GBR 830 (n=2).

695 [a]Excludes subjects from the randomized population (GBR 830, n=2) who did not receive
696 ≥1 partial or full dose of study treatment.

697 [b]Excludes subjects from the ITT population (GBR 830, n=17; placebo, n=5) who did not receive
698 both doses of study drug and have ≥1 post-baseline skin biopsy (Day 29 or Day 71).

699 *ITT,* intent-to-treat.

700

701 Figure 3. Immunohistochemistry images of OX40 target from representative GBR 830- and
702 placebo-treated subjects

703 Immunohistochemistry staining of (A) OX40 and (B) OX40L at baseline and after treatment
704 (Day 29 and Day 71); protein expression is shown in red staining and the images in each line
705 were taken from the same subject. Mean fold change (FCH) from baseline in (C) OX40
706 expression and (D) OX40L expression. Symbols under the bar graphs indicate statistical
707 differences between post-treatment versus pre-treatment within each treatment arm. Symbols

above the bar graphs indicate significant differences between GBR 830 versus placebo for FCH. +*P*<0.1, **P*<0.05, ***P*<0.01, ****P*<0.001.

Figure 4. Immunohistochemistry images for representative drug and placebo subjects, at baseline and after treatment (A-C), and quantification of epidermal proliferation markers (D-F)
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. Symbols under the bar graphs indicate statistical differences between post-treatment versus pre-treatment within each treatment arm. Symbols above the bar graphs indicate significant differences between GBR 830 versus placebo for FCH. +*P*<0.1, **P*<0.05, ***P*<0.01, ****P*<0.001.
*H&E*, hematoxylin and eosin; *K16*, keratin 16; *RT-PCR*, real-time polymerase chain reaction.

Figure 5. Changes in quantitative RT-PCR mRNA expressions following treatment
Significant reductions in mRNA expressions of representative inflammatory markers of Th1 (A-B), Th2 (C-F), and Th17/Th22 (G-J) pathways were observed in subjects treated with GBR 830, as compared to baseline and also to placebo. Symbols under the bar graphs indicate statistical differences between post-treatment versus pre-treatment within each treatment arm. Symbols above the bar graphs indicate significant differences between GBR 830 versus placebo for FCH. +*P*<0.1, **P*<0.05, ***P*<0.01, ****P*<0.001.
*mRNA*, messenger ribonucleic acid; *RT-PCR*, real-time polymerase chain reaction.

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731 Figure 6. Percentage change in EASI from baseline through Day 85

732 In the ITT population (A) and severe subjects with SCORAD score >50 (B). Yellow stars

733 indicate intravenous dose administration.

734 Significance GBR 830 vs Placebo: +P<0.1, *P<0.05, **P<0.01

735 *EASI*, Eczema Area and Severity Index; *ITT*, intent-to-treat; SCORAD, Scoring of Atopic

736 Dermatitis.

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TABLES

Table I. Subject demographics and baseline disease characteristics (ITT and BAS population)

| | 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 (55.2) | 8 (72.7) |
| Female | 25 (54.3) | 5 (31.2) | 13 (44.8) | 3 (27.3) |
| Race, no. (%) | | | | |
| 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 |
| SCORAD | | | | |
| Mean ± SD | 61.8 ± 14.3 | 55.5 ± 10.4 | 61.6 ± 15.8 | 54.7 ± 10.8 |
| Median (min, max) | 61.0 (36.6, 94.4) | 56.4 (37.8, 81.1) | 59.9 (36.6, 94.4) | 54.0 (37.8, 81.1) |
| EASI | | | | |
| Mean ± SD | 25.1 ± 12.3 | 23.3 ± 9.4 | 25.4 ± 13.7 | 22.2 ± 9.6 |

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| | | | | |
|---|---|---|---|---|
| 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) |
| DLQI, mean ± SD | 14.5 ± 6.7 | 9.4 ± 5.7 | 14.6 ± 6.9 | 7.9 ± 5.1 |
| IGA, no. (%) | | | | |
| Moderate | 26 (56.5) | 11 (68.8) | 16 (55.2) | 8 (72.3) |
| Severe/very severe | 20 (43.5) | 5 (31.2) | 13 (44.8) | 3 (27.3) |
| Epidermal thickness, μm | | | | |
| Lesional | | | | |
| 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) |
| Non-lesional | | | | |
| 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) |
| Pruritus NRS, mean ± SD | 6.4 ± 2.5 | 4.1 ± 2.6 | 6.3 ± 2.2 | 4.3 ± 1.9 |

*BAS*, Biological Activity Set; *BSA*, body surface area; *DLQI*, Dermatology Life Quality Index; *EASI*, Eczema Area and Severity Index; *IGA*, investigator's global assessment (5-point scale); *ITT*, intent-to-treat; *NA*, not applicable; *NRS*, numeric rating scale; *SCORAD*, Scoring of Atopic Dermatitis; *SD*, standard deviation.

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Table II. Treatment-emergent adverse events reported in ≥5% of subjects in either treatment group

| TEAE by MedDRA preferred term, n (%) | GBR 830 (n = 46) | Placebo (n = 16) | Overall (n = 62) |
|---|---|---|---|
| Any TEAE | 29 (63.0) | 10 (63.0) | 39 (62.9) |
| Headache | 6 (13.0) | 4 (25.0) | 10 (16.1) |
| Dermatitis atopic | 6 (13.0) | 2 (12.5) | 8 (12.9) |
| Nasopharyngitis | 4 (8.7) | 2 (12.5) | 6 (9.7) |
| Upper respiratory tract infection | 4 (8.7) | 2 (12.5) | 6 (9.7) |
| Post-procedural infection | 4 (8.7) | 0 | 4 (6.5) |
| Fatigue | 2 (4.3) | 1 (6.3) | 3 (4.8) |
| Myalgia | 3 (6.5) | 0 | 3 (4.8) |
| Gastroenteritis | 0 | 2 (12.5) | 2 (4.8) |
| Insomnia | 0 | 2 (12.5) | 2 (4.8) |
| Pruritus | 0 | 2 (12.4) | 2 (4.8) |
| Tooth abscess | 1 (2.2) | 1 (6.3) | 2 (4.8) |
| Arthritis | 0 | 1 (6.3) | 1 (1.6) |
| Eczema | 0 | 1 (6.3) | 1 (1.6) |
| Laceration | 0 | 1 (6.3) | 1 (1.6) |
| Lice infestation | 0 | 1 (6.3) | 1 (1.6) |
| Supraventricular tachycardia | 0 | 1 (6.3) | 1 (1.6) |
| Syncope | 0 | 1 (6.3) | 1 (1.6) |
| Toothache | 0 | 1 (6.3) | 1 (1.6) |
| Swelling face | 0 | 1 (6.3) | 1 (1.6) |
| Asthma | 0 | 1 (6.3) | 1 (1.6) |

*MedDRA*, Medical Dictionary for Regulatory Activities; *TEAE*, treatment-emergent adverse event.

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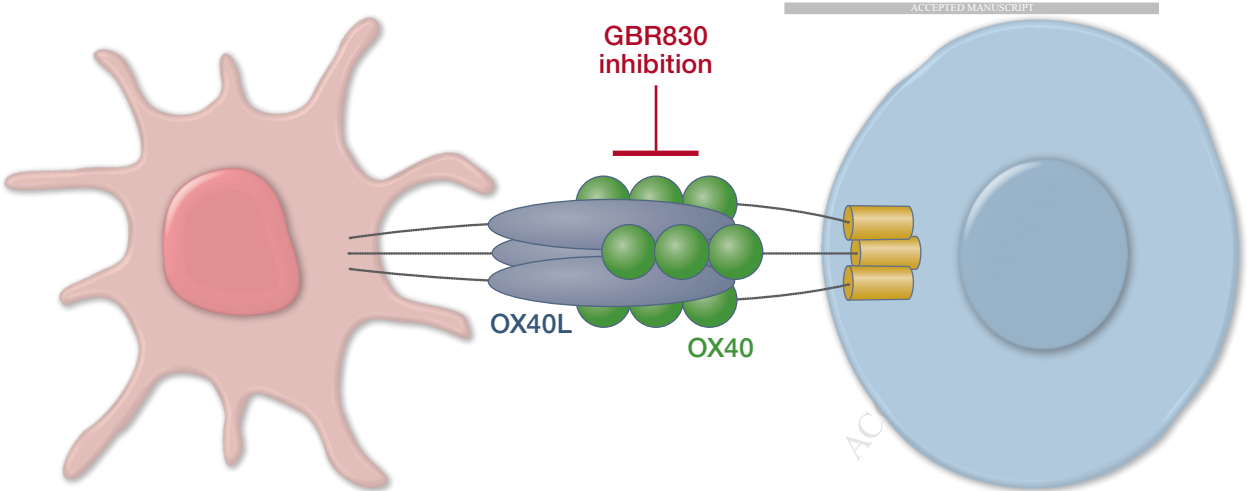


**OX40L/OX40 ligation potentiates T-cell responses**

| | |
|---|---|
| Migration; survival; proliferation; cytokine production | Th2, Th1, Th22, Th17 function |
| Memory differentiation | Chronicity |
| Decreased suppressive function? | Loss of tolerance |

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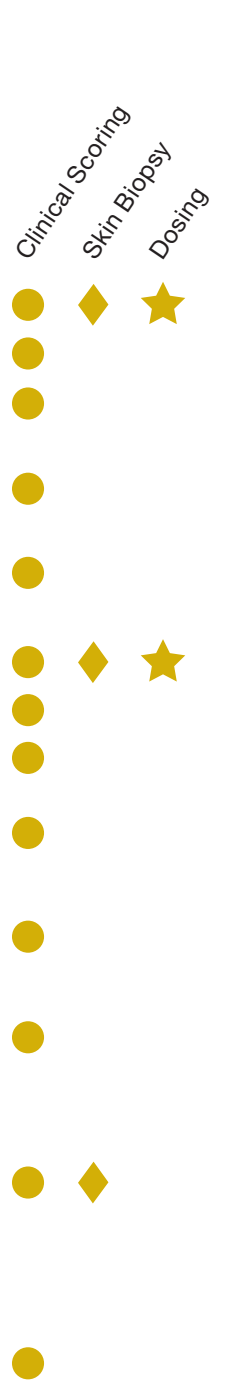
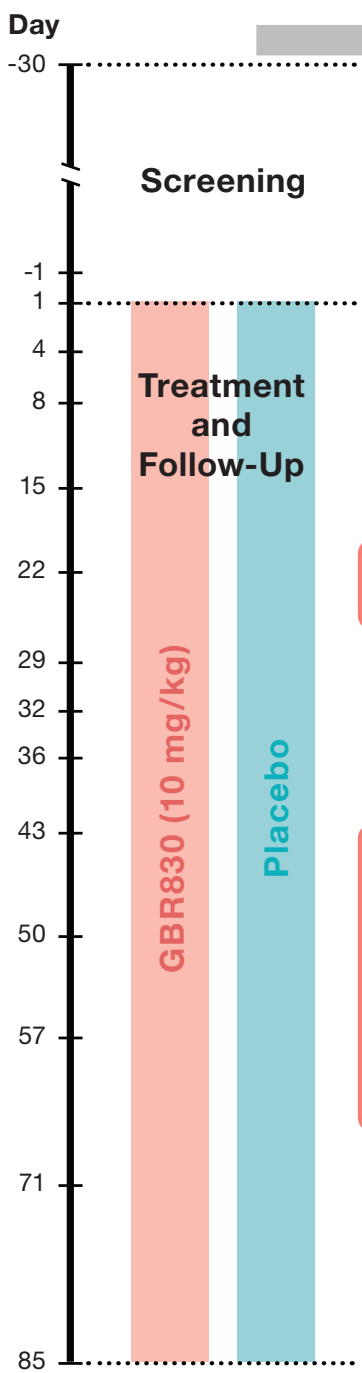



Screened (N=100)

Screen failures (n=36)

Randomized (n=64)

Did not receive study drug (n=2)

GBR830 (n=46)

Placebo (n=16)

| Discontinued | 22* |
|---|---|
| Withdrawal of consent | 11 |
| Adverse event | 2 |
| Protocol violation | 1 |
| Required rescue medication | 4 |
| Lost to follow-up | 1 |
| Other | 3 |

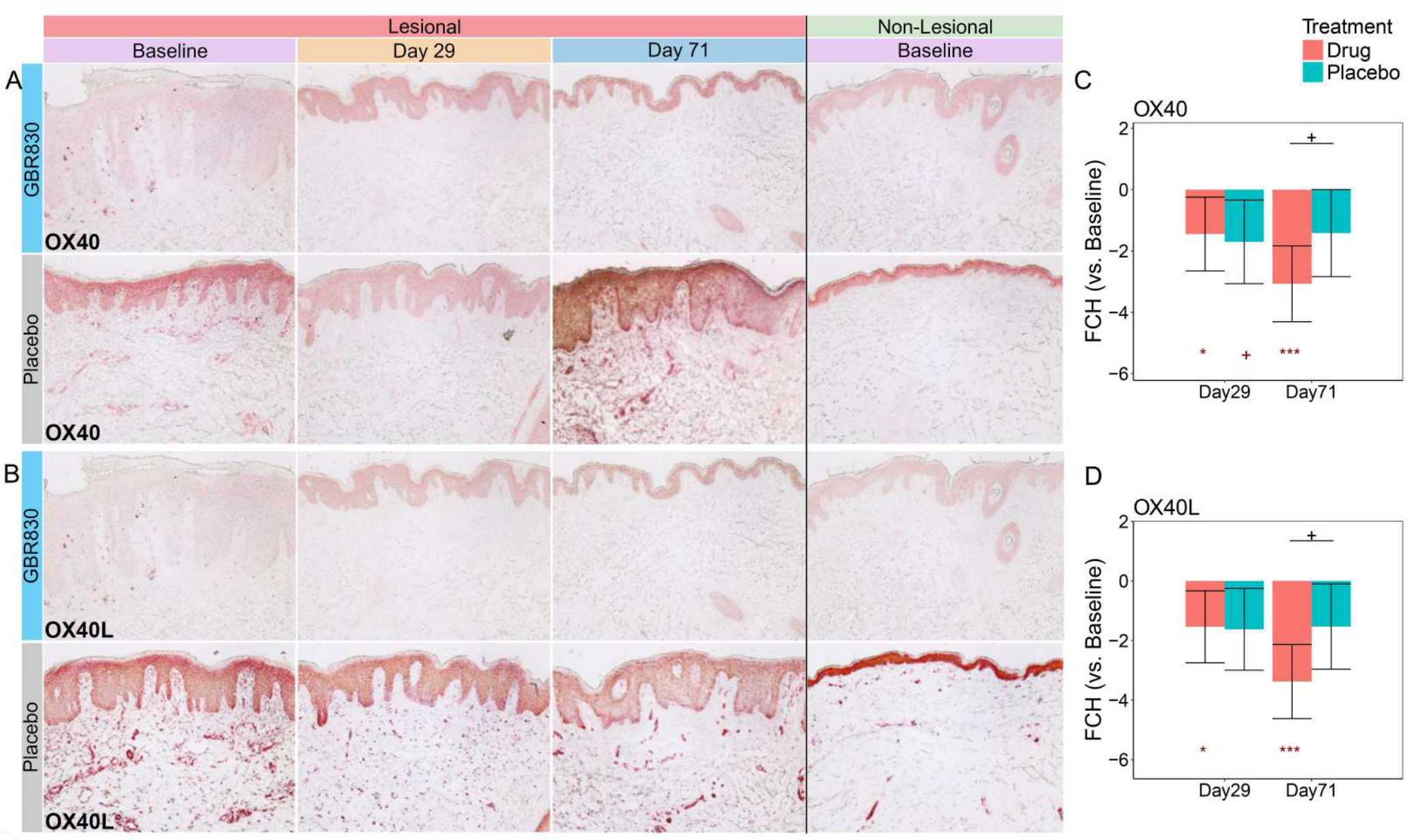
| Discontinued | 8 |
|---|---|
| Withdrawal of consent | 2 |
| Adverse event | 1 |
| Protocol violation | 0 |
| Required rescue medication | 4 |
| Lost to follow-up | 0 |
| Other | 1 |

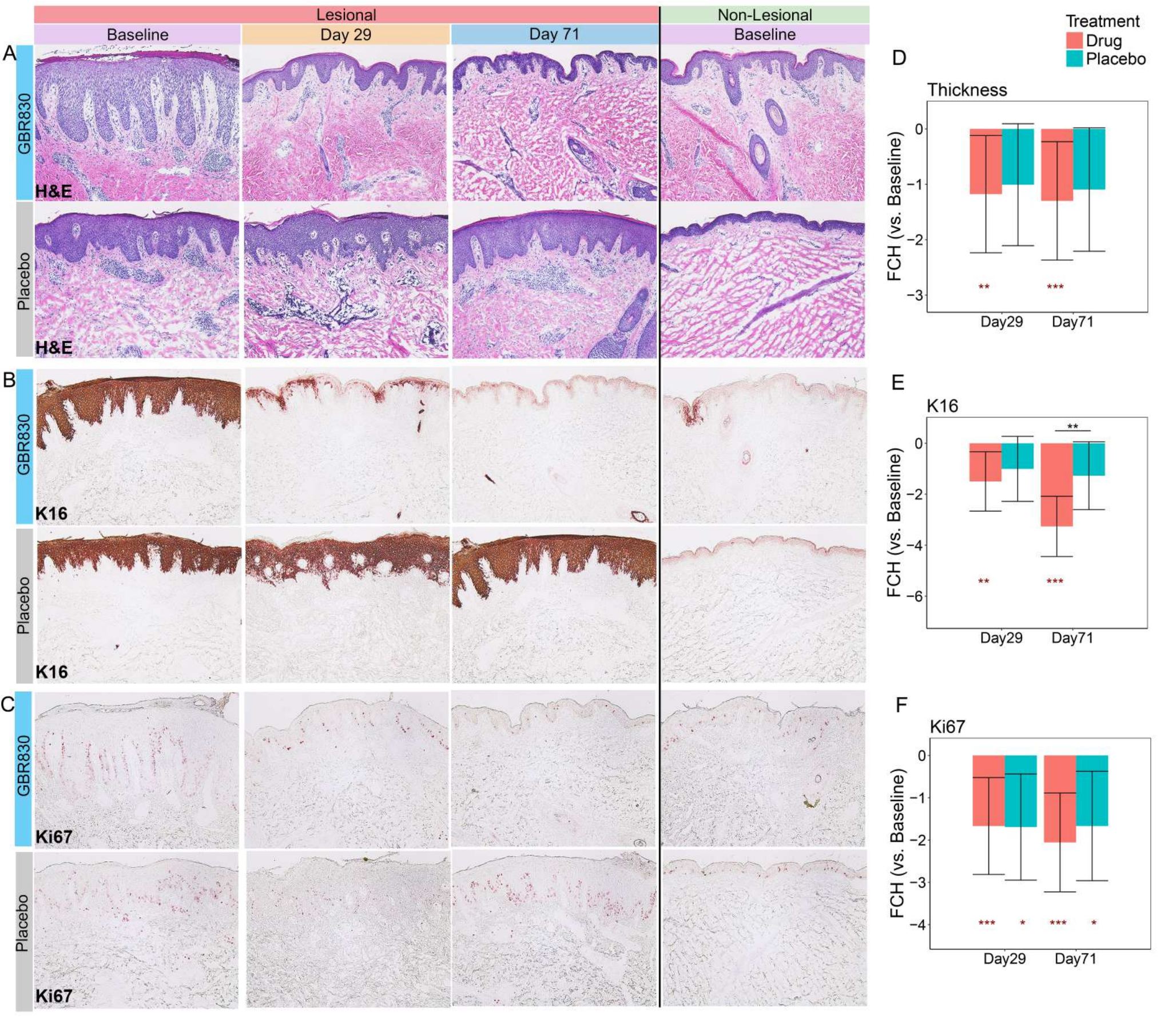
Completed (n=26)

Completed (n=8)

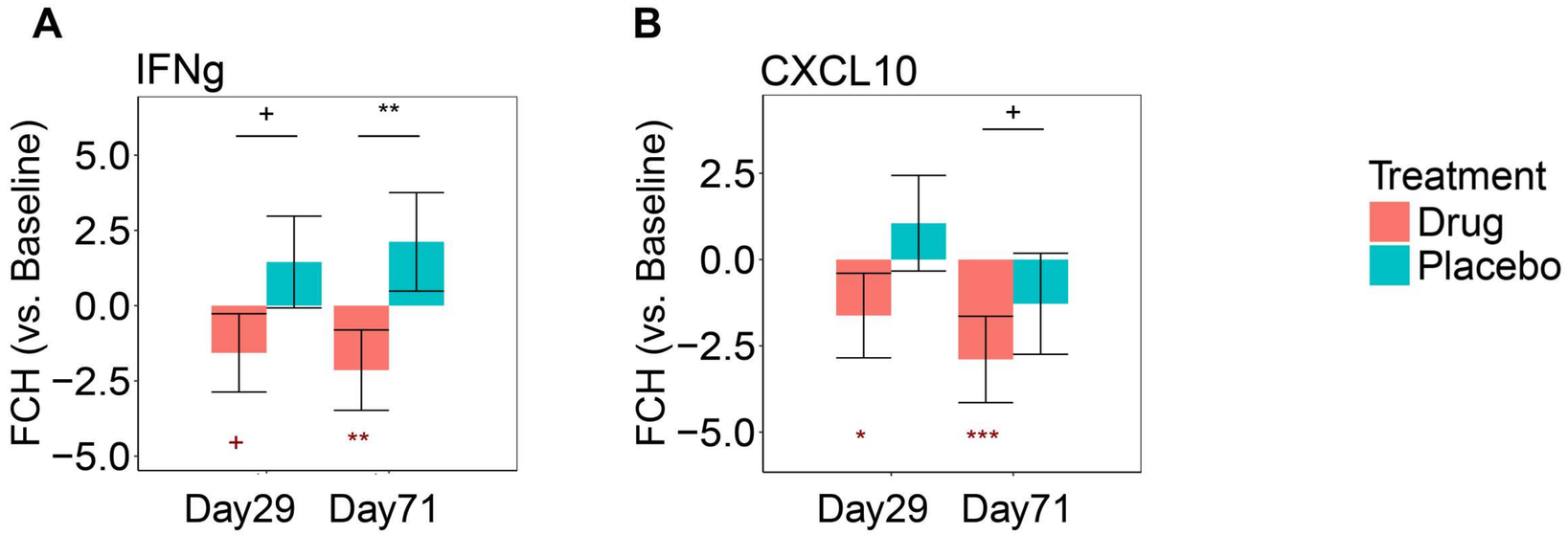
ITT/Safety (n=46)[a] Biological Activity Set (n=29)[b]

ITT/Safety (n=16) Biological Activity Set (n=11)[b]

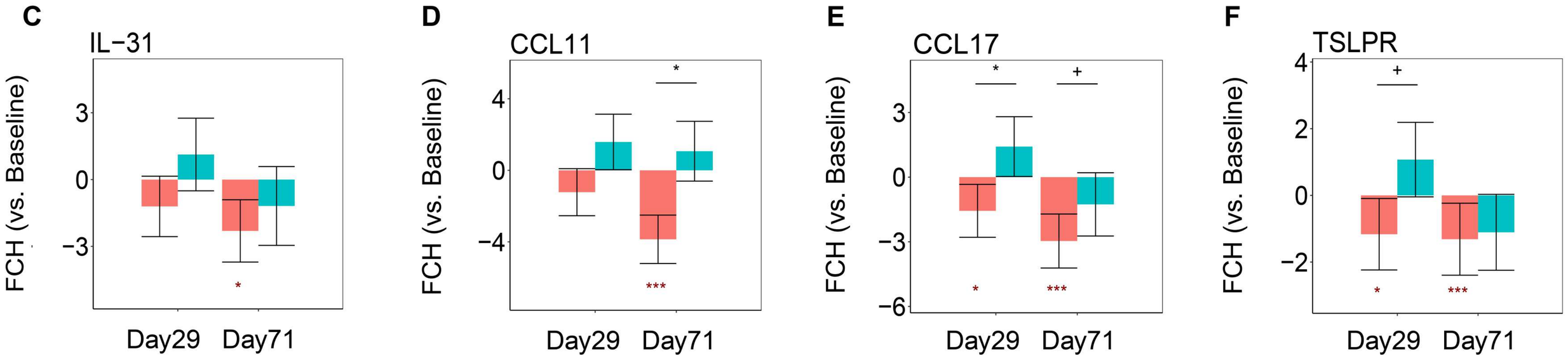

Lesional
Non-Lesional
Baseline
Day 29
Day 71
Baseline
A
GBR830
OX40
Placebo
OX40
B
GBR830
OX40L
Placebo
OX40L
Treatment
Drug
Placebo
C
OX40
FCH (vs. Baseline)
2
0
−2
−4
−6
*
+
***
+
Day29
Day71
D
OX40L
FCH (vs. Baseline)
2
0
−2
−4
−6
*
***
+
Day29
Day71


Lesional
Non-Lesional
Baseline
Day 29
Day 71
Baseline
A
GBR830
Placebo
H&E
H&E
B
GBR830
Placebo
K16
K16
C
GBR830
Placebo
Ki67
Ki67
Treatment
Drug
Placebo
D
Thickness
FCH (vs. Baseline)
0
−1
−2
−3
**
***
Day29
Day71
E
K16
FCH (vs. Baseline)
0
−2
−4
−6
**
**
***
Day29
Day71
F
Ki67
FCH (vs. Baseline)
0
−1
−2
−3
−4
***
*
***
*
Day29
Day71

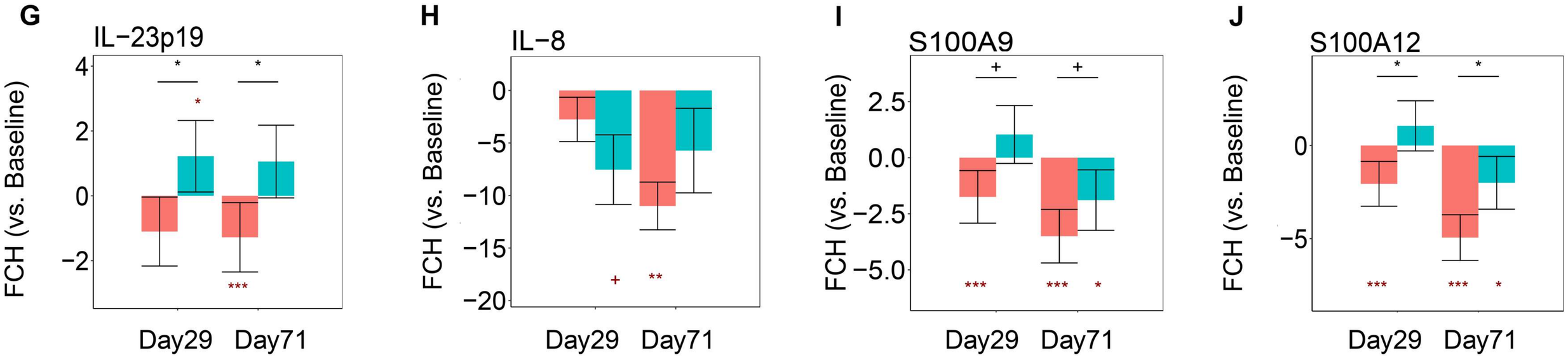
## Th1




## Th2




## Th17/Th22



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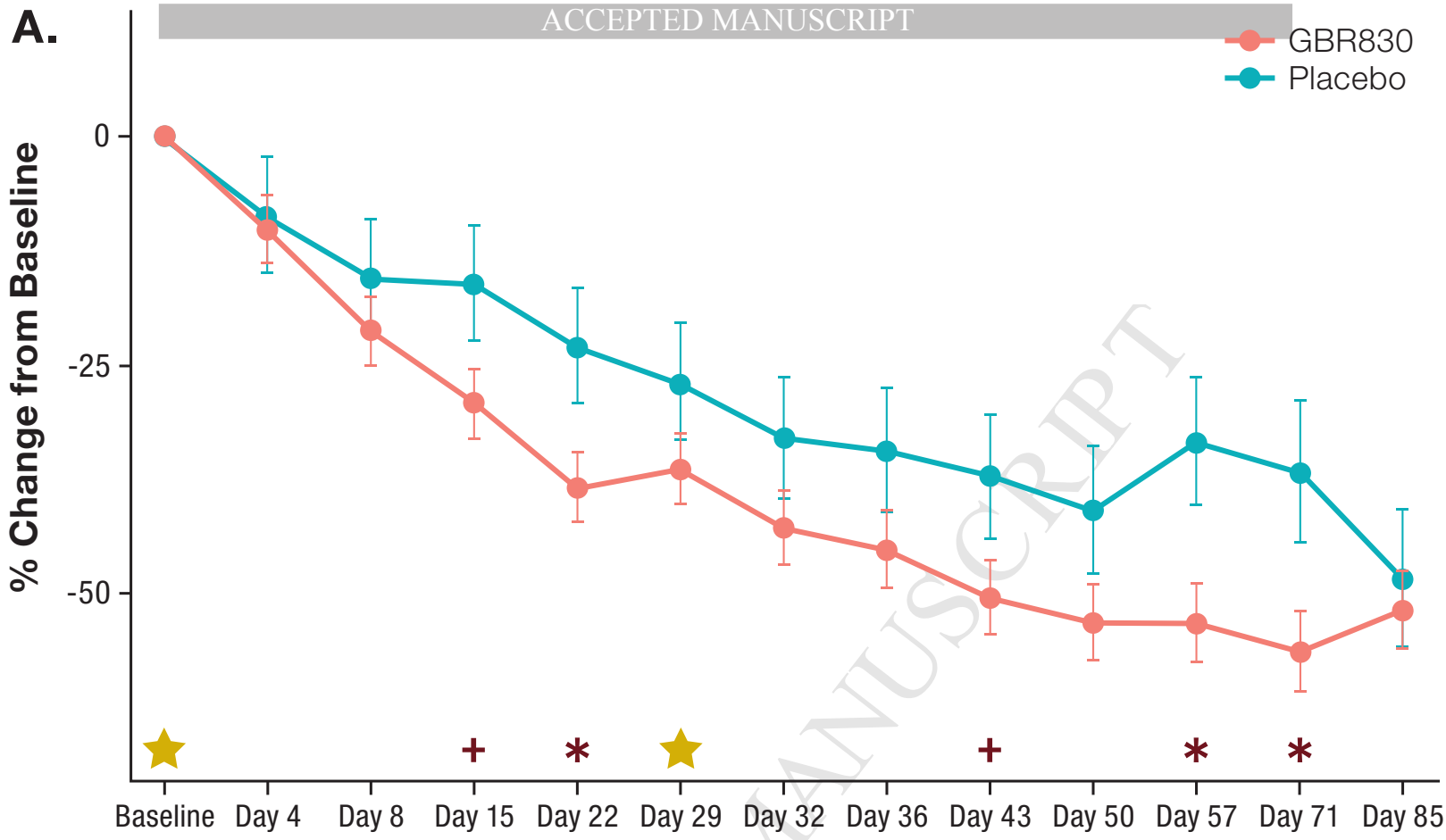


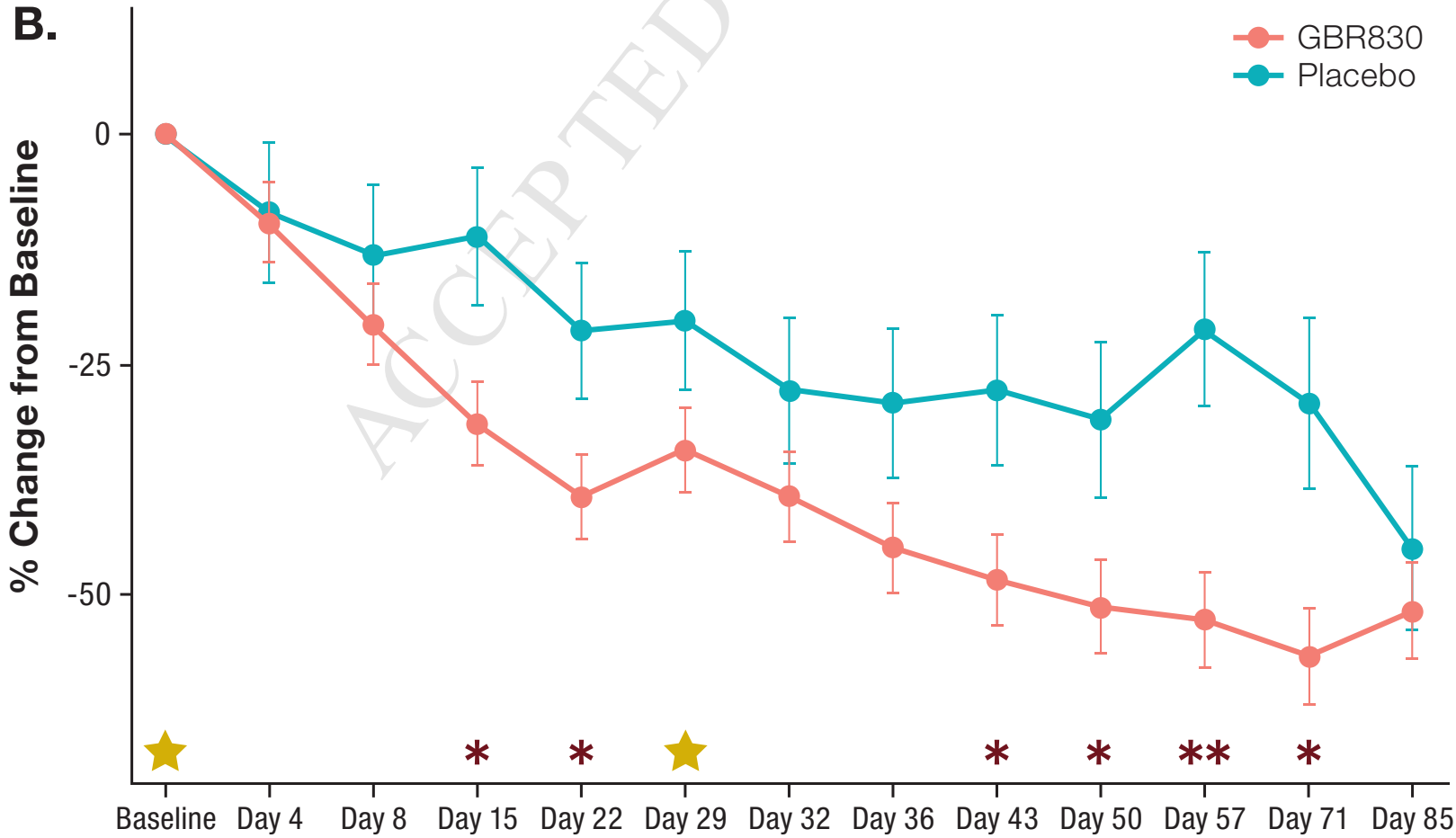


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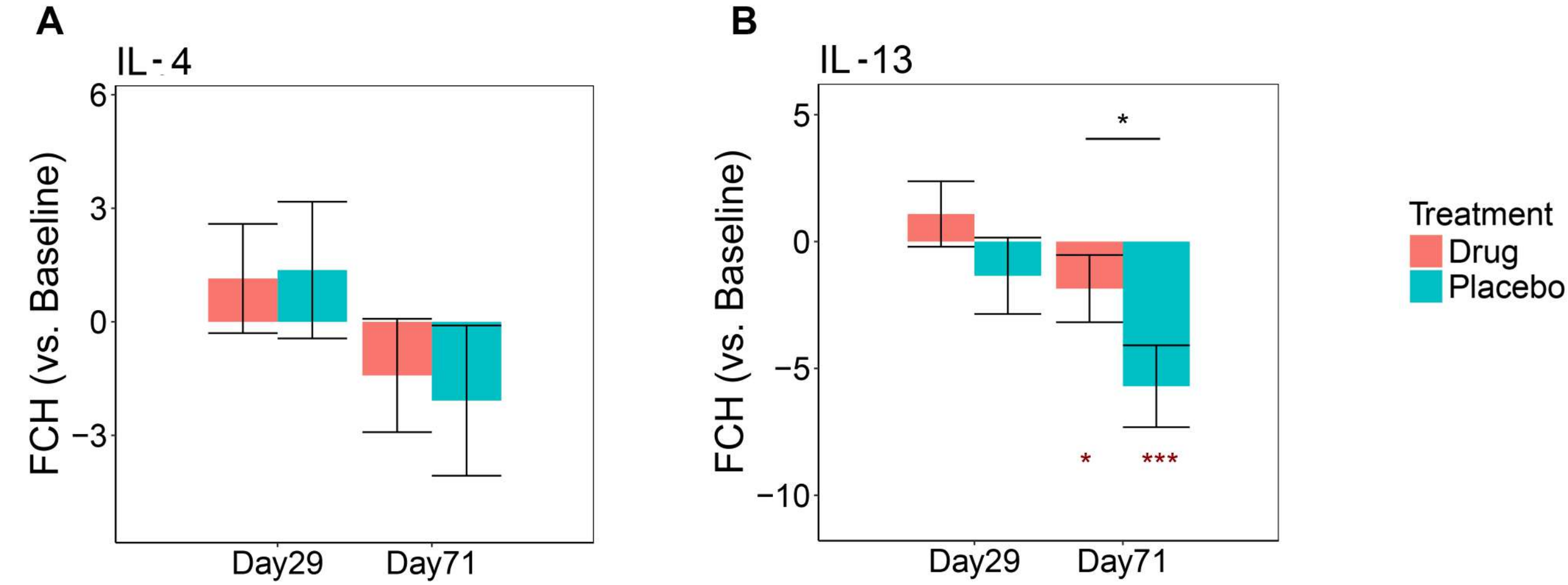
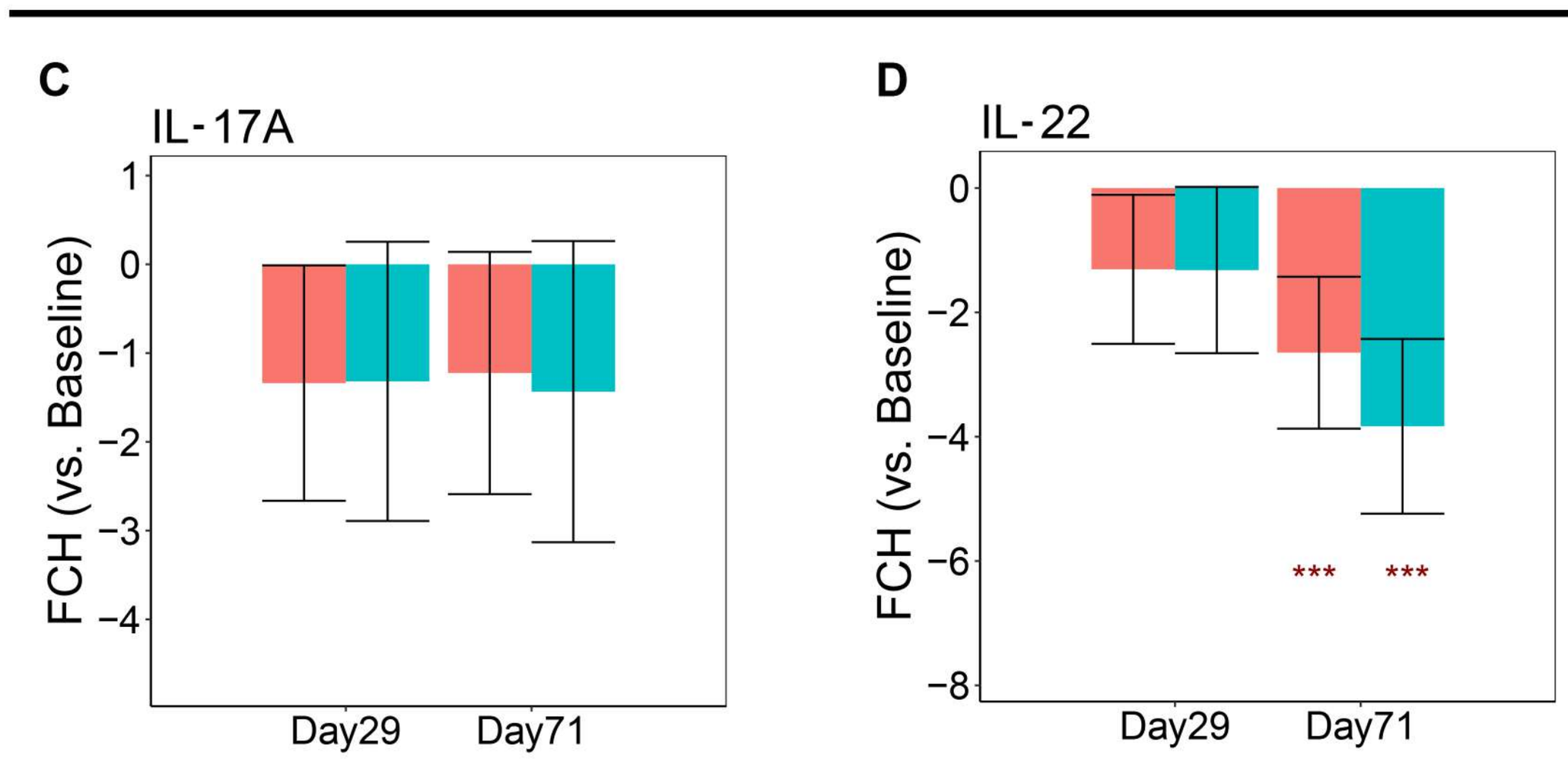
# Figure E1


Th2
A
IL-4
FCH (vs. Baseline)
6
3
0
−3
Day29
Day71
B
IL-13
FCH (vs. Baseline)
5
0
−5
−10
*
*
***
Day29
Day71
Treatment
Drug
Placebo


Th17/Th22
C
IL-17A
FCH (vs. Baseline)
1
0
−1
−2
−3
−4
Day29
Day71
D
IL-22
FCH (vs. Baseline)
0
−2
−4
−6
−8
***
***
Day29
Day71

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ONLINE REPOSITORY

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**On behalf of the GBR 830 in AD study team*

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Methods

*Exclusion Criteria*

Patients were excluded from participation for any of the following reasons: history of drug or other allergy considered clinically significant by the Investigator; live vaccination within 12 weeks before randomization; history of serious infection, including latent or active tuberculosis; skin conditions at screening that would interfere with study drug evaluations; immunocompromised or current serious systemic or local infection suggestive of immunocompromise; history of lymphoproliferative, malignant, inflammatory, auto-immune, or rheumatological disease; and prior treatment with systemic corticosteroids, topical steroids/tacrolimus and/or pimecrolimus, phototherapy, immunosuppressive drugs (ie, cytotoxic agents, cyclophosphamide), cell-depleting agents (ie, rituximab), biologics, and/or allergen immunotherapy.

*Sample Size Determination*

No formal sample size calculations were performed. The same size was chosen based on experience from previous studies of similar nature.[1] A sample size of 40 with a 3:1 GBR 830-to-placebo randomization ratio was considered sufficient to provide descriptive information on the safety, tolerability, and preliminary efficacy of GBR 830.

*Statistical Methods*

The proportion of subjects who achieved an IGA score of 0 (clear) or 1 (almost clear) were summarized at Day 29 and Day 71, as were EASI50 response (≥50% reduction from baseline in EASI score) and EASI75 response (≥75% reduction). Percent improvements from baseline to Day 29 and Day 71 were summarized for SCORAD and BSA affected. Mean changes from baseline to Week 4 and Week 10 in pruritus NRS score were also analyzed. All safety and clinical outcomes were analyzed descriptively.

*Biopsy sampling methods*

Punch biopsies (4.5 mm) were obtained from lesional skin on Days 1, 29, and 71 and non-lesional skin (>10 cm from active lesions) at Day 1. Baseline punch biopsies were taken from the most involved chronic active erythematous, scaly lesions. Biopsies from the folds of the

upper extremities, followed by lower extremities were preferred, followed by the trunk. Skin samples for Days 28 and 71 were ideally taken from the same area location as the baseline lesional sample. If the lesion was cleared at Day 28 or 71, a sample closest to the previous biopsy scar (>5 mm to <1 cm from scar) was collected. Biopsy of the previous scar was not allowed. Systemic corticosteroids (within 4 weeks before baseline) or topical treatments (within 1 week before baseline) were not allowed except for emollients and mild steroids (class 6 or 7).

Case Report: Severe/Serious Coronary Artery Occlusion

The subject was a 54-year-old white male with AD for 37 years, who was randomized to GBR 830 in January 2018 and received both intravenous doses (Day 1 and Day 29). Significant relevant medical history included: mild increased blood pressure (2010 to 2011), skin infection (2016), latex irritation (unknown to ongoing), and asthma (unknown to ongoing).
No concomitant medications at screening or baseline were relevant to the serious treatment-emergent adverse event (TEAE) of coronary artery occlusion.

The subject reported recent recurrent episodes of shortness of breath with exertion as well as fatigue. He denied any frank syncope and any other signs or symptoms of decompensated heart failure. On Day 57, the 12-lead electrocardiogram (ECG) showed a sinus rhythm with heart rate of 76 beats per minute and ST segment and T-wave inversion on V1 through V4, suggestive of possible myocardial ischemia. On the same day, the subject was referred to a cardiology specialist who confirmed the abnormal ECG. On Day 60, a nuclear stress test showed mild systolic dysfunction with an ejection fraction of 51% with mild anterior ischemic changes and abnormal echocardiogram findings. On Day 71, a scheduled cardiac catheterization showed left anterior descending coronary artery blockage. The subject received midazolam hydrochloride 1 mg IV once, bivalirudin 60 mg once and 129.5 mg once, lidocaine 2% once, and fentanyl 25 mcg IV once, all for the cardiac stent placement done that day. The clinical laboratory work-up on Day 71 was essentially normal. Vital signs remained stable throughout. The subject was hospitalized for post percutaneous coronary intervention care and observation overnight and received oral prasugrel hydrochloride 60 mg once.

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A final angiogram showed the vessel was widely patent and 2 views showed no evidence of dissection. On Day 72, the clinical laboratory work-up remained clinically normal. On the same day, the event resolved and the subject remained asymptomatic. He was discharged from the hospital. The Investigator assessed the event as not related to the study drug or study procedure and reported that the left anterior descending coronary artery blockage was due to pre-existing multiple risk factors.

References

1. Beck LA, Thaci D, Hamilton JD, Graham NM, Bieber T, Rocklin R, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 2014; 371:130-9.

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Table E1. Number of samples at different time points

| Subjects, n (%) | Subjects with Biopsies (BAS) | | Subjects with Clinical Data (ITT) | |
|---|---|---|---|---|
| | GBR 830 | Placebo | GBR 830 | Placebo |
| Day 1 (baseline) | 29 (100) | 11 (100) | 46 (100) | 16 (100) |
| Day 29 | 29 (100) | 11 (100) | 39 (84.7) | 15 (93.7) |
| Day 71 | 21 (72.4) | 7 (63.6) | 26 (56.5) | 8 (50.0) |

*BAS*, Biological Activity Set; *ITT*, intent-to-treat.

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Table E2. Purified mouse anti-human monoclonal antibodies for immunohistochemistry staining

| Antibody | Vendor | Clone | Isotype | Dilution |
|---|---|---|---|---|
| Ki67 | Santa Cruz Biotechnology | MIB-1 | Mouse $IgG_{1K}$ | 1:25 |
| OX40L | R&D Systems | 159403 | Mouse $IgG_{1K}$ | 1:50 |
| OX40 | BD Biosciences | ACT35 | Mouse $IgG_{1K}$ | 1:50 |

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Table E3. Primers

| Gene Symbol | Sequence |
|---|---|
| hARP | Forward CGCTGCTGAACATGCTCAA<br>Reverse TGTCGAACACCTGCTGGATG<br>Probe 6-FAM-TCCCCCTTCTCCTTTGGGCTGG-2TAMRA |
| | Assay ID |
| K16 | Hs00955082_g1 |
| IL-8 | Hs00174103_m1 |
| IL-23p19 | Hs00900828_g1 |
| IL-31 | Hs01098710_m1 |
| IFNγ | Hs00989291_m1 |
| S100A9 | Hs00610058_m1 |
| S100A12 | Hs00942835_g1 |
| CCL17 | Hs00171074_m1 |
| CCL11 | Hs00237013_m1 |
| CXCL10 | Hs01124251_g1 |
| TSLPR | Hs00845692_m1 |

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Table E4. Clinical endpoint outcomes (ITT population)

| Clinical Endpoint | GBR 830 (n = 46) | Placebo (n = 16) |
|---|---|---|
| IGA Response (score of 0 or 1), n/N (%) | | |
| Day 29 | 2/39 (5.1) | 0 |
| Day 71 | 6/26 (23.1) | 1/8 (12.5) |
| EASI50 (≥50% score reduction from baseline), n/N (%) | | |
| Day 29 | 17/39 (43.6) | 3/15 (20.0) |
| Day 71 | 20/26 (76.9) | 3/8 (37.5) |
| EASI75 (≥75% score reduction from baseline), n/N (%) | | |
| Day 29 | 5/39 (12.8) | 1/15 (6.7) |
| Day 71 | 11/26 (42.3) | 2/8 (25.0) |
| SCORAD, mean ± SD | | |
| Baseline | 62.2 ± 14.3 | 55.5 ± 10.4 |
| Day 29, % change from baseline | -28.2 ± 26.6 | -15.5 ± 21.7 |
| Day 71, % change from baseline | -45.4 ± 26.9 | -31.0 ± 16.9 |
| BSA affected, mean ± SD | | |
| Baseline | 38.6 ± 23.4 | 39.3 ± 21.5 |
| Day 29, % change from baseline | -28.5 ± 28.0 | -26.3 ± 30.7 |
| Day 71, % change from baseline | -47.1 ± 32.6 | -43.4 ± 34.9 |
| Pruritus NRS, mean ± SD | | |
| Baseline | 6.4 ± 2.2 | 4.9 ± 2.1 |
| Week 4, change from baseline | -1.6 ± 2.1 | -1.2 ± 1.6 |
| Week 10, change from baseline | -2.7 ± 2.5 | -1.5 ± 1.6 |

*BSA*, body surface area; *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; *NRS*, numeric rating scale; *SCORAD*, Scoring of Atopic Dermatitis; *SD*, standard deviation.

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Table E5. Clinical endpoint outcomes (BAS population)

| Clinical Endpoint | GBR 830 (n = 29) | Placebo (n = 11) |
|---|---|---|
| IGA Response (score of 0 or 1), n/N (%) | | |
| Day 29 | 2/29 (6.9) | 0 |
| Day 71 | 6/24 (25.0) | 1/7 (14.3) |
| EASI50 (≥50% score reduction from baseline), n/N (%) | | |
| Day 29 | 15/29 (51.7) | 3/11 (27.3) |
| Day 71 | 18/24 (75) | 3/7 (42.9) |
| EASI75 (≥75% score reduction from baseline), n/N (%) | | |
| Day 29 | 4/29 (13.8) | 1/11 (9.1) |
| Day 71 | 10/24 (41.7) | 2/7 (28.6) |
| SCORAD, mean ± SD | | |
| Baseline | 61.5 ± 15.8 | 54.5 ± 10.8 |
| Day 29, % change from baseline | -30.5 ± 25.3 | -21.5 ± 17.4 |
| Day 71, % change from baseline | -44.0 ± 27.6 | -31.4 ± 18.2 |
| BSA affected, mean ± SD | | |
| Baseline | 38.6 ± 24.0 | 38.4 ± 21.6 |
| Day 29, % change from baseline | -32.2 ± 28.5 | -35.6 ± 30.9 |
| Day 71, % change from baseline | -45.6 ± 33.3 | -48.1 ± 34.7 |
| Pruritus NRS, mean ± SD | | |
| Baseline | 6.3 ± 2.2 | 4.3 ± 1.9 |
| Week 4, change from baseline | -2.0 ± 2.3 | -0.9 ± 1.4 |
| Week 10, change from baseline | -3.0 ± 2.6 | -1.3 ± 1.6 |

*BAS,* Biological Activity Set; *BSA,* body surface area; *EASI*, Eczema Area and Severity Index; *IGA*, investigator's global assessment (5-point scale); *n*, number of subjects who met response criterion; *N*, number of subjects with non-missing values at the study visit; *NRS,* numeric rating scale; *SCORAD,* Scoring of Atopic Dermatitis; *SD,* standard deviation.

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Figure E1. Th2 and Th17/Th22 markers did not change in GBR 830-treated subjects compared to placebo

*$P$<0.05, ***$P$<0.001.

FCH, fold change.

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