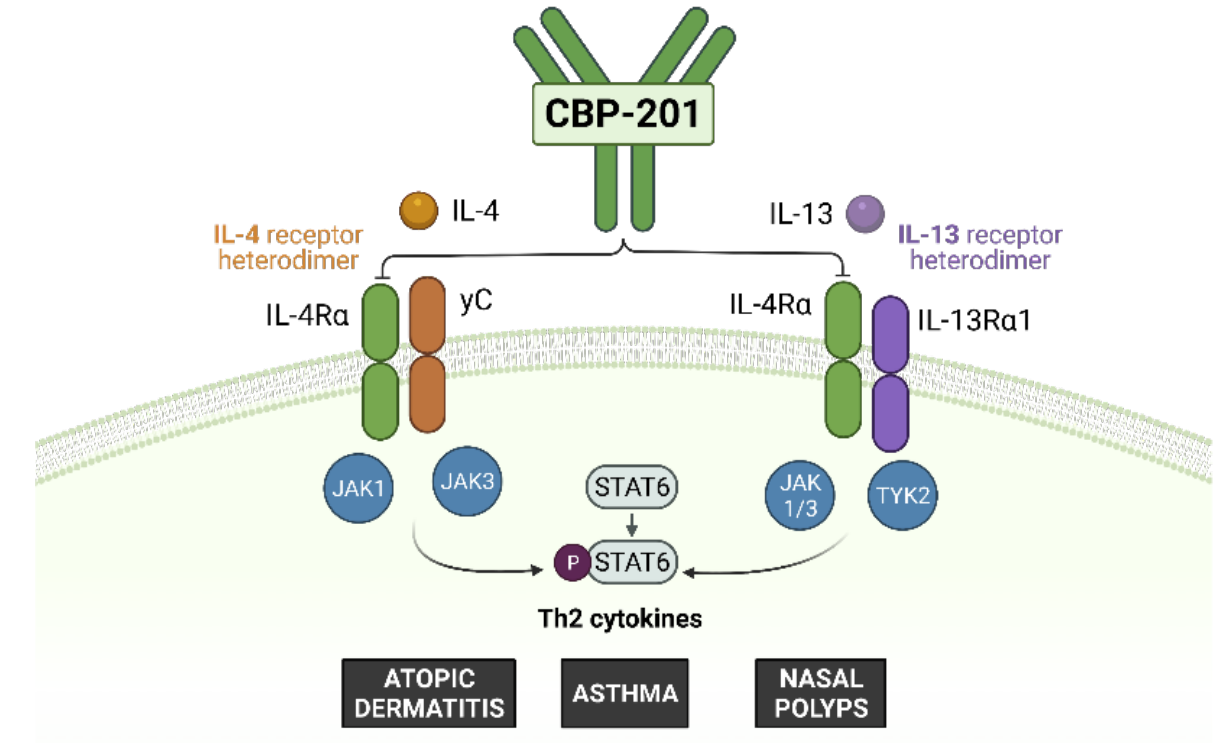


# The Effect of Baseline Disease Characteristics on Efficacy Outcomes: Results from a Phase 2b, Randomized, Double-blind, Placebo-controlled Trial (CBP-201-WW001)

Jonathan I. Silverberg,<sup>1</sup> Brian Feinstein,<sup>2</sup> Emma Guttman-Yassky,<sup>3</sup> Eric Simpson,<sup>4</sup> Bruce Strober,<sup>5,6</sup> Jinhua Xu,<sup>7,8</sup> Pauline Li,<sup>9</sup> Jing Song,<sup>9</sup> Malinda Longphre,<sup>9</sup> Paul Smith,<sup>9</sup> Zheng Wei,<sup>9</sup> Selwyn Ho<sup>9</sup>

<sup>1</sup>Department of Dermatology, George Washington University School of Medicine and Health Sciences, Washington, DC, USA; <sup>2</sup>Encore Medical Research LLC, FL, USA; <sup>3</sup>Department of Dermatology and Laboratory of Inflammatory Skin Diseases, Icahn School of Medicine at Mount Sinai, New York, NY; <sup>4</sup>Department of Dermatology, Oregon Health and Science University, Portland, OR, USA; <sup>5</sup>Yale University, New Haven, CT, USA; <sup>6</sup>Central Connecticut Dermatology, Cromwell, CT, USA; <sup>7</sup>Department of Dermatology, Huashan Hospital, Fudan University, Shanghai, China; <sup>8</sup>Shanghai Institute of Dermatology, Shanghai, China; <sup>9</sup>Connect Biopharma, San Diego, CA, USA and Suzhou, China.

- CBP-201 is a novel monoclonal antibody targeting IL-4Ra.



- A Phase 2b trial of CBP-201 (WW001) met its primary endpoint and key secondary endpoints in the treatment of moderate-to-severe AD (see Strober et al, Maui Derm 2022).
- Serum thymus- and activation-regulated chemokine (TARC; also known as CCL17) has an important role in allergic diseases such as atopic dermatitis. High serum concentrations of TARC are observed in patients with atopic dermatitis, and its concentration is closely related to disease activity.
- Patients enrolled in WW001 had markedly lower baseline disease severity than the trials of the approved anti-IL-4Ra (see Strober et al, Maui Derm 2022).
- Here, we present post hoc analyses conducted to determine whether baseline biomarkers of disease severity and efficacy outcomes with CBP-201 in the WW001 Phase 2b trial.

## Methodology

- This Phase 2b, randomized, double-blind, placebo-controlled, international trial (NCT04444752) comprised 16-week treatment and 8-week follow-up periods. Patients were randomized (1:1:1:1) to subcutaneous CBP-201 (300 mg every 2 weeks [Q2W], 150 mg Q2W, 300 mg Q4W) or placebo, across 59 centers in the USA (38), China (9), Australia (8), and New Zealand (4). A China subgroup analysis was specifically conducted to address local health authority requirements necessary for future regulatory review.
- The full trial design, as well as key inclusion and exclusion criteria, are detailed in Strober et al (Maui Derm 2022).
- In two CBP-201 Phase 1a trials that had been conducted previously with healthy volunteers, the maximum TARC level was 254 pg/ml (minimum was below quantifiable levels) in assays utilizing the Luminex technology.
- Endpoints and statistics:
  - The post hoc subgroup analyses presented here are exploratory and not powered for statistical analysis.

## Results

### Disease characteristics

- All patients (N=226) had moderate-to-severe AD, although disease severity was lower (Table 1) than in Phase 3 trials of the currently approved anti-IL-4Ra.
- Median (range) EASI (21.2, 16.0–68.4) was ~11 points lower, duration of AD (13 years, 1–58) was ~13 years lower, and BSA involvement (35%) was ~18% lower than in Phase 3 trials of the currently approved anti-IL-4Ra. The proportion of patients with an Investigator's Global Assessment (IGA) score of 4 (severe, 31%) was ~17% lower.
- TARC (median 166 pg/ml, interquartile range (IQR) 92–444) and IgE (median 16,590 IU/ml, IQR 368–8,235) biomarker levels were also lower than in Phase 3 trials of the currently approved anti-IL-4Ra.
- Patients with higher baseline TARC levels (>291 pg/ml) had higher baseline EASI (median 27.8) than subgroups of patients with mid TARC (>116.74–291 pg/ml; median EASI, 19.9) or low TARC (≤116.74 pg/ml; median EASI, 18.4). This correlation between baseline TARC and baseline EASI had a coefficient of 0.273 (P<0.0001). By contrast, no correlation was seen between baseline TARC and baseline peak pruritus-numerical rating scale (PP-NRS; correlation coefficient 0.0006, p=0.99).

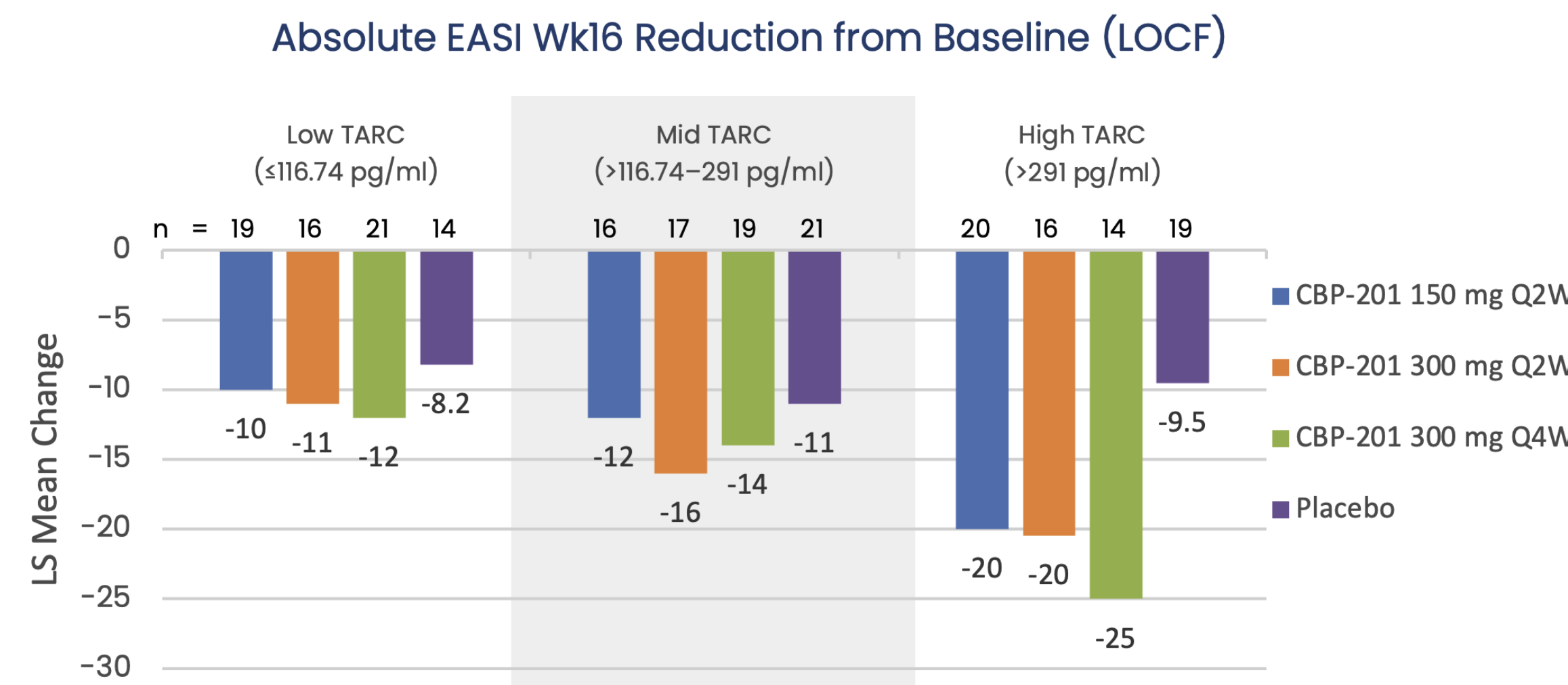
**Table 1: Disease characteristics at baseline by high and low TARC level in this Phase 2b trial**

	CBP-201 150mg Q2W N=57	CBP-201 300mg Q2W N=57	CBP-201 300mg Q4W N=56	Placebo N=56
TARC ≤116.74 pg/ml	n=19	n=19	n=21	n=15
Duration of AD, Median (Q1, Q3), years	10.0 (4.5, 20.0)	10.0 (3.0, 21.0)	18.0 (10.0, 31.0)	10.0 (5.0, 23.0)
EASI score, mean (SD)	20.29 (4.29)	24.09 (9.49)	19.77 (3.55)	21.77 (9.41)
PP-NRS, mean (SD)	6.26 (2.08)	6.68 (2.13)	6.2 (2.33)	7.28 (1.63)
IGA score, mean (SD)	3.05 (0.23)	3.26 (0.45)	3.28 (0.46)	3.13 (0.35)
IGA=3, n (%)	18 (94.7)	14 (73.7)	15 (71.4)	13 (86.7)
IGA=4, n (%)	1 (5.3)	5 (26.3)	6 (28.6)	2 (13.3)
TARC levels, median (Q1, Q3), pg/ml	55 (27, 84)	57 (44, 93)	75 (47, 101)	70 (59, 85)
IgE level, median (Q1, Q3), IU	337 (273, 882)	462 (223, 1170)	960 (284, 5667)	302 (185, 925)
TARC >291 pg/ml	n=21	n=20	n=14	n=19
Duration of AD, Median (Q1, Q3), years	20.0 (4.0, 27.0)	18.5 (8.0, 24.0)	10.5 (3.0, 14.0)	19.0 (4.0, 25.0)
EASI score, mean (SD)	30.29 (14.14)	31.85 (12.38)	30.66 (10.48)	28.66 (9.18)
PP-NRS, mean (SD)	7.55 (1.50)	6.89 (1.55)	7.13 (2.05)	7.42 (1.37)
IGA score, mean (SD)	3.48 (0.51)	3.55 (0.51)	3.43 (0.51)	3.47 (0.51)
IGA=3, n (%)	11 (52.4)	9 (45.0)	8 (57.1)	10 (52.6)
IGA=4, n (%)	10 (47.6)	11 (55.0)	6 (42.9)	9 (47.4)
TARC levels, median (Q1, Q3), pg/ml	1212 (524, 2989)	720 (440, 1010)	943 (408, 2677)	566 (438, 1200)
IgE level, median (Q1, Q3), IU	10166 (2556, 50403)	15411 (3189, 55512)	7471 (495, 32944)	5098 (624, 31742)

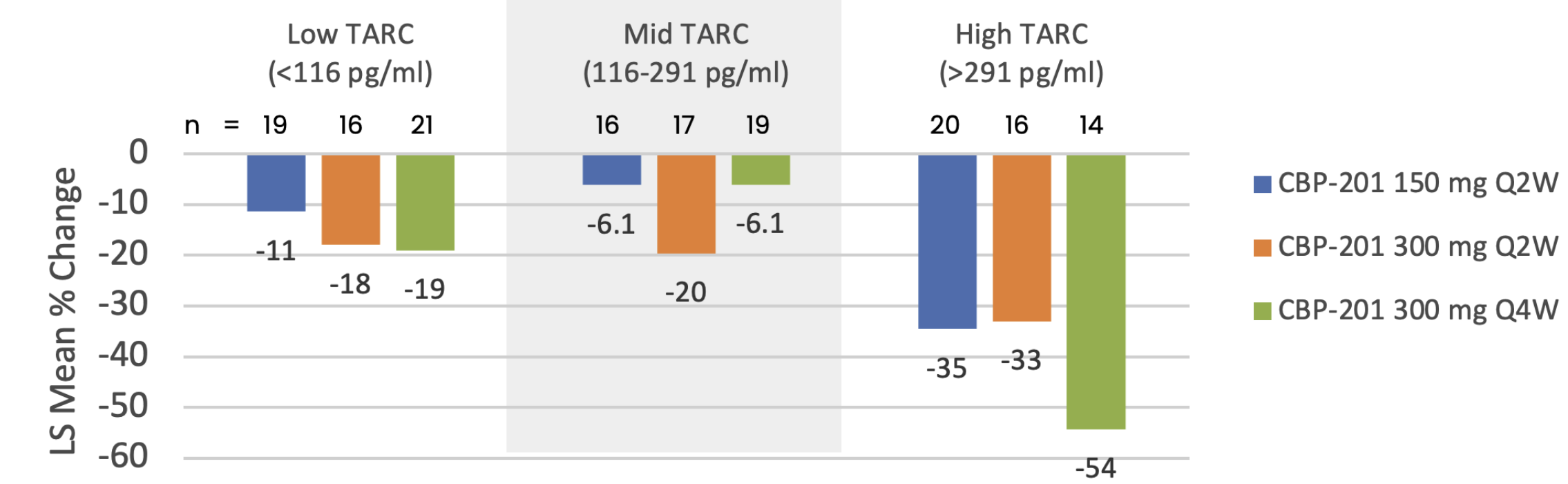
### Efficacy by baseline TARC

- Post hoc analyses demonstrated that CBP-201 responses at Week 16 were greatest in patients with elevated baseline TARC (>291 pg/ml) (Figure 1).
- In all subgroups greater reductions in absolute LS mean EASI at Week 16 were observed with all doses of CBP-201 compared with placebo (Figure 1). In the high TARC group, the reductions with CBP-201 were higher than those in the low and middle TARC subgroups.
- Much greater reductions in LS mean EASI change from baseline with CBP-201 vs placebo – and much higher PP-NRS response rates with CBP-201 than with placebo – were also observed in the high-TARC subgroup at Week 16 (Figure 1).

**Figure 1: Efficacy endpoints by TARC level subgroup**

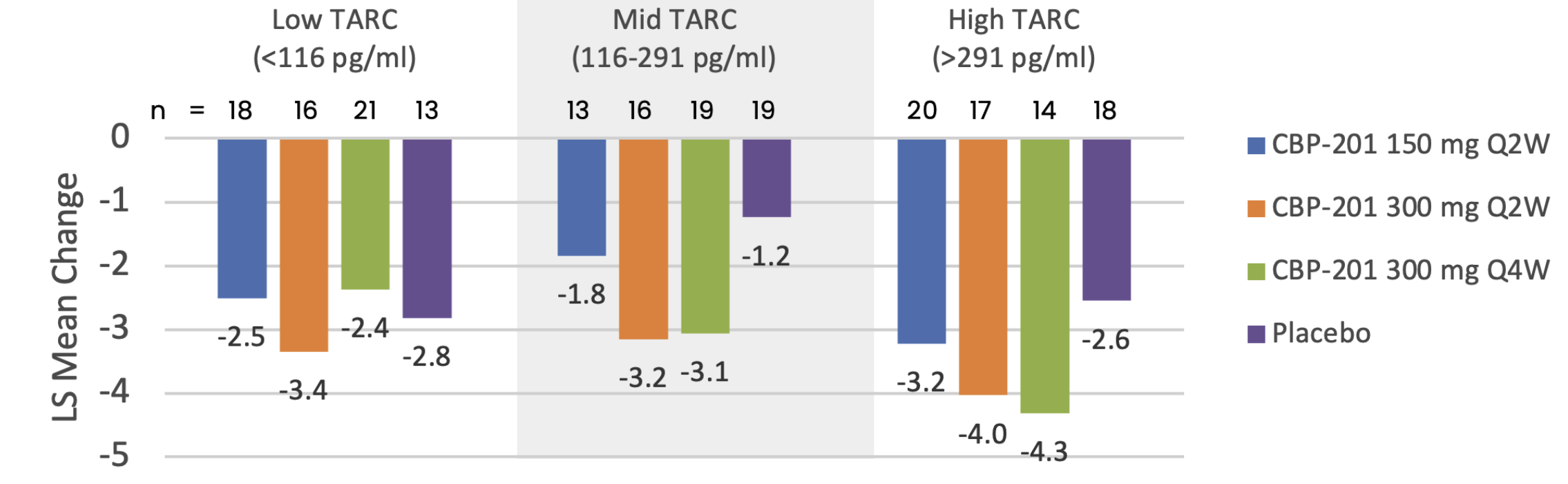


**EASI Wk16 % Change from Baseline (LOCF) – Placebo Adjusted**

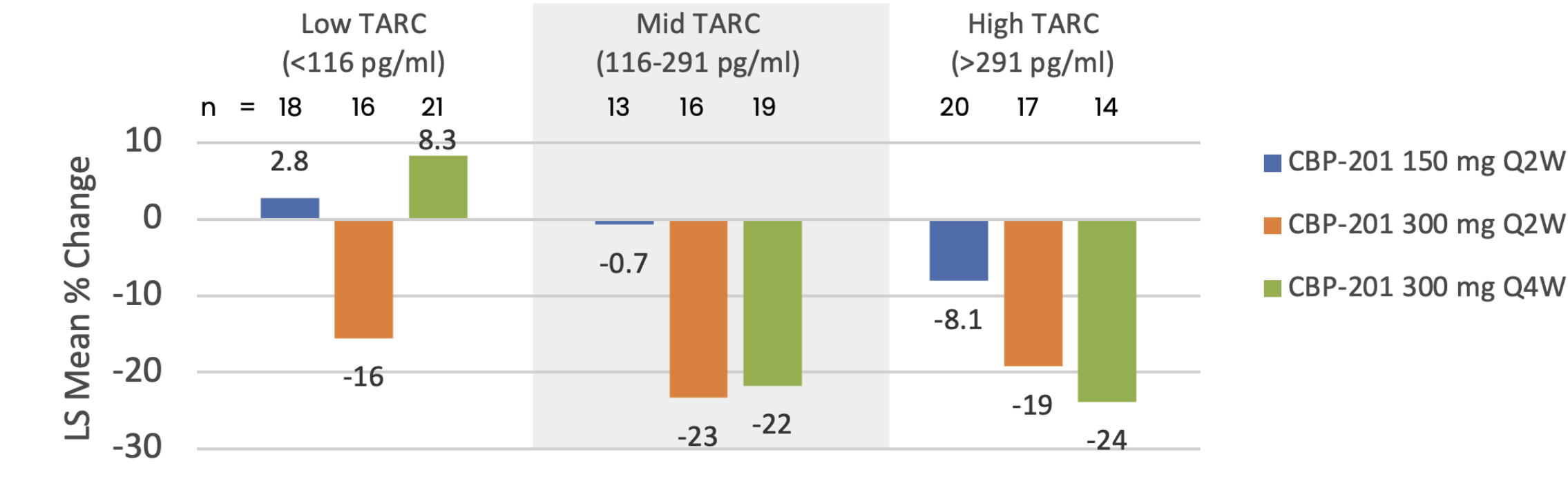


Placebo values were -35% (low TARC; n=14), -51% (mid TARC; n=21) and -29% (high TARC; n=19)

**Absolute PP-NRS Change from Baseline (LOCF)**



**PP-NRS Wk16 % Change from Baseline (LOCF) – Placebo Adjusted**



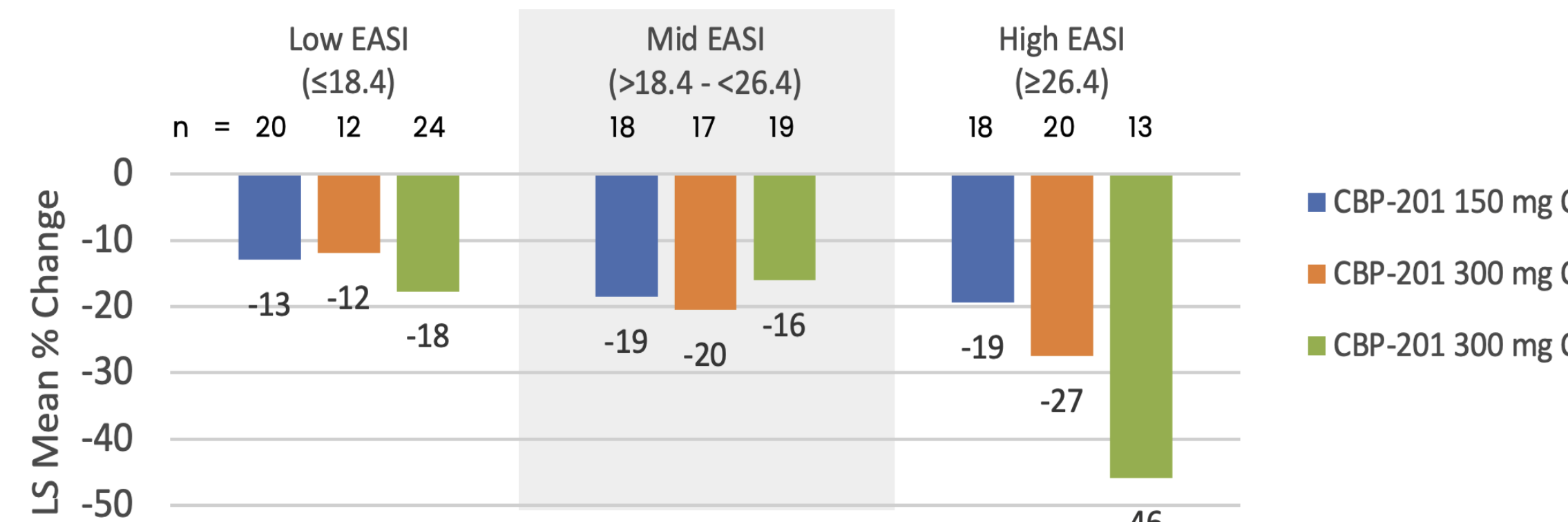
Placebo values were -29% (low TARC, n=13), -21% (mid TARC, n=19) and -36% (high TARC, n=18)

### Efficacy by baseline EASI

- In another post hoc analysis, patients with higher baseline EASI score tended to experience a greater treatment effect in terms of % change in EASI score from baseline (Figure 2).

**Figure 2: Relationship between baseline EASI score and treatment effect (% change in EASI score from baseline, placebo adjusted)**

**EASI Wk16 % Reduction from Baseline (LOCF) – Placebo Adjusted**

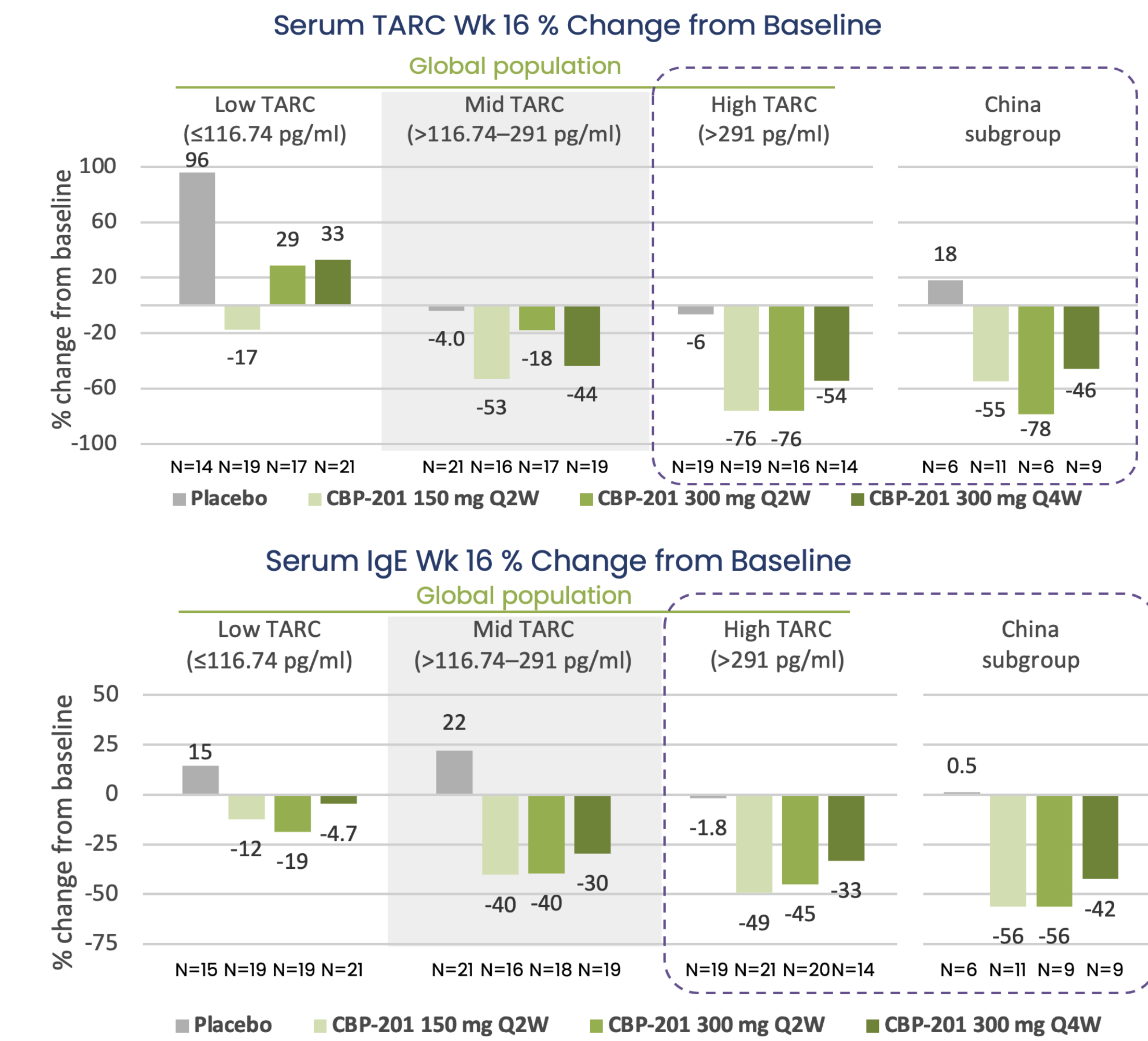


Placebo values were -41% (low EASI, n=17), -43% (mid EASI, n=20) and -35% (high EASI, n=18)

### Change in TARC and IgE

- A post hoc analysis of biomarkers showed that serum TARC level at Week 16 was not meaningfully reduced from baseline with any dose in the low TARC tertile, whereas >50% reductions were seen with all doses of CBP-201, but not placebo, in the high TARC tertile (Figure 3). Similar results were seen with IgE levels\*.
- TARC and IgE % reductions in the China subgroup were similar to those in the high TARC tertile (Figure 3). Like the high TARC subgroup, patients in China (N=32) had higher baseline TARC (median 457.6 pg/ml) and corresponding EASI (median 26.9) when compared with the global trial population. Also similar to the high TARC subgroup, patients in China also experienced greater reductions in efficacy endpoints when compared with the global trial population (Strober et al, Maui Derm 2022).

**Figure 3: Week 16 % change from baseline in serum TARC or IgE, by baseline tertiles (global population) or China subgroup**



### Safety by baseline TARC

- No new safety signals were noted and adverse events were balanced across all groups.
- AEs were similar to placebo (See Strober et al, Maui Derm 2022).

## Conclusion

- This Phase 2b trial of CBP-201 met its primary and key secondary endpoints in the treatment of moderate-to-severe AD (see Strober et al, Maui Derm 2022), with pre-specified analyses also showing greater improvements in patients with more severe disease at baseline.
- Post hoc analyses also demonstrated further efficacy improvements as baseline disease severity increased, both in patients with higher baseline TARC levels, a biomarker of inflammatory activity, and more severe AD and efficacy outcomes that vary with baseline disease severity that have also been shown in other AD studies.
- Comparison with other AD studies is hampered by differences between trials, such as recruitment of patients with less severe AD in this Phase 2b trial and conduct during the COVID-19 pandemic.

**Funding:** Connect Biopharma

**Footnotes:** \* Extreme values for TARC or IgE were imputed with 0 (lowest) or largest values of TARC or IgE assays

**References:** 1. Hamilton et al. 49th ESDR 2019, Bordeaux, France. 2. Wang et al. 29th EADV 2020, Vienna, Austria. Poster P0269, abstract 2647.

**Abbreviations:** AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; IQR, interquartile range; LOCF, last observed carried forward; LS, least squares; PP-NRS, Peak Pruritus-Numerical Rating Scale; NR, non-responder imputation; TARC, thymus- and activation-regulated chemokine.