Efficacy and Safety of CBP-201 in Adults with Moderate-to-Severe Atopic Dermatitis (AD): A Phase 2b, Randomized, Double-blind, Placebo-controlled Trial (CBP-201-WW001)

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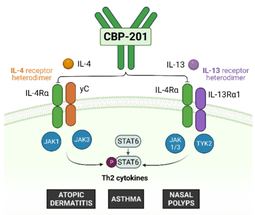
Atopic dermatitis (AD) is a chronic inflammatory skin condition primarily characterized by intense pruritus and recurrent eczematous skin lesions.[1]

CBP-201 is a novel monoclonal antibody that binds to a region of IL-4Rα that is different than dupilumab.

Early phase trial data suggest the potential for efficacy and safety in AD, with more convenient dosing frequency than current biologics.[2]

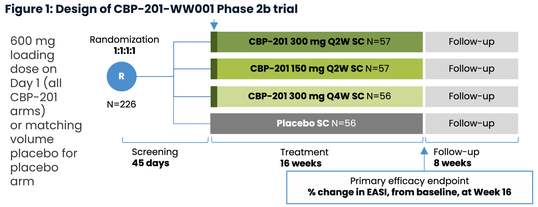
This Phase 2b trial (WW001) assessed three regimens of CBP-201 in adults with moderate-to-severe AD.



Methodology

- This Phase 2b, randomized, double-blind, placebo-controlled, international trial (NCT04444752) comprised 16-week treatment and 8-week follow-up periods (Figure 1).
- From July 2020 to September 2021, patients were randomized (1:1:1:1) to subcutaneous CBP-201 (300 mg every 2 weeks [Q2W], 150 mg Q2W, or 300 mg Q4W) or placebo, across 59 centers in the USA (38), China (9), Australia (8), and New Zealand (4).
- Key inclusion and exclusion criteria:
  - Moderate-to-severe AD (IGA ≥3, EASI ≥16, AD BSA ≥10%) inadequately controlled with, or not suitable for, topical treatments.
  - No prior dupilumab or other anti-IL-4Rα/IL-13 agents.
  - No concomitant topical AD treatment, except for bland emollient applied twice daily and rescue medication.
  - Key differences from Phase 3 trials of an approved anti-IL-4Rα agent[3] included a shorter (≥1 year) history of AD, a long screening period of 45 days and different definitions for 'prior' and 'inadequate response'.
- Endpoints and statistics:
  - The primary endpoint was percent EASI change from baseline at Week 16.
  - Secondary endpoints included proportion of patients with IGA 0 or 1 and a reduction of ≥2 points, and proportion of patients achieving EASI-50, EASI-75, and EASI-90.
  - Trial populations described here include the Randomized Set (all randomized patients irrespective of whether they received a treatment or not) and Full Analysis Set (FAS) / Safety Set (all randomized patients receiving ≥1 dose of treatment). A China subgroup analysis was specifically conducted to address local health authority requirements necessary for future regulatory review.
  - Continuous variables, including the primary endpoint, were analyzed using an ANCOVA model, with last observation carried forward (LOCF).
  - Binary secondary endpoints were analyzed using the Clopper-Pearson method in the FAS; for responder endpoints, missing values were imputed by

Figure 1: Design of CBP-201-WW001 Phase 2b trial



Results

Demographic & Baseline Characteristics

- 226 patients were randomly assigned to CBP-201 or placebo (Figure 1), with patients recruited across the USA (n=172), China (n=32), New Zealand (n=19), and Australia (n=3).
- Baseline characteristics were generally well balanced across the treatment arms (Table 1).
- Key baseline differences from Phase 3 trials of the currently approved anti-IL-4Rα agent[3,4] included different country locations recruited from, a population with less severe AD (median EASI 21.2; 31% with IGA score of 4), shorter AD duration (median 13.0 years), lower BSA (median 35.1%), and higher BMI (median 28.4 kg/m^2).
- In China, baseline characteristics were generally well balanced, while AD was more severe (median EASI 26.9; 38% IGA 4), BSA was higher (median 42.5%), and BMI was lower (median 25.6 kg/m^2) compared with the overall WW001 population. Overall, the China subgroup population was more consistent with that reported for the Phase 3 trials for the currently approved anti-IL-4Rα.[3,4]

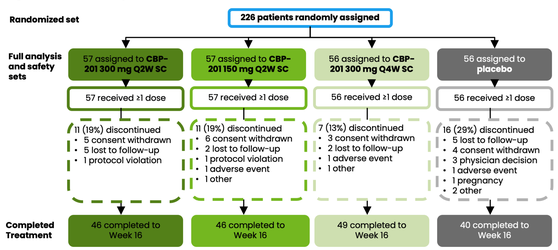
Table 1: Demographics of trial participants

Characteristics*	300 mg Q2W N=57	150 mg Q2W N=57	300 mg Q4W N=56	All CBP-201 N=170	Placebo N=56	Total N=226
Median age, years	38.0 (19, 70)	35.0 (19, 73)	43.0 (18, 73)	38.5 (18, 73)	40.0 (18, 67)	38.5 (18, 73)
Female, n (%)	27 (47%)	30 (53%)	28 (50%)	85 (50%)	36 (64%)	121 (54%)
Race, n (%)†						
White	38 (67%)	30 (53%)	32 (57%)	100 (59%)	32 (57%)	132 (58%)
Asian	9 (16%)	17 (30%)	12 (21%)	38 (22%)	14 (25%)	52 (23%)
Black/African American	7 (12%)	8 (14%)	10 (18%)	25 (15%)	6 (11%)	31 (14%)
Not Hispanic/Latino, n (%)	33 (58%)	40 (70%)	29 (52%)	102 (60%)	32 (57%)	134 (59%)
Median BMI, kg/m^2	29.1 (20.0, 57.8)	26.9 (17.6, 57.5)	29.8 (18.3, 66.4)	28.5 (17.6, 66.4)	28.1 (14.8, 57.2)	28.4 (14.8, 66.4)
Median AD duration, years	10.5 (1, 53)	11.0 (1, 56)	14.0 (1, 58)	13.0 (1, 58)	13.5 (2, 51)	13.0 (1, 58)
IGA score, n (%)						
3 (moderate)	34 (60%)	43 (75%)	40 (71%)	117 (69%)	39 (70%)	156 (69%)
4 (severe)	23 (40%)	14 (25%)	16 (29%)	53 (31%)	17 (30%)	70 (31%)
Median EASI score (IQR)	20.8 (16.8, 35.2)	21.2 (17.6, 28.2)	20.1 (17.6, 26.2)	20.9 (17.7, 28.8)	22.1 (18.3, 30.9)	21.2 (17.8, 29.0)
Mean (SD) EASI score	27.6 (11.8)	24.6 (10.5)	23.1 (8.2)	25.1 (10.4)	25.2 (9.0)	25.1 (10.0)
Median PP-NRS score (IQR)	7.1 (5.6, 8)	6.9 (5.9, 7.9)	6.7 (5.3, 7.7)	6.9 (5.6, 7.9)	7.0 (6.4, 8)	6.9 (5.9, 8)
Median % BSA involvement	37.0 (14.9, 85.0)	36.1 (12.0, 94.0)	32.5 (11.0, 89.5)	35.4 (11.0, 94.0)	35.1 (11.5, 87.0)	35.1 (11.0, 94.0)

*Median values (min, max) unless otherwise stated. †11 patients, not shown under 'race', were Native Hawaiian/Pacific Islander (n=3), Native American/Alaskan (n=1), multiple (n=3), or other (n=4); 4 in the placebo arm, ≤3 per CBP-201 dose arm.

- During the COVID-19 pandemic, trial conduct was impacted, with movement restrictions likely contributing to higher discontinuation rates (13%–19% per active drug arm; Figure 2) compared with anti-IL-4Rα Phase 3 trials (6.3–9.5%)[3]; none were attributable directly to COVID-19 infection.
- Patients with rescue medication use by Week 16, imputed as non-responders (NRI), ranged from 3.5% (150 mg Q2W) to 12.5% (placebo); this was lower than in Phase 3 trials for the currently approved anti-IL-4Rα, which ranged from 17.1% (Q2W 300 mg) to 51.7% (placebo).[3]

Figure 2: Patient disposition to Week 16

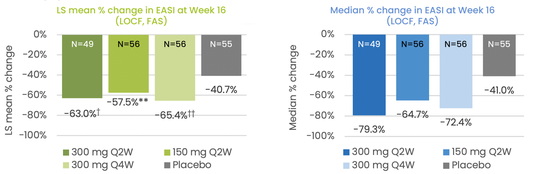


Efficacy

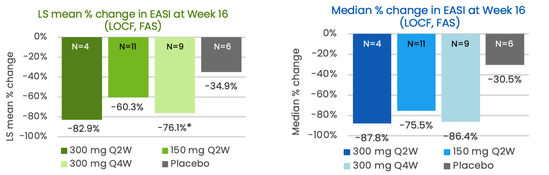
- All doses of CBP-201 met the primary endpoint (LS mean percent change in EASI at Week 16, from baseline, vs placebo), with greater reductions in the 300 mg Q2W and Q4W groups.
- As expected with the non-normal distributed baseline EASI, median EASI percent reductions were greater than LS mean percent reductions, with a similar placebo response (Figure 3).
- In the China subgroup, higher baseline AD severity, and no discontinuations in CBP-201 groups, may have contributed to greater CBP-201 and less placebo response vs the overall study population.

Figure 3: Primary endpoint: Percent change from baseline in EASI at Week 16

Overall population



China subgroup

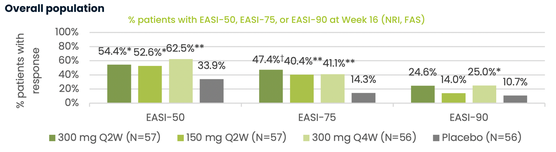


*p<0.05 vs placebo **P=0.01 vs placebo. †P=0.0012 vs placebo †† P=0.0002 vs placebo

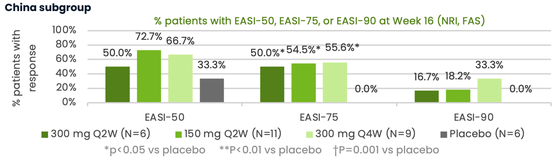
- Significant improvements with CBP-201 were also seen for a range of secondary efficacy endpoints, including proportions of EASI and IGA 0 or 1 responders, and change in PP-NRS (Figure 4 and Figure 5).
- CBP-201 300 mg efficacy responses were generally numerically greater than with 150 mg Q2W.

Figure 4: Key secondary endpoints: Proportion of EASI-50, EASI-75, EASI-90 responders at Week 16

Overall population



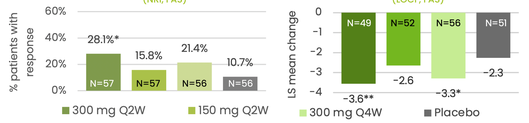
China subgroup



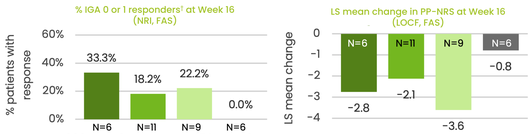
*p<0.05 vs placebo **P<0.01 vs placebo †P=0.001 vs placebo

Figure 5: Key secondary endpoints: Proportion of IGA 0/1 responders† and change in PP-NRS at Week 16

Overall population



China subgroup



*P<0.05 vs placebo **P<0.01 vs placebo †with ≥2-point improvement from baseline

Safety

- CBP-201 and placebo had similar incidences of TEAEs, serious TEAEs, and TEAEs leading to discontinuation (Table 2).
- For adverse events of special interest, CBP-201 had low rates of injection site reactions, herpes virus infections and conjunctivitis.

Table 2: Adverse events

n (%) patients with…	CBP-201 300 mg Q2W N=57	CBP-201 150 mg Q2W N=57	CBP-201 300 mg Q4W N=56	All CBP-201 N=170	Placebo N=56
Any TEAE	26 (45.6%)	24 (42.1%)	32 (57.1%)	82 (48.2%)	30 (53.6%)
Serious TEAE	0	1 (1.8%)	2 (3.6%)	3 (1.8%)	2 (3.6%)
Grade ≥3 TEAE	1 (1.8%)	1 (1.8%)	4 (7.1%)	6 (3.5%)	1 (1.8%)
Discontinuation due to TEAE	0	1 (1.8%)	1 (1.8%)	2 (1.2%)	1 (1.8%)
Treatment-related TEAE	6 (10.5%)	6 (10.5%)	8 (14.2%)	20 (11.8%)	5 (8.9%)
COVID-19 infections	2 (3.5%)	4 (7.0%)	1 (1.8%)	7 (4.1%)	4 (7.1%)
Conjunctivitis	2 (3.5%)	2 (3.5%)	1 (1.8%)	5 (2.9%)	0
Conjunctivitis allergic	0	0	1 (1.8%)	1 (0.6%)	0
Injection site reaction	1 (1.8%)	1 (1.8%)	1 (1.8%)	3 (1.8%)	1 (1.8%)
Herpes virus					
Oral herpes	0	0	0	0	1 (1.8%)
Ophthalmic herpes simplex	0	0	1 (1.8%)	1 (0.6%)	0

Conclusion

Despite the COVID-19 pandemic, clinical outcomes were significantly improved for all doses of CBP-201, meeting both primary and key secondary endpoints. 300 mg Q2W and Q4W efficacy responses were generally numerically greater than with 150 mg Q2W.

This trial recruited a patient population with less severe AD, more discontinuations, higher BMI and less rescue medication use than in Phase 3 trials of the currently approved anti-IL-4Rα agent.[3]

A priori analyses of populations with more severe AD than the overall WW001 population, and that were more comparable to Phase 3 trials for the approved anti-IL-4Rα agent,[3] showed that CBP-201 responses increased and placebo response was similar or lower than the overall WW001 population (see also Silverberg et al, Maui Derm 2022).

The overall safety profile of CBP-201 was similar to placebo, except for a low incidence of conjunctivitis, and was consistent with the approved anti-IL-4Rα with no new safety signals.

These results support further investigation in Phase 3 trials of CBP-201 300 mg in moderate-to-severe AD that take into consideration how differences in trial design and the patient populations recruited may impact efficacy and safety outcomes.

Funding: Connect BioPharma

References: 1. Weidinger et al. Nat Rev Dis Primers. 2018;4:1. 2. Wang et al. 29th EADV 2020, Vienna, Austria. Poster P0269, abstract 2647. 3. Thaçi et al. J Dermatol Sci. 2019;94:266–75. 4. Dupixent INN. https://www.ema.europa.eu/en/documents/assessment-report/dupixent-epar-public-assessment-report_en.pdf.

Abbreviations: AD, atopic dermatitis; ADAb, anti-drug antibody; BMI, body mass index; BSA, body surface area; EASI, Eczema Area and Severity Index; FAS, full analysis set; IGA, Investigator's Global Assessment; LOCF, last observation carried forward; NRI, non-responder imputation; Q2W, every 2 weeks; Q4W, every 4 weeks; PP-NRS, Peak Pruritus Numerical Rating Scale; TEAE, treatment-emergent adverse event.