

Rademikibart (IL-4R α Blocker) Integrated Exposure-Response Analysis Supports Differentiated Once Monthly Dosing Regimen

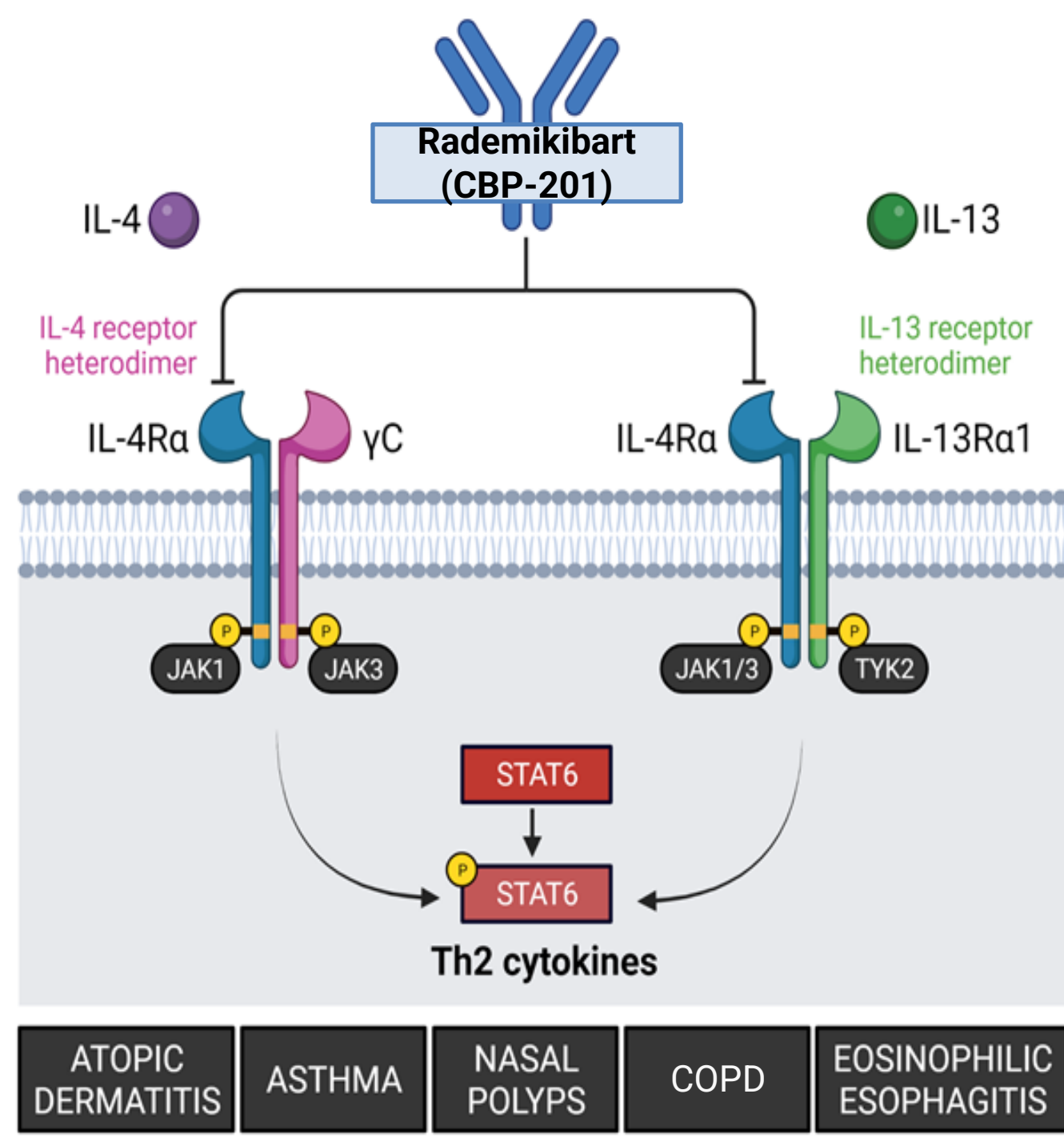
EADV 2024

P0714

Abstract 6546

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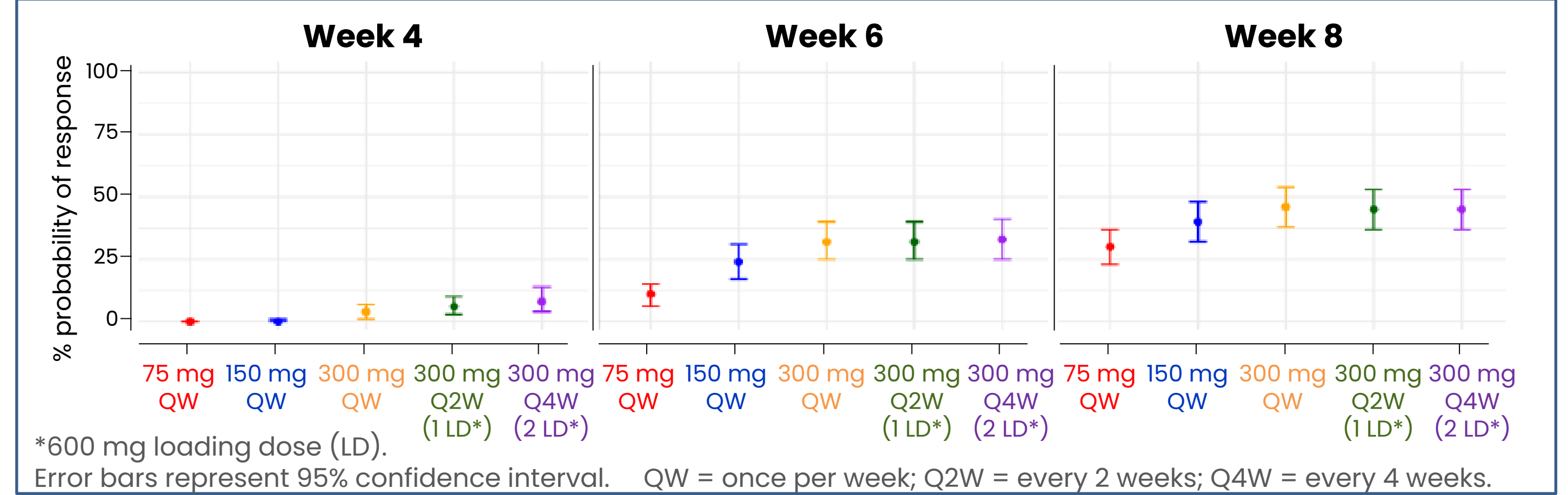


- Rademikibart (formerly CBP-201) is a next-generation mAb targeting IL-4R α .
- Rademikibart bound with higher affinity than dupilumab to distinct IL-4R α epitopes, potentially downregulating signaling and cytokine gene expression.^{1,2}
- In patients with moderate-to-severe atopic dermatitis (AD), rademikibart therapy resulted in meaningful improvements in three trials:
 - An Australian Phase 1 study (trial ID: ACTRN12619000395134).³
 - A global Phase 2 study, known as WW001 (NCT04444752).⁴
 - A Chinese pivotal study, known as SEAS/DE CHINA or CN002 (NCT05017480), which showed highly maintained response across one year.⁵⁻⁸
- Fixed dosing every 4 weeks (Q4W) achieved the primary endpoint at Week 16 in the global Phase 2 study, and both Q4W and Q2W dosing post Week 16 maintained and improve disease control for responders in the China pivotal study.⁴⁻⁸

Two once-weekly 600 mg loading doses, before 300 mg Q4W fixed dosing, drive strong clinical response

Loading doses (600 mg) at Weeks 0 and 1, before 300 mg Q4W dosing from Week 2, resulted in strong early EASI-75 response, when compared with more frequent dosing regimens with one or no loading dose (Figure 1).

Figure 1: Simulated EASI-75 response versus dose group



The Q4W fixed dosing regimen provides an appropriate rademikibart concentration for all body weights

Fixed 300 mg Q4W dosing after two 600 mg loading doses has a Week 18 C_{trough} value of 8.0 μ g/mL, compared with 10.0 μ g/mL for weight-based dosing, indicating that a fixed-dose regimen of rademikibart is acceptable (Figure 2).

The fixed dosing regimen provided an appropriate rademikibart concentration for all body weights (Figure 2 and Table 2). As shown by the red box (Table 2), higher body weight was associated with exposure that was higher than rademikibart's clinical response IC₅₀ level of 3.6 μ g/mL.

Figure 2: Steady-state exposure predictions: fixed vs weight-based dosing

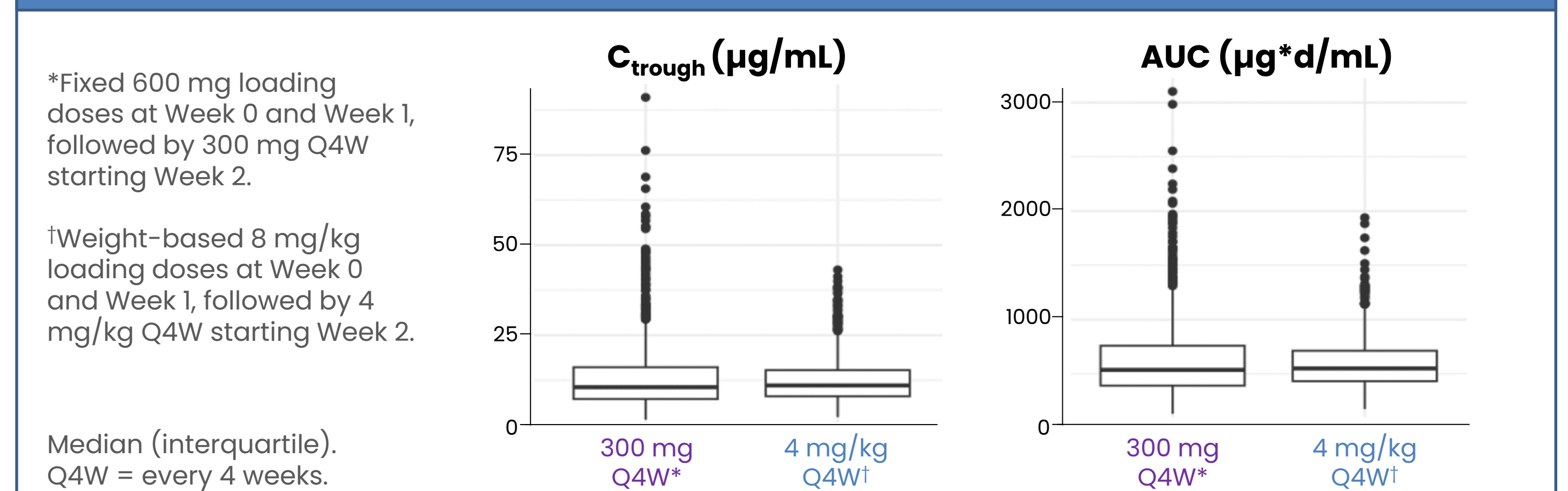


Table 2: Steady-state exposure predictions: fixed vs weight-based dosing

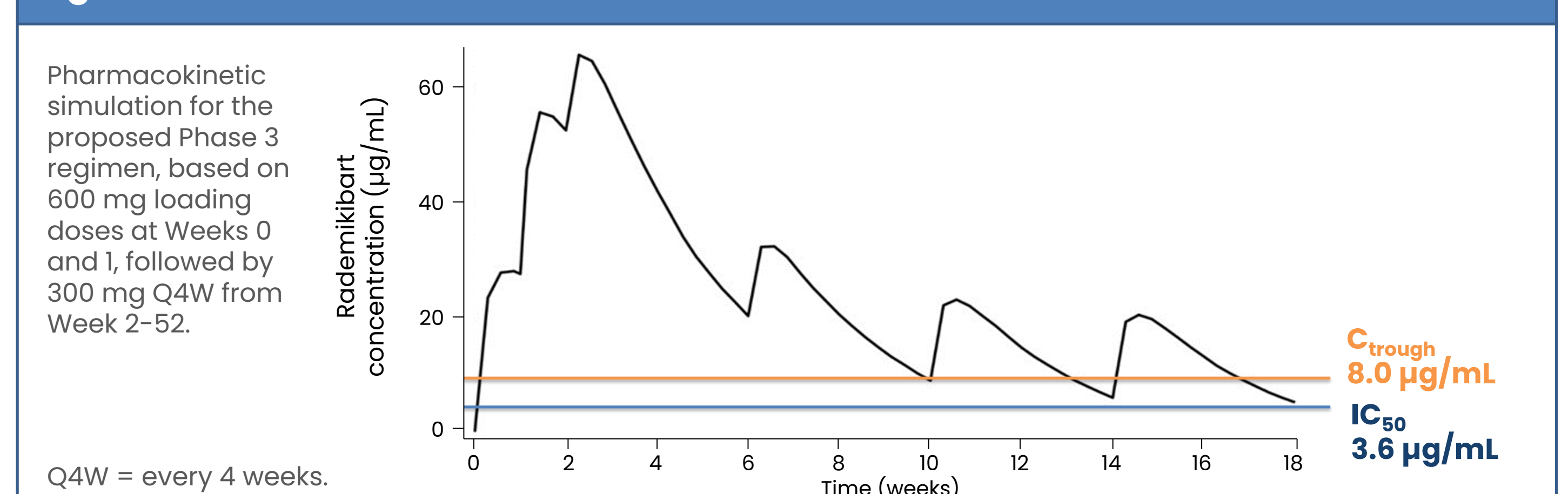
Weight (kg)	C _{trough} (μ g/mL)		AUC (μ g*d/mL)	
	300 mg Q4W*	4 mg/kg Q4W*	300 mg Q4W*	4 mg/kg Q4W*
40-50	23.2 (9.7, 54.2)	13.3 (5.6, 31.2)	1058 (555, 2032)	635 (340, 1190)
51-60	17.1 (7.3, 38.8)	12.4 (5.0, 27.6)	843 (433, 1590)	595 (313, 1089)
61-70	13.6 (5.6, 31.7)	11.3 (5.0, 26.4)	677 (341, 1261)	582 (303, 1089)
71-80	10.4 (4.4, 23.2)	10.3 (4.5, 22.4)	541 (292, 963)	540 (289, 961)
81-90	8.8 (3.7, 19.5)	9.9 (4.3, 22.4)	463 (242, 875)	515 (282, 930)
91-100	7.5 (3.0, 16.9)	9.8 (4.2, 21.8)	390 (204, 734)	514 (271, 969)
101-110	6.4 (2.9, 14.0)	9.5 (4.1, 21.0)	347 (183, 629)	498 (282, 970)
111-120	5.9 (2.6, 13.4)	9.1 (4.1, 20.0)	321 (161, 615)	482 (266, 914)
121-130	5.0 (2.2, 10.9)	9.1 (3.9, 20.9)	277 (149, 519)	466 (253, 930)
131-140	4.8 (2.0, 10.4)	8.7 (3.8, 18.7)	254 (138, 489)	449 (238, 876)
141-150	4.2 (1.9, 9.4)	8.5 (3.9, 18.8)	232 (126, 448)	449 (239, 839)
All weights	8.0 (2.7, 30.1)	10.0 (4.3, 23.6)	421 (168, 1264)	519 (273, 987)

Median (interquartile). Q4W = every 4 weeks. *See Figure 2 for loading doses for fixed and weight-based dosing.

The Q4W fixed dosing regimen provides early high exposure

The Q4W fixed dosing regimen provides adequate exposure to rademikibart to maximize efficacy (Figure 3), including the aforementioned IC₅₀ for clinical response of 3.6 μ g/mL and average C_{trough} at Week 18 of 8.0 μ g/mL, 2.2 times above the IC₅₀.

Figure 3: Median rademikibart concentration versus time



Conclusions

- Based on the ER model, the rademikibart dose regimen recommended for the Phase 3 program comprises a fixed dosing regimen of 600 mg loading doses at Week 0 and Week 1, followed by 300 mg Q4W starting at Week 2.
- The ER profile for the fixed Q4W regimen includes a Week 18 median C_{trough} value (8.0 μ g/mL) that is 2.2-fold higher than its IC₅₀ (3.6 μ g/mL), suggesting adequate drug exposure over the dosing interval to maximize target engagement.
- The Week 18 median C_{trough} value (8.0 μ g/mL) for the fixed Q4W regimen, compared with that of the 4 mg/kg weight-based dosing regimen (10.0 μ g/mL), indicates that a fixed dose regimen for rademikibart is acceptable.

Presented at: EADV 2024, September 25th-28th, 2024, Amsterdam. Funding: Connect Biopharma.

References: 1. Yang et al. SID 2022, Portland, OR (Poster LB945). 2. Zhang et al. Sci Rep. 2023;13:12411. 3. Wang et al. Clin Transl Sci 2023;16:2614-27. 4. Silverberg et al. J Allergy Clin Immunol. 2024;153:1040-9. 5. Zhang et al. Poster 3240, WCD 2023, Singapore. 6. Zhang et al. Poster 3242, WCD 2023, Singapore. 7. Zhang et al. Poster 3243, WCD 2023, Singapore. 8. Zhang et al. Poster 3247, WCD 2023, Singapore.

Objective

To support the use of once monthly dosing in the Phase 3 program, we developed an exposure-response (ER) model, characterizing the relationship between the proportion of patients with 75% reduction in EASI score (EASI-75) and rademikibart administration. We investigated (a) the benefits of loading doses, administered before fixed doses Q4W, and (b) fixed versus weight-based dosing in adults with moderate-to-severe AD.

Methodology

Study design

We developed an integrated population ER model using pooled data from two clinical trials (the Australian Phase 1 study and Chinese pivotal study [SEAS/DE CHINA]). We investigated the effects of selected covariates on efficacy parameters and predicted efficacy outcomes for various rademikibart dosing conditions.

Model development

A combined (placebo + drug effect) model was developed to characterize the relationship of response over time in the presence of rademikibart. An indirect relationship between exposure and response was observed. A nonlinear inhibitory effect of rademikibart concentration on response was used and the equation of the indirect response model is:

$$dR/dt = kin * (1 - (Imax * C(t)) / (IC_{50} + C(t))) - kout * R$$

C(t) = rademikibart concentration at time, t; d = differential; IC₅₀ = concentration at which 50% of the maximum effect; Imax = maximum drug effect; kin = apparent zero-order rate constant for production of response; kout = first-order rate constant for the loss of response; R = response variable (i.e., EASI-75) and the baseline response.

Model applications

Exposure-response predictions

Simulations were performed to predict longitudinal and landmark EASI-75 response with several dosing regimens.

Fixed versus weight-based dosing

Baseline body weight was a significant covariate in the population PK model. PK and ER simulations were conducted to explore the implications of fixed versus weight-based dosing.

To demonstrate the impact of body weight on PK, virtual subjects were assigned to a fixed dose (600 mg loading doses at Week 0 and Week 1, followed by 300 mg Q4W starting Week 2), or weight-based dosing 8 mg/kg loading doses at Week 0 and Week 1, followed by 4 mg/kg Q4W starting Week 2).

Rademikibart exposure metrics were calculated at steady state (Day 266-294) for all body weights or by body weight group for each dose regimen.

Results

Parameter estimates for the combined model

Final estimates of inhibition of response using a combined (placebo + drug effect) indirect response model (Table 1).

Table 1: Parameter estimates

Parameter	Estimate (95% CI)	Relative standard error (%)	Shrinkage (%)
BASE*	6.82 (6.62, 7.03)	1.53	-
Pmax*	-2.04 (fixed)	-	-
Placebo onset rate (1/day)	0.03 (fixed)	-	-
Imax*	0.449 (0.376, 0.524)	-	-
IC ₅₀ (ng/mL)	3.58x10 ³ (1.79x10 ³ , 7.16x10 ³)	36.5	-
Kout (1/day)	0.0278	9.69	-
IIV-BASE*	0.0516, CV% 23.0	10.2	8.51
IIV-Imax	2.23, SD 1.5	18.5	39.0
Additive variance (SD)	1.17	4.09	11.3

*Transformed EASI scale.

CI = confidence interval; CV = coefficient of variation; EASI = Eczema Area and Severity Index; IC₅₀ = concentration achieving half the maximum drug effect; IIV = inter-individual variability; Imax = maximum drug effect; Kout = first-order rate constant for loss of response; Pmax = maximum placebo effect; SD = standard deviation.

Model equations:

$$\frac{EASI^{0.4}-1}{0.4} = R + Pmax * (1 - e^{-kp*time}), \text{ where at time} = 0, \text{ then } \frac{EASI^{0.4}-1}{0.4} = BASE.$$

$$\frac{dR}{dt} = kin * \left(1 - \frac{Imax * C(t)}{IC_{50} + C(t)}\right) - kout * R$$

kin = apparent zero-order rate constant for production of response; R = response variable (i.e., EASI-75); baseline response, BASE, is defined as kin/kout.