



Semi-mechanistic Population Pharmacokinetic/Pharmacodynamic (Pop PK/PD) Modeling of Dupilumab on Nasal Congestion (NC) Score in Patients with Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)

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OBJECTIVES

- Dupilumab, a fully human anti-interleukin (IL)-4R α monoclonal antibody, inhibits signaling of IL-4/IL-13, key drivers of Type-2 inflammatory diseases.
- Dupilumab is approved for subcutaneous (SC) treatment of adult patients with CRSwNP, as well as adult and pediatric patients aged ≥ 6 years with moderate-to-severe atopic dermatitis (AD) and patients aged ≥ 12 years with moderate-to-severe asthma.
- This analysis aimed to develop a Pop PK/PD model to characterize the relationship between time course NC score and dupilumab PK exposure, and to identify intrinsic and/or extrinsic factors significantly contributing to NC score variability in CRSwNP patients.

METHODS

- The Pop PK/PD model was developed using data pooled from one phase 2 study (ACT12340) and two phase 3 studies (EFC14146 and EFC14280) in CRSwNP patients who received subcutaneous dupilumab 300 mg (with 600 mg loading dose) every week (qw) for 16 weeks, 300 mg every two weeks (q2w) for 24 or 52 weeks, 300 mg q2w for 24 weeks followed by a switch to every four weeks (q4w) until 52 weeks (q2w-q4w), or placebo.
- The Pop PK/PD model was developed in a sequential manner, where the estimated individual PK parameters from a previously published Pop PK model^[1] were used to derive serum dupilumab concentrations, which then served as exposure input to drive the effect on NC score.
- Demographic variables, baseline disease characteristics, Type 2 inflammation biomarkers, anti-drug antibodies (ADA), and asthma history were tested as covariates by forward selection and backward elimination.
- The model was validated with visual predictive check and bootstrap.

RESULTS

- The final Pop PK/PD dataset included 11342 NC observations from 777 CRSwNP patients (N=312 treated with placebo, N=465 treated with dupilumab). The baseline characteristics of CRSwNP patients for the model development population are summarized in **Table 1**.

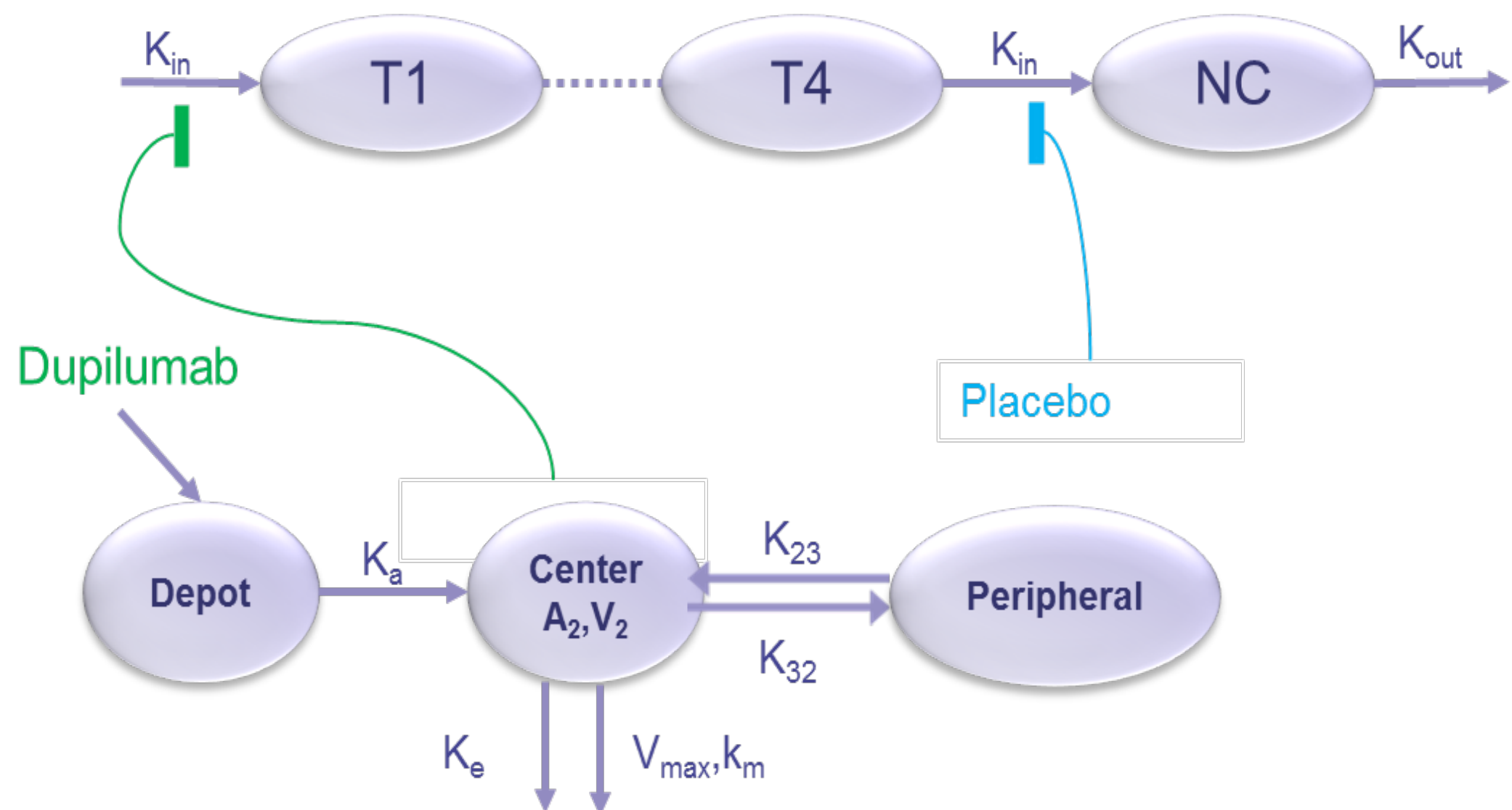
Table 1. Baseline Characteristics of CRSwNP patients in the Final Dataset

Continuous variables								
Covariates	ACT12340 (N=60)		EFC14146 (N=273)		EFC14280 (N=444)		Total (N=777)	
	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)
EOS (cells/ μ L)	428 (502)	330 (90 - 3920)	429 (312)	350 (0 - 2110)	430 (353)	340 (0 - 3030)	430 (353)	340 (0 - 3920)
Age	48.4 (9.41)	49 (25 - 64)	50.5 (13.4)	51 (22 - 85)	52 (12.4)	52 (18 - 83)	51.2 (12.6)	52 (18 - 85)
Weight (kg)	82.6 (15.4)	83 (55.2 - 126)	81.9 (18.6)	80 (38 - 156)	79.8 (17.9)	79 (39.4 - 150)	80.8 (18)	80 (38 - 156)
NC	1.67 (0.702)	1.71 (0.571 - 3)	2.35 (0.57)	2.14 (1 - 3)	2.44 (0.574)	2.5 (0 - 3)	2.35 (0.616)	2.29 (0 - 3)
NPS	5.77 (0.945)	6 (3 - 8)	5.74 (1.28)	6 (2 - 8)	6.11 (1.21)	6 (1.5 - 8)	5.95 (1.23)	6 (1.5 - 8)
UPSIT	2.61 (0.752)	3 (0.167 - 3)	14.6 (8.46)	12 (0 - 39)	13.7 (7.92)	11 (0 - 40)	13.1 (8.39)	11 (0 - 40)
Categorical variables								
Covariate	Subgroup	ACT12340 (N=60)		EFC14146 (N=273)		EFC14280 (N=444)		Total (N=777)
SEX	Male	Count (%)		Count (%)		Count (%)		Count (%)
	Female	34 (56.7)		157 (57.5)		276 (62.2)		467 (60.1)
RACE	Caucasian	26 (43.3)		116 (42.5)		168 (37.8)		310 (39.9)
	Black	59 (98.3)		263 (96.3)		383 (86.3)		705 (90.7)
Static antidrug antibody	Asian	1 (1.67)		9 (3.3)		7 (1.58)		17 (2.19)
	Negative	0 (0)		1 (0.366)		54 (12.2)		55 (7.08)
Asthma history	Pre-existing	39 (65)		243 (89)		392 (88.3)		674 (86.7)
	Treatment-emergent	14 (23.3)		3 (1.1)		22 (4.95)		39 (5.02)
	Yes	7 (11.7)		27 (9.89)		30 (6.76)		64 (8.24)
	No	35 (58.3)		158 (57.9)		265 (59.7)		458 (58.9)
	No	25 (41.7)		115 (42.1)		179 (40.3)		319 (41.1)

EOS: blood eosinophils; NC: nasal congestion; NPS: nasal polyp score; SD: standard deviation; UPSIT: University of Pennsylvania smell identification test.

- The base model structure used for Pop PK/PD model of NC in this analysis is provided in **Figure 1**. Both placebo and treatment effects were described by Emax type of models with time or serum dupilumab concentration driving the NC inhibition indirectly. Four transit compartments were employed to describe the delayed treatment effect relative to placebo.

Figure 1 Structure of Pop PK/PD model of NC in this analysis



Abbreviation K_{in} : first-order absorption rate constant; K_{out} : linear elimination rate constant; k_{in} : the rate constant of the production of NC; k_{out} : the rate constant of the elimination of NC; K_{23} and K_{32} : inter-compartment distribution rate constants; V_2 : volume of central compartment; V_3 : volume of peripheral compartment; V_{max} : maximum nonlinear clearance; K_m : concentration achieves 50% of V_{max} .

- The parameter estimates of final Pop PK/PD model of NC and their relationship to covariates are summarized in **Table 2**.

RESULTS

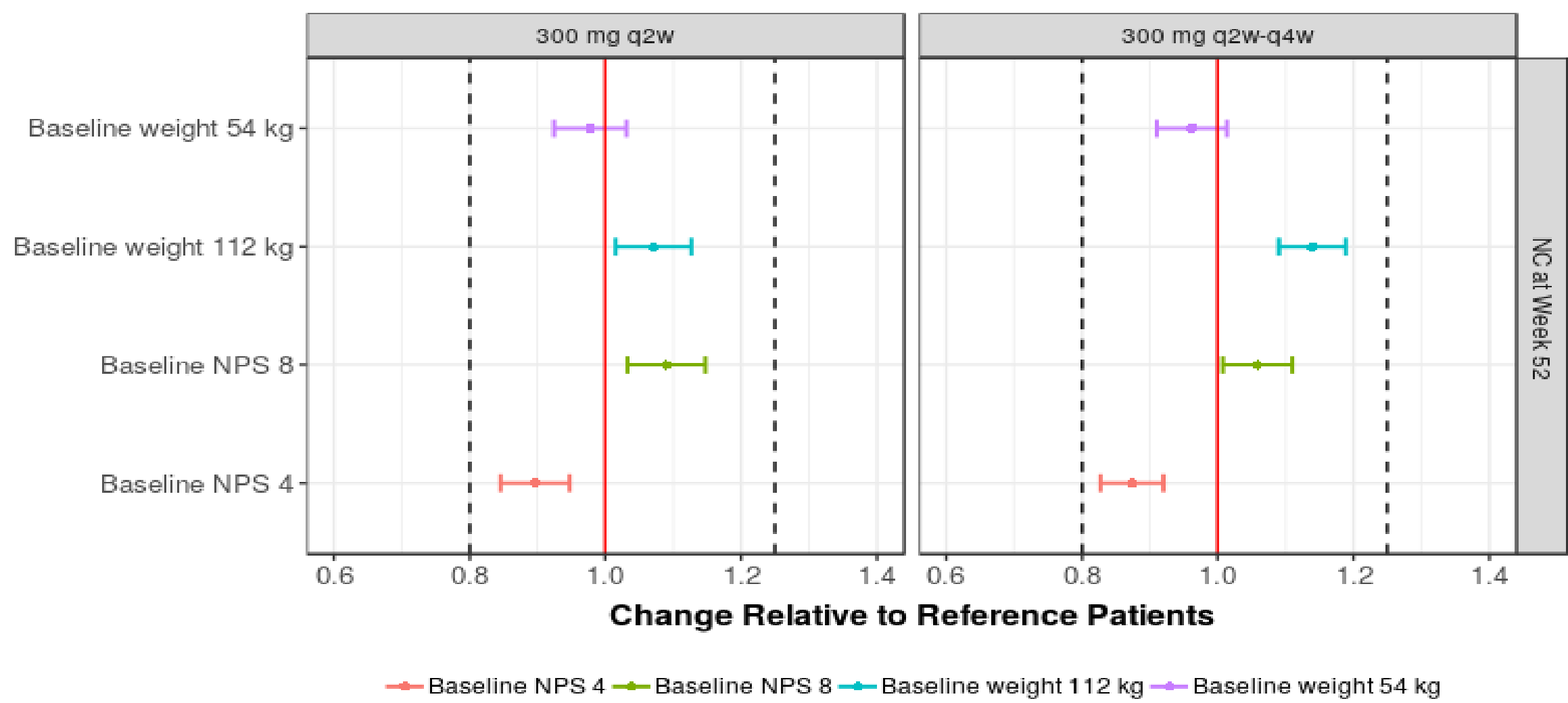
Table 2. Parameters estimates of final Pop PK/PD model of NC

Parameter	Estimate (RSE%)	IIV (RSE%)	95% CI	Shrinkage (%)
Base	2.59 (6.90)	156 (9.74)	[5.37,7.09]	20.6
P_{max}	0.0785 (FIX)	323 (9.62)	-	34.0
T_{50} (days)	7.47 (FIX)	228 (21.3)	-	62.2
IC_{50} (mg/L)	3.05 (5.39)	-	[2.72,3.37]	-
I_{max}	0.573 (14.7)	266 (10.3)	[0.945,1.73]	42.8
k_{out} (1/day)	0.0460 (4.72)	86.6 (9.02)	[0.0416,0.0503]	30.6
Power coefficient of weight on Imax	-1.56 (41.6)	-	[-2.86,-0.262]	-
Power coefficient of BNPS on Base	1.74 (14.7)	-	[1.22,2.25]	-
Additive residual error	0.287 (0.375)	-	[0.286,0.288]	-

Abbreviation: %RSE: Percentage of Relative Standard Error (100% * SE / Estimate); 95% CI: 95% confidence interval; Base: baseline NC; CI: confidence interval; CV: coefficient of variation; Base: Baseline NC; I_{max} : maximum dupilumab effect on NC; IC_{50} : concentration that achieves 50% of maximum treatment effect; IIV: inter-individual variability; T_{50} : Time to 50% of maximum placebo effect; k_{out} : first-order NC elimination rate; P_{max} : maximum placebo effect on NC.

- In covariates analysis, two statistically significant covariates were identified. The maximum treatment effect was related to body weight, with a better effect in patients with lower body weight. Baseline NC value was related to baseline nasal polyp score (NPS), with a higher baseline NC in patients with a higher baseline NPS.
- These two statistically significant covariates were not deemed to be clinically relevant based on simulations, as shown in **Figure 2**.
- None of the other tested covariates, including age, gender, race, region, baseline Type 2 inflammation biomarkers and ADA, were statistically significant. Concomitant use of common NP medication (i.e. systemic corticosteroids) and other comorbidities (asthma history, exacerbated respiratory disease history and allergic rhinitis history) showed no effect on NC response based on covariate analysis and post-hoc analysis.

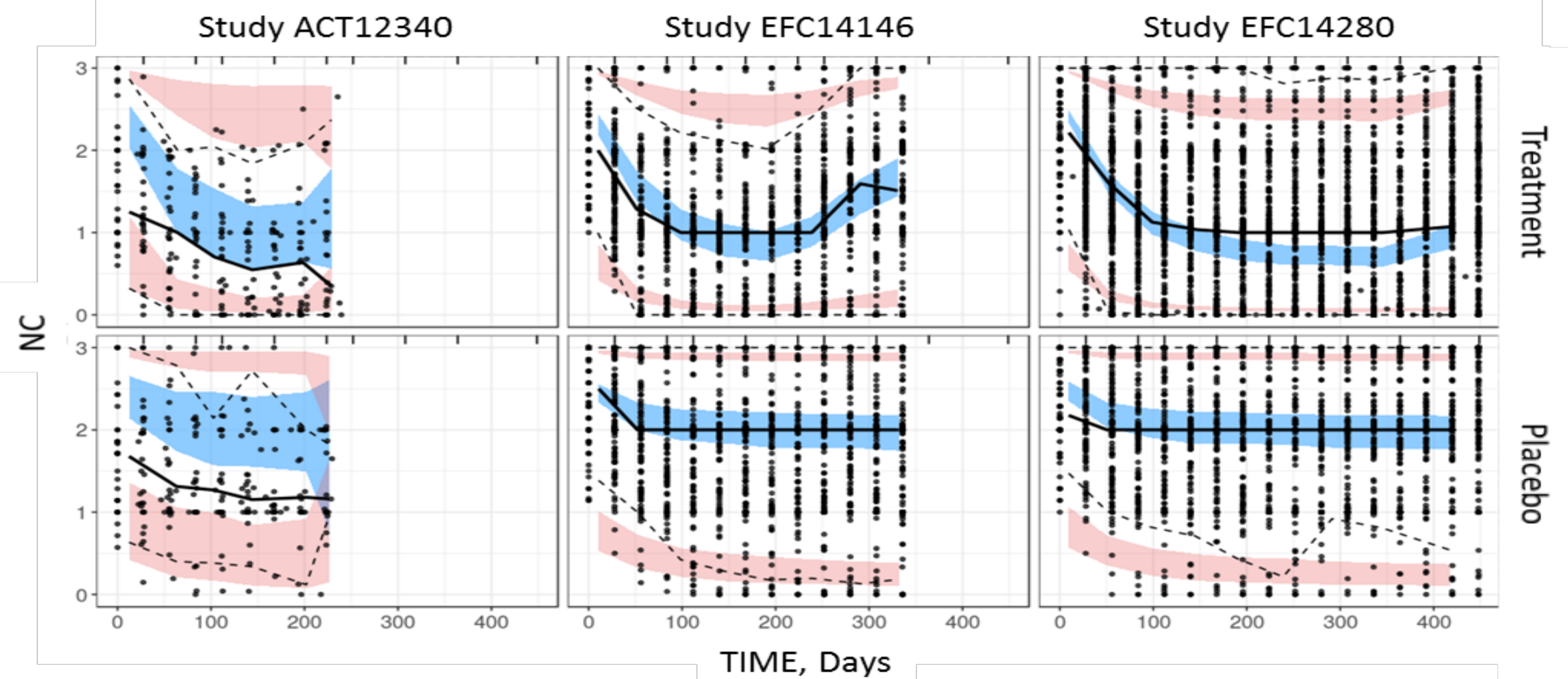
Figure 2. Impact of covariates on NC score at Week 52 relative to typical patients



The demographic characteristics of simulated typical patients (n=1000) were as follows: patients with baseline weight of 80 kg and baseline NPS of 6. The cut off covariate value for simulated patients (n = 1000) represented 5% and 95% percentile of covariates of Pop PK/PD model development population. NC at Week 52 for the simulated typical patients is represented by the red solid vertical line. The black dashed vertical lines represent 80 and 125% of the reference NC at Week 52 for simulated patients. The solid square and error bars represent the mean and 90% confidence interval for the fold change of NC at Week 52 in simulated patients relative to the typical patients.

- The predictive performance of final model was acceptable based on VPC results (**Figure 3**), which indicated robustness and good predictive performance of the final Pop PK/PD model.

Figure 3. VPC for final Pop PK/PD model stratified by study and treatment group



Legend: black dots: observations; solid black line: median of observed NC; dashed lines: 5th and 95th percentiles of observed NC; pink and light blue areas: confidence intervals of median and centiles of predicted NC.

CONCLUSIONS

- The NC scores over time in CRSwNP patients treated with dupilumab were well characterized by an indirect response model with transit compartments relating dupilumab concentration to NC score.
- Baseline body weight and NPS were identified as statistically significant, but not clinically relevant, covariates on dupilumab treatment effect in CRSwNP patients.

REFERENCES

- Yue Gao, Christine Xu, John D. Davis, Vanaja Kanamaluru, Qiang Lu. Population pharmacokinetic analysis of dupilumab in adult patients with chronic rhinosinusitis with nasal polyposis. ACOP 10, Orlando, FL. Oct 20-23, 2019.