

Supplementary Materials

Model-Based Meta-Analysis on the Efficacy of Biologics and Small Targeted Molecules for Crohn's Disease

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References and Time Points of Included Studies

Supplementary Table 1 Time points for studies included in the model-based meta-analysis.

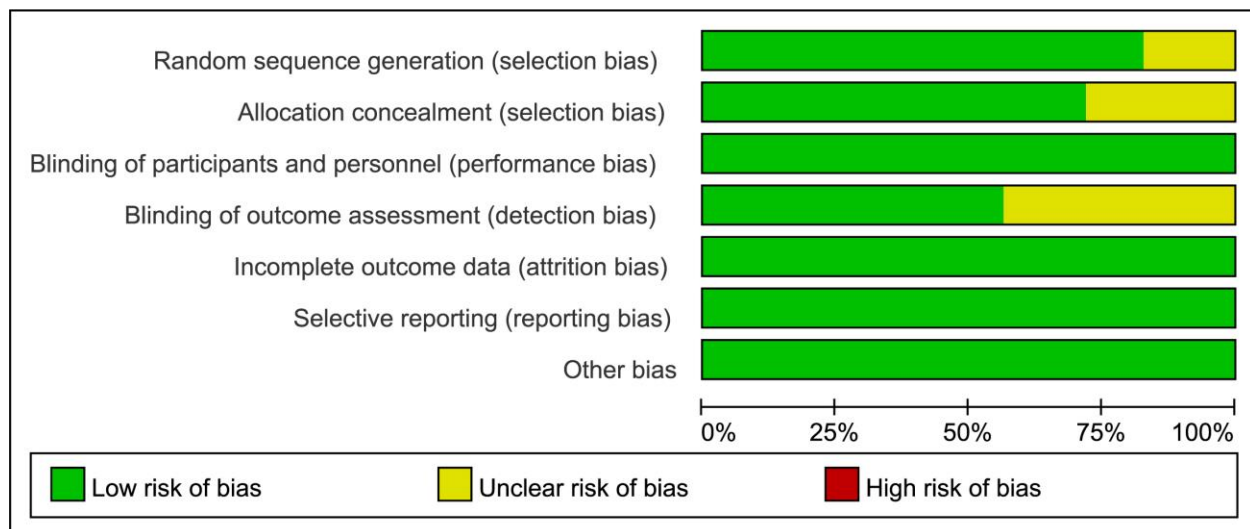
No.	Study	Patients	Drug	Regimen	Time points (week)					
					CDAI	CDAI70	CDAI100	CDAI150	IBDQ	CRP
1	Targan, 1997	108	infliximab	5 mg/kg 10 mg/kg 20 mg/kg	2,4	2,4,12		2,4,12	4	2,4
2	D'haens 1999	30	infliximab	5 mg/kg 10 mg/kg 20 mg/kg	4					4
3	Colombel, 2010 (SONIC)	339	infliximab	5 mg/kg 0,2,6 q8w		2,6,10,18, 26	2,6,10,18, 26	2,6,10,18, 26	2,6,10,18, 26	26
4	Gordon, 2001	30	natalizumab	3 mg/kg	1,2,4			2		
5	Ghosh, 2003	248	natalizumab	3 mg/kg 0w 3 mg/kg 0,4w 6 mg/kg 0,4w		2,4,6,8,12		2,4,6,8,12	6,12	
6	Sandborn, 2005 (ENACT-1)	905	natalizumab	300 mg 0,4,8w		2,4,6,8,10, 12		2,4,6,8,10, 12		
7	Targan, 2007 (ENCORE)	509	natalizumab	300 mg 0,4,8w	4,8,12	4,8,12	4,8,12	4,8,12	12	4,8,12
8	Stack, 1997	31	CDP571	5 mg/kg	2,4,6,8			2		2,4,6,8
9	Sandborn, 2004	395	CDP571	10 mg/kg q8w	2,4,8,12,1 6,24,28	2,4,8,12,1 6,24,28		2,4,8,12,1 6,24,28	2,4,8,16,2 4,28	4,8,16,28
10	Sandborn, 2001	43	etanercept	25 mg biw	2,4,8	2,4,8		2,4,8	2,4,8	
11	Winter, 2004	90	certolizumab	5 mg/kg 10 mg/kg 20 mg/kg	2,4,8,12			2,4,8,12		2,4,8,12
12	C87037	94	certolizumab	200 mg q2w 400 mg q2w		2,4,6	2,4,6	2,4,6		
13	Schreiber, 2005	291	certolizumab	100 mg q4w 200 mg q4w 100 mg q4w				2,4,6,8,10, 12		2,4,6,8,10, 12

14	Sandborn, 2011	439	certolizumab	400 mg q2w	2,4,6		2,4,6	2,4,6		2,4,6
15	Sandborn, 2007 (PRESISE-1)	660	certolizumab	400 mg 0,2,4 q4w	2,4,6,8,12,16,20,24,26	2,4,6,8,12,16,20,24,26	2,4,6,8,12,16,20,24,26	2,4,6,8,12,16,20,24,26	26	2,4,6,8,12,16,20,24,26
16	Hanauer, 2006 (CLASS-I)	299	adalimumab	40 mg 0w+20 mg 2w 80 mg 0w+40 mg 2w 160 mg 0w+80 mg 2w	1,2,4	1,2,4	1,2,4	1,2,4	1,2,4	1,2,4
17	Watanabe, 2011	90	adalimumab	80 mg 0w+40 mg 2w 160 mg 0w+80 mg 2w	2,4	4	4	2,4		
18	Sandborn, 2007 (GAIN)	325	adalimumab	160 mg 0w+80 mg 2w	1,2,4	1,2,4	1,2,4	1,2,4	4	4
19	Chen, 2020	205	adalimumab	160 mg 0w+80 mg 2w	2,4	2,4		2,4		2,4
20	Rutgeerts, 2006	207	onercept	10 mg tiw 25 mg tiw 35 mg tiw 50 mg tiw			8	8		
21	Feagan, 2008	185	vedolizumab	0.5 mg/kg q4w 2 mg/kg q4w	8	1,2,4,6,8	8,16	1,2,4,6,8	8	
22	Sandborn, 2013 (GEMINI2)	368	vedolizumab	300 mg 0,2w			6	6		6
23	Sands, 2014 (GEMINI3)	416	vedolizumab	300 mg 0,2,6w			6,10	6,10		
24	Watanabe 2019		vedolizumab	300 mg 0,2,6w			10	10		2,6,10
25	Sandborn, 2008	104	ustekinumab	90 mg qw 4.5mg/kg		2,4,6,8,12,14,16	2,4,6,8,12,14,16	2,4,6,8,12,14,16		8
26	Sandborn, 2012	526	ustekinumab	1 mg/kg 3 mg/kg 6 mg/kg	4,6,8	4,6,8	4,6,8	4,6,8	6	4,6,8
27	Feangan, 2016 (UNITI1)	741	ustekinumab	130 mg 6 mg/kg	3,6,8	3,6,8	3,6,8	3,6,8	8	3,6,8
28	Feangan, 2016 (UNITI2)	628	ustekinumab	130 mg 6 mg/kg	3,6,8	3,6,8	3,6,8	3,6,8		3,6,8

29	Dotan, 2010	152	semapimod	60 mg qd 3d 60 mg qd 1d	4,8			4,8	4,8
30	Sands, 2010	701	apilimod	50 mg qd 100 mg qd		4,6,24	4,6,24	4,6	
31	Schreiber, 2017	187	andecaliximab	150 mg q2w 150 mg qw 300mg_qw			8		
32	Sandborn, 2014	139	tofacitinib	1 mg bid 5 mg bid 15 mg bid	1,2,4,8	1,2,4	4	4	1,2,4,8
33	Panes, 2017	280	tofacitinib	5 mg bid 10 mg bid	2,4,8	2,4,8	2,4,8	2,4,8	8
34	Vermerire, 2016 (FITZROY)	174	filgotinib	200 mg qd	2,4,6,10		2,4,6,10	2,4,6,10	10
35	Sandborn, 2012	451	abatacept	3 mg/kg 0,2,4,10w 10 mg/kg 0,2,4,10w 30 mg/kg 0,2w+10 mg/kg 4,10w	2,4,8,12				12
36	Feagan, 2017	121	risankizumab	200 mg q4w 600 mg q4w	4,8,12			4,8,12	12
37	Danese, 2017 (ANDANTE 1)	249	PF-04236921	10 mg q4w 50 mg q4w 200 mg q4w	2,4,6,8,10 ,12	2,4,6,8,10 ,12	2,4,6,8,10 ,12	2,4,6,8,10 ,12	2,4,6,8,10 ,12
38	Sandborn, 2018 (OPERA)	265	ontamalimab	22.5 mg q4w 75 mg q4w 225 mg q4w		2,4,6,8,10 ,12	2,4,6,8,10 ,12	8,12	4,8,12
39	Sands, 2017	119	brazikumab	700 mg 0,4w	2,4,8,12	8	8	8,12	
40	Sandborn, 2020 (ELEST)	220	upadacitinib	3 mg bid 6 mg bid 12 mg bid 24 mg bid 24 mg qd		2,4,8,12,1 6	16	2,4,8,12,1 6	8,16
41	Hommes, 2006	133	fontolizumab	4 mg/kg q4w 10 mg/kg q4w	2,4,6,8,12 ,16		4,6,8	4,6,8	4,6,8,12,1 6,28
42	Reinish, 2010	201	fontolizumab	1 mg/kg 0w+0.1 mg/kg q4w 1 mg/kg 0w+1 mg/kg q4w	4,6,8,12,		4,6,8,12	4,6,8,12	4,6,8,12

				4 mg/kg 0w+0.1 mg/kg q4w					
				4 mg/kg 0w+1 mg/kg q4w					
43	Sandborn, 2017	78	abrilumab	21 mg 1,2,3,q4w 70 mg 1,2,3,q4w 210 mg 1,2,3,q4w	8,12			8,12	
44	Keshav, 2013 (PROTECT- 1)	436	vercimon	250 mg qd 250 mg bid 500 mg qd	12	4,8,12	4,8,12	4,8,12	12
45	Feagan, 2015 (SHIELD-1)	608	vercimon	500 mg qd 500 mg bid			8,12	8,12	8,12 12
46	D'Haens, 2014	180	laquinimod	0.5 mg qd 1 mg qd 1.5 mg qd 2 mg qd		1,2,4,6,8, 12	1,2,4,6,8, 12	1,2,4,6,8, 12	8

Risk of Bias Assessment



Supplementary Figure 1 Risk of bias assessment. Overall risk of bias, using Cochrane's risk of bias assessment tool.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
C87037	?	+	+	+	+	+	+
Chen, 2020	+	+	+	+	+	+	+
Colombel, 2010	+	+	+	+	+	+	+
D'haens 1999	?	?	+	?	+	+	+
Danese, 2017	+	+	+	?	+	+	+
Dotan, 2010	+	?	+	?	+	+	+
D'Haens, 2014	+	?	+	?	+	+	+
Feagan, 2008	+	?	+	?	+	+	+
Feagan, 2015	+	+	+	+	+	+	+
Feagan, 2017	+	+	+	+	+	+	+
Feagan, 2016 (UNIT1)	+	?	+	+	+	+	+
Feagan, 2016 (UNIT2)	+	?	+	+	+	+	+
Ghosh, 2003	+	?	+	?	+	+	+
Gordon, 2001	?	?	+	?	+	+	+
Hanauer, 2006	+	+	+	?	+	+	+
Hommes, 2006	?	+	+	?	+	+	+
Keshav, 2013	+	+	+	+	+	+	+
Panes, 2017	+	+	+	+	+	+	+
Reinish, 2010	?	+	+	?	+	+	+
Rutgeerts, 2006	+	+	+	+	+	+	+
Sandborn, 2001	+	+	+	?	+	+	+
Sandborn, 2004	+	+	+	+	+	+	+
Sandborn, 2005	+	?	+	+	+	+	+
Sandborn, 2007 (GAIN)	+	+	+	+	+	+	+
Sandborn, 2007 (PRESISE-1)	+	?	+	+	+	+	+
Sandborn, 2008	+	?	+	?	+	+	+
Sandborn, 2011	+	+	+	+	+	+	+
Sandborn, 2012	+	?	+	?	+	+	+
Sandborn, 2012 (CERTIFI)	+	?	+	?	+	+	+
Sandborn, 2013	+	+	+	+	+	+	+
Sandborn, 2014	+	+	+	+	+	+	+
Sandborn, 2017	+	+	+	?	+	+	+
Sandborn, 2018	+	+	+	+	+	+	+
Sandborn, 2020	+	+	+	+	+	+	+
Sands, 2010	+	+	+	+	+	+	+
Sands, 2014	+	+	+	+	+	+	+
Sands, 2017	+	+	+	+	+	+	+
Schreiber, 2005	+	+	+	?	+	+	+
Schreiber, 2017	+	+	+	?	+	+	+
Stack, 1997	+	+	+	+	+	+	+
Targan, 1997	?	+	+	+	+	+	+
Targan, 2007	?	+	+	?	+	+	+
Vermerine, 2016	+	+	+	+	+	+	+
Watanabe, 2011	+	+	+	+	+	+	+
Watanabe 2019	+	+	+	+	+	+	+
Winter, 2004	?	+	+	?	+	+	+

Supplementary Figure 2 Risk of bias assessment. Study-level risk of bias, using Cochrane's risk of bias assessment tool.

Model Development

After graphics exploration, the longitudinal profiles of efficacy outcomes were characterized using a hierarchical regression model with maximum likelihood estimation method. A nonparametric method was implemented to model the outcomes from placebo arms to obtain estimation of placebo effects at each trial and at each time point, so as to avoid misestimation of placebo effects and reduce biases due to placebo model misspecification. The general model could be described as:

$$E_{ijt} = E_{0it} + E_{drug} \quad (1)$$

$$E_{drug} = f(\text{drug, dose, regimen, time, } \theta, X_{ij}) \quad (2)$$

Where E_{ijt} represents the efficacy outcome in j th treatment arm of i th trial at t time, which is the sum of E_{0it} (the placebo effects of i th trial at t time), and E_{drug} (the drug effects in j th treatment arm of i th trial at t time). Drug effects (E_{drug}) is a function dependent on type of drug, dose, regimen, time, fixed-effect model parameters θ , and covariates X .

At first, the drug effects were set not to change with time. Then, in the process of modeling, if the fit degree of the model was improved, a time variable was added to create a nonlinear model to describe the time-varying drug effects, showing as follows:

$$E_{drug} = E_{\max drug} \cdot (1 - e^{-k \cdot \text{time}}) \quad (3)$$

Where $E_{\max drug}$ presented the maximum efficacy of each treatment. The parameter k , as the onset rate constant of drug effect, was initially estimated as a shared parameter for all treatments. With the assumption that drugs in the same class shares similar active mechanism, with a common saturation relationship. Drugs sharing a same pathway were also thought to have a similar absorption process. For drugs without enough data for estimation of a common rate constant, a shared parameter for a drug class or a route was used in the time-varying model. Both shared and separated parameters were acceptable in our model development, only the best fitted one was used for the time-varying drug effect in the final model.

During the model development, the maximum efficacy of each treatment was initially incorporated to be constant over dose and described by a scaling factor, $E_{\max}$. Then, the parameter $E_{\max}$ was separated into several parameters matching different doses, routes, and

regimens of a drug. For drugs with a dose range, a dose-response relationship was estimated with linear, Emax, and sigmoid Emax model. Functions of these models are listed as follows:

1 linear model

$$f = E_0 + \delta \cdot \text{dose} \quad (4)$$

2 Emax model

$$f = E_0 + \frac{E_{\max} \cdot \text{dose}}{ED_{50} + \text{dose}} \quad (5)$$

3 sigmoid Emax model

$$f = E_0 + \frac{E_{\max} \cdot \text{dose}^h}{ED_{50}^h + \text{dose}^h} \quad (6)$$

Where E_0 represented the placebo efficacy, while $E_{\max}$ represented the maximum efficacy of the drug. δ was the slope parameter of linear model. h was the slope parameter of Emax model, called Hill factor.

Model for $\Delta CDAI$, ΔCRP , $\Delta IBDQ$

The model for $\Delta CDAI$, ΔCRP , and $\Delta IBDQ$ was very similar, which can be shown as:

$$\Delta Y_{ijt} = E_{0it} + E_{drugijt} \quad (7)$$

where ΔY_{ijt} represented the values of $\Delta CDAI$, ΔCRP , and $\Delta IBDQ$ at t time in j treatment arm of i trial. E_{0it} represented the placebo effect of i trial at t time. $E_{drugijt}$ represented the drug effects of j treatment arm in i trial at t time.

Weight was calculated based on the inverse of the variance for each arm, and the sample size (N) of the treatment arm was also taken into consideration, as shown in the following equation:

$$\text{Weight} = \frac{SD}{\sqrt{N}} \quad (8)$$

SD and N were considered when calculating weights to ensure that more accurate and larger sample size outcomes had a greater impact on the final model.

Model for $CDAI-100$, $CDAI-70$, $CDAI150$

$$N_{effectijt} \sim \text{binomial}(P_{ijt}, N_{ij}) \quad (9)$$

$$P_{ijt} = g(E_{oit} + E_{drugijt}) \quad (10)$$

For ratio outcomes, efficacy of a treatment arm was considered as P_{ijt} (the probability of patients achieving endpoints at t time in j treatment arm of i trial), from a binomial distribution of $N_{effectijt}$ (the number of patients achieving endpoint at t time in j treatment arm of i trial) with probability (P_{ijt}) and sample size (N_{ij}). g was a logit translate of the efficacy of treatment, which was a sum of E_{oit} (placebo effect of i trial at t time) and $E_{drugijt}$ (drug effect of j treatment arm in i trial at t time), to limit the probability to a range of 0-1.

For CDAI-100, CDAI-70, CDAI150, the weight was based on the standard error of observed values and was generated by the following equation with P and N , avoiding the possible deviations in the final model cause by the extreme outcome values, and ensuring that more larger sample size outcomes had a greater impact.

$$\text{Weight} = \sqrt{\frac{P \cdot (1 - P)}{N}} \quad (11)$$

Covariate

Baseline characteristics, including age, percentage of male, duration of Crohn's Disease, smoking status, CDAI, IBDQ, CRP, were considered as the covariate in the model. In the process of model development, covariates were investigated for their possible impact on the treatment efficacies by the following function where θ was introduced as the parameter quantifying the impact of baseline characteristics on the treatment efficacies.

$$\text{Effect}_{\text{Covariate}} = \frac{\text{Covariate}^\theta}{\text{mean}(\text{Covariate})} \quad (12)$$

Final Models

Parameters and model fitted time-course plots CDAI150 model

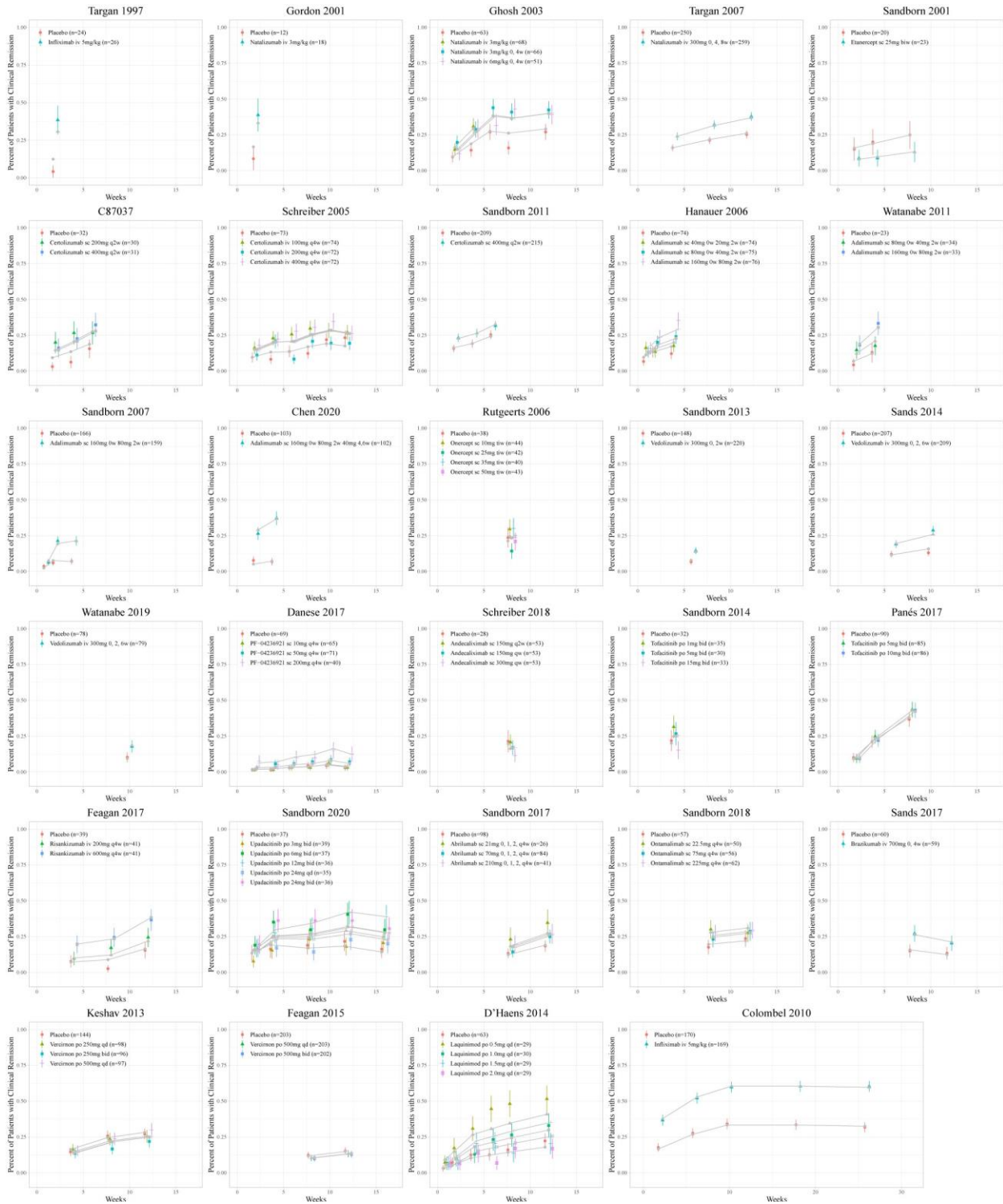
Supplementary Table 2 Parameter estimates for CDAI150 model.

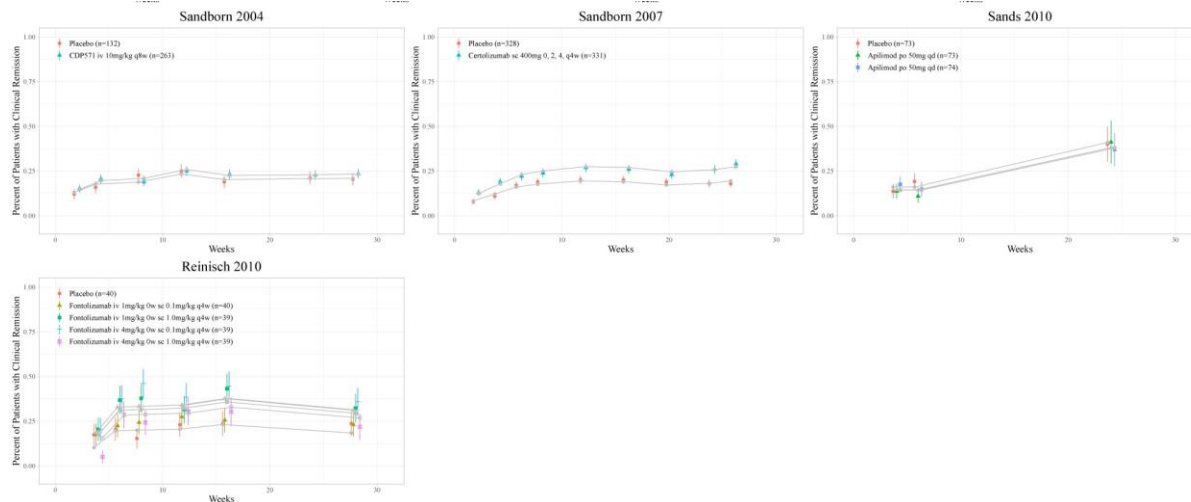
Parameter	Route (regimen)	Estimate	95%CI
E_{max}			
Infliximab	i.v. (5 mg/kg) i.v. (5 mg/kg 0, 2, 6, q8w)	1.16	(0.87, 1.46)
Natalizumab	i.v. (3mg/kg) i.v. (3, 6 mg/kg q4w) i.v. (300mg q4w)	0.44	(0.31, 0.57)
CDP571	i.v. (10 mg/kg q8w)	0.18	(-0.14, 0.50)
Etanercept	s.c. (25 mg biw)	-0.70	(-1.68, 0.27)
Certolizumab pegol	s.c. (100, 200, 400 mg q4w) s.c. (200, 400 mg q2w) s.c. (400 mg 0, 2, 4, q4w)	0.47	(0.31, 0.63)
Adalimumab (slope) ^a	s.c. (40, 80, 160 mg 0w followed by 20, 40, 80 mg 2w) s.c. (160 mg 0w followed by 80 mg 2w followed by 40 mg 4, 6w)	6.00×10 ⁻³	(4.22×10 ⁻³ , 7.78×10 ⁻³)
Onercept	s.c. (10, 25, 35, 50 mg tiw)	0.18	(-0.56, 0.92)
Vedolizumab	i.v. (0.5, 2 mg/kg q4w) i.v. (300 mg 0, 2, 6w)	0.70	(0.45, 0.95)
Ustekinumab	s.c. (90 mg qw)	0.44	(-0.45, 1.33)
Apilimod	p.o. (50, 100 mg qd)	-0.12	(-0.55, 0.31)
Andecaliximab	s.c. (150 mg q2w) s.c. (150, 300 mg qw)	-0.26	(-1.40, 0.87)
Tofacitinib	p.o. (1, 5, 10, 15 mg bid)	0.76	(-1.14, 2.66)
Filgotinib	p.o. (200 mg qd)	1.50	(-1.02, 4.01)
Risankizumab (slope) ^a	i.v. (200, 600 mg q4w)	2.55×10 ⁻³	(8.88×10 ⁻⁴ , 4.22×10 ⁻³)
PF-04236921 (slope) ^a	s.c. (10, 50, 200 mg q4w)	8.33×10 ⁻³	(2.92×10 ⁻³ , 1.37×10 ⁻²)
Brazikumab	i.v. (700 mg q4w)	0.69	(-0.04, 1.42)
Upadacitinib	p.o. (3, 6, 12, 24 mg bid) p.o. (24 mg qd)	1.09	(-0.39, 2.58)
Fontolizumab	i.v.-s.c. (1, 4 mg/kg 0w followed by 0.1, 1 mg/kg q4w) i.v. (4, 10 mg/kg q4w)	0.78	(0.39, 1.16)
Abrilumab	s.c. (21, 70, 210 mg 0, 1, 2, q4w)	0.51	(-0.03, 1.06)
Vercirmon	p.o. (250, 500 mg qd) p.o. (250, 500 mg bid)	-0.19	(-0.48, 0.11)
Laquinimod	p.o. (0.5, 1, 1.5, 2 mg qd)	0.88	(0.45, 1.32)
Ontamalimab	s.c. (22.5, 75, 225 mg q4w)	0.45	(-0.13, 1.02)
k_{JAK}			
Rate constant for the onset of JAK inhibitor	NA	0.11	(0.01, 1.40)
Covariate			
Baseline CDAI	NA	-5.22	(-7.90, -2.54)
Baseline CRP	NA	0.51	(0.20, 0.83)

CDAI150, an absolute CDAI score of less than 150; CDAI, Crohn's Disease Activity Index; 95%CI, 95% confidence interval; Emax, maximum drug efficacy; NA, not available; qd, once daily; bid, twice daily; qw, once weekly; tiw, 3 times weekly; q2w, once every 2 weeks; q4w, once every 4 weeks; q8w, once every 8 weeks.

^a *The dose-response relationship is linear, which means that the Emax of any dose of the drug = drug (slope) * dose.*

^b *The dose-response relationship is E_{max} model, which means that the Emax of any dose of the drug = drug (Emax) * dose / (drug (ED50) * dose).*





Supplementary Figure 3 Model fitted time-course plots of response rate for CDAI150. Color symbols and vertical bars are observed mean and calculated weight of time points; gray symbols and lines are the model predictions. CDAI150, an absolute CDAI score of less than 150; CDAI, Crohn's Disease Activity Index; qd, once daily; bid, twice daily; qw, once weekly; tiw, three times weekly; q2w, once every 2 weeks; q4w, once every 4 weeks.

Parameters and model fitted time-course plots CDAI-100 model

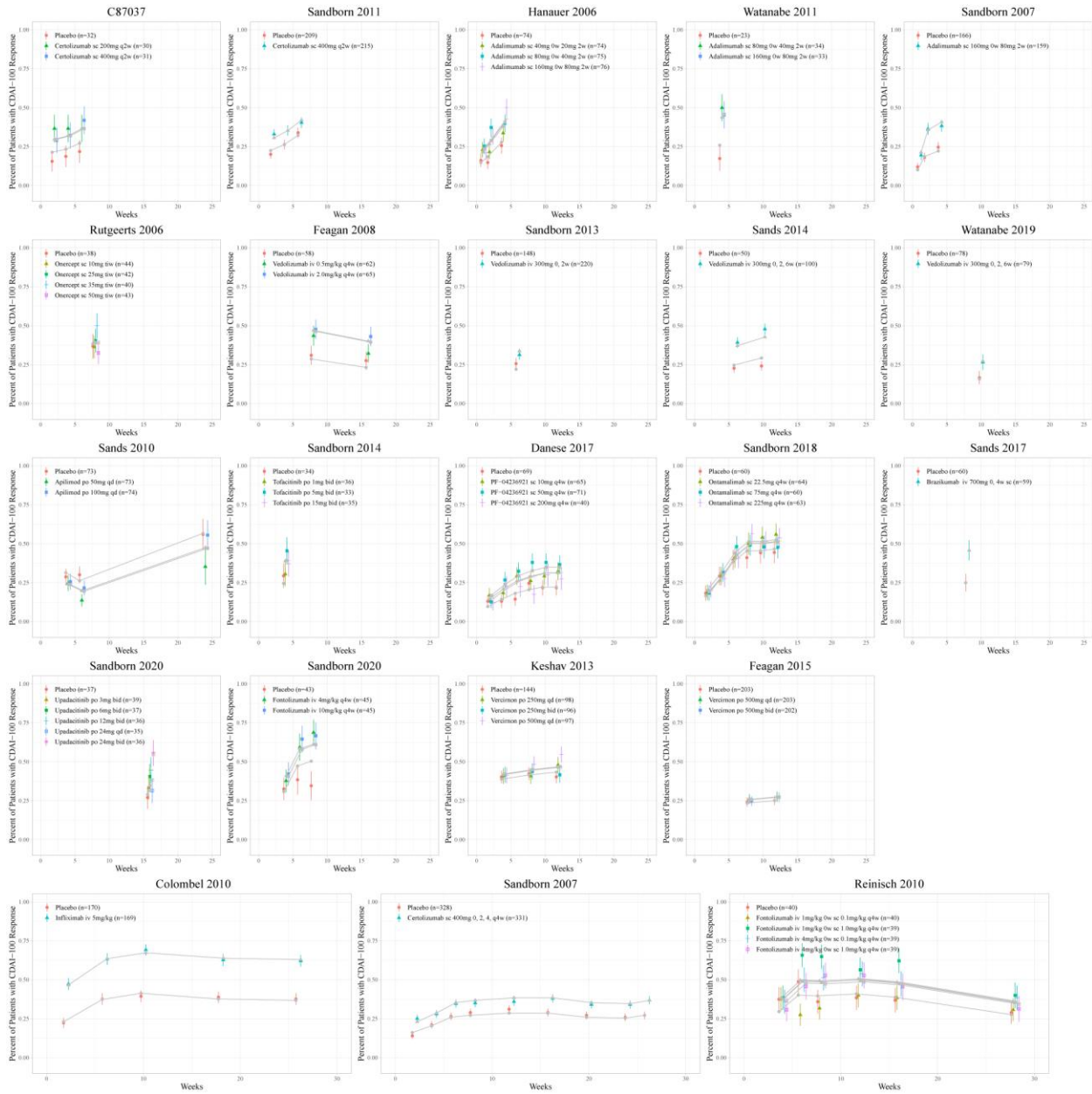
Supplementary Table 3 Parameter estimates for CDAI-100 model.

Parameter	Route (regimen)	Estimate	95%CI
E_{max}			
Infliximab	i.v. (5 mg/kg 0, 2, 6, q8w)	1.05	(0.83, 1.28)
Natalizumab	i.v. (300mg q4w)	0.57	(0.34, 0.80)
Certolizumab pegol	s.c. (200, 400 mg q2w) s.c. (400 mg 0, 2, 4, q4w)	0.43	(0.22, 0.64)
Adalimumab (E _{max}) ^a	s.c. (40, 80, 160 mg 0w followed by 20, 40, 80 mg 2w)	0.93	(0.30, 1.56)
Adalimumab (ED ₅₀) ^a	NA	34.13	(1.66, 703.51)
Onercept	s.c. (10, 25, 35, 50 mg tiw)	0.04	(-0.61, 0.69)
Vedolizumab	i.v. (0.5, 2 mg/kg q4w) i.v. (300 mg 0, 2, 6w)	0.62	(0.39, 0.85)
Ustekinumab	s.c. (90 mg qw)	0.51	(-0.16, 1.18)
Apilimod	p.o. (50, 100 mg qd)	-0.35	(-0.76, 0.06)
Tofacitinib	p.o. (1, 5, 10, 15 mg bid)	0.61	(0.15, 1.08)
Filgotinib	p.o. (200 mg qd)	0.44	(0.02, 0.85)
PF-04236921	s.c. (10, 50, 200 mg q4w)	0.53	(0.12, 0.94)
Brazikumab	i.v. (700 mg q4w)	0.95	(0.19, 1.71)
Upadacitinib (slope) ^b	p.o. (3, 6, 12, 24 mg bid) p.o. (24 mg qd)	4.34×10 ⁻²	(6.32×10 ⁻³ , 8.04×10 ⁻²)
Fontolizumab	i.v.-s.c. (1, 4 mg/kg 0w followed by 0.1, 1 mg/kg q4w) i.v. (4, 10 mg/kg q4w)	0.40	(0.06, 0.75)
Vercimon	p.o. (250, 500 mg qd) p.o. (250, 500 mg bid)	0.15	(-0.08, 0.37)
Laquinimod	p.o. (0.5, 1, 1.5, 2 mg qd)	0.51	(0.10, 0.93)
Ontamalimab	s.c. (22.5, 75, 225 mg q4w)	0.23	(-0.18, 0.64)
Covariate			
Baseline CDAI	NA	-3.21	(-7.39, 0.96)
Baseline CRP	NA	0.29	(-0.14, 0.71)

CDAI-100, a reduction of at least 100 points in the CDAI score; CDAI, Crohn's Disease Activity Index; 95%CI, 95% confidence interval; E_{max}, maximum drug efficacy; NA, not available; qd, once daily; bid, twice daily; qw, once weekly; tiw, 3 times weekly; q2w, once every 2 weeks; q4w, once every 4 weeks; q8w, once every 8 weeks.

^a The dose-response relationship is E_{max} model, which means that the E_{max} of any dose of the drug = drug (E_{max}) * dose / (drug (ED₅₀) * dose).

^b The dose-response relationship is linear, which means that the E_{max} of any dose of the drug = drug (slope) * dose.



Supplementary Figure 4 Model fitted time-course plots of response rate for CDAI-100. Color symbols and vertical bars are observed mean and calculated weight of time points; gray symbols and lines are the model predictions. CDAI-100, reduction of at least 100 points in the CDAI score; CDAI, Crohn's Disease Activity Index; qd, once daily; bid, twice daily; tiw, three times weekly; q2w, once every other week; q4w, once every 4 weeks.

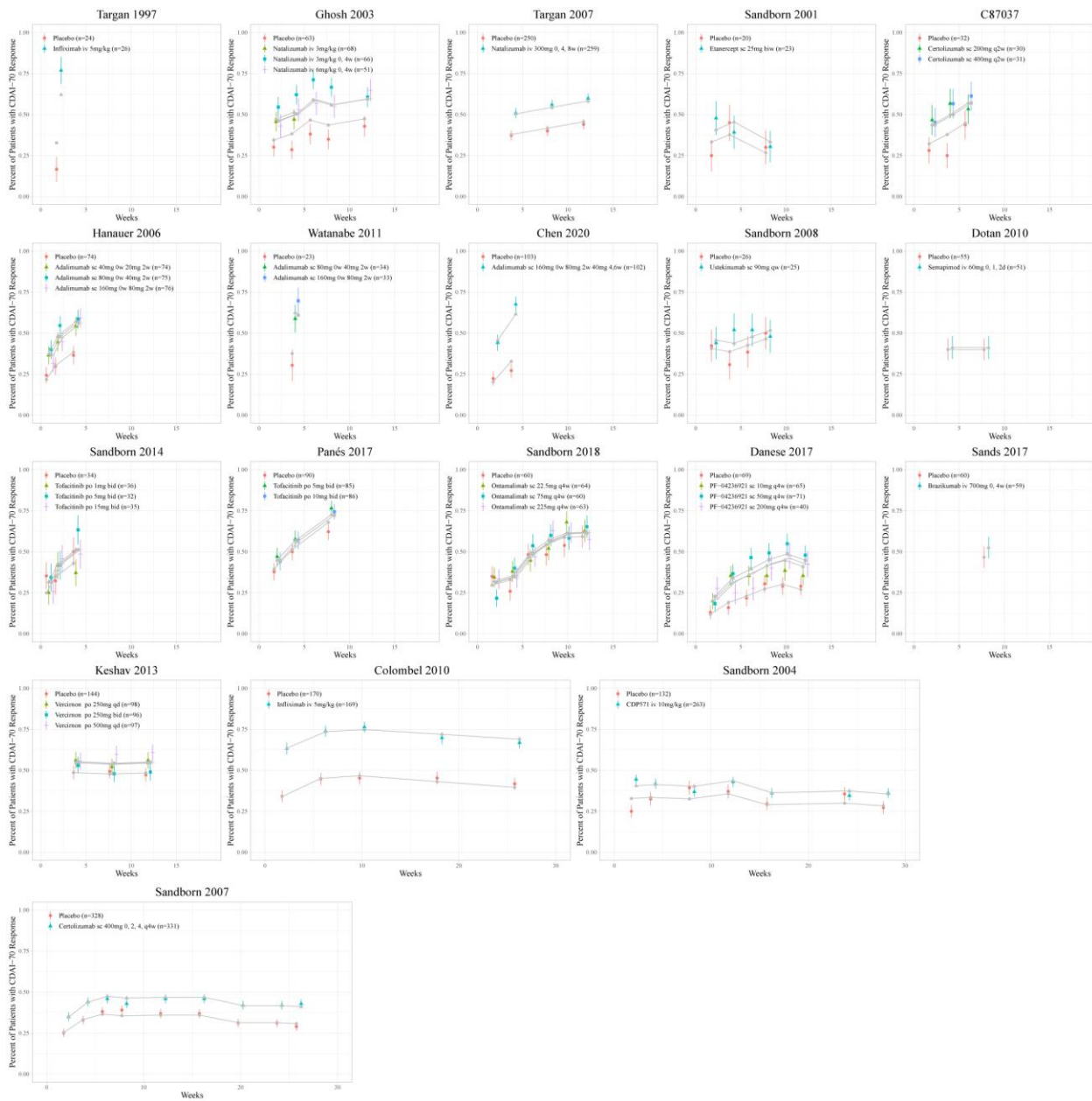
Parameters and model fitted time-course plots CDAI-70 model

Supplementary Table 4 Parameter estimates for CDAI-70 model.

Parameter	Route (regimen)	Estimate	95%CI
E_{max}			
Infliximab	i.v. (5 mg/kg) i.v. (5 mg/kg 0, 2, 6, q8w)	1.20	(0.96, 1.44)
Natalizumab	i.v. (3mg/kg) i.v. (3, 6 mg/kg q4w)	0.48	(0.33, 0.63)
CDP571	i.v. (10 mg/kg q8w)	0.41	(0.09, 0.72)
Etanercept	s.c. (25 mg biw)	0.31	(-0.58, 1.21)
Certolizumab pegol	s.c. (200, 400 mg q2w) s.c. (400 mg 0, 2, 4, q4w)	0.49	(0.26, 0.71)
Adalimumab	s.c. (40, 80, 160 mg 0w followed by 20, 40, 80 mg 2w) s.c. (160 mg 0w followed by 80 mg 2w followed by 40 mg 4, 6w)	0.87	(0.62, 1.11)
Vedolizumab	i.v. (0.5, 2 mg/kg q4w)	0.34	(-0.06, 0.73)
Ustekinumab	s.c. (90 mg qw)	0.23	(-0.62, 1.08)
Semapimod	i.v. (60 mg for 3d)	0.04	(-0.51, 0.59)
Tofacitinib	p.o. (1, 5, 10, 15 mg bid)	0.32	(-0.11, 0.75)
PF-04236921	s.c. (10, 50, 200 mg q4w)	0.71	(0.28, 1.15)
Brazikumab	i.v. (700 mg q4w)	0.23	(-0.48, 0.95)
Upadacitinib (E _{max}) ^a	p.o. (3, 6, 12, 24 mg bid) p.o. (24 mg qd)	0.89	(0.09, 1.69)
Upadacitinib (ED50) ^a	NA	3.91	(0.19, 79.30)
Vercimon	p.o. (250, 500 mg qd) p.o. (250 mg bid)	0.26	(-0.06, 0.58)
Laquinimod	p.o. (0.5, 1, 1.5, 2 mg qd)	0.37	(-0.07, 0.80)
Ontamalimab	s.c. (22.5, 75, 225 mg q4w)	0.11	(-0.32, 0.54)
Covariate			
Baseline CDAI	NA	-2.03	(-5.37, 1.32)
Baseline CRP	NA	0.27	(-0.12, 0.67)

CDAI-70, reduction of at least 70 points in the CDAI score; CDAI, Crohn's Disease Activity Index; 95%CI, 95% confidence interval; E_{max}, maximum drug efficacy; NA, not available; qd, once daily; bid, twice daily; q4w, once every 4 weeks; q8w, once every 8 weeks.

^a The dose-response relationship is E_{max} model, which means that the E_{max} of any dose of the drug = drug (E_{max}) * dose / (drug (ED50) * dose).



Supplementary Figure 5 Model fitted time-course plots of response rate for CDAI-70. Color symbols and vertical bars are observed mean and calculated weight of time points; gray symbols and lines are the model predictions. CDAI-70, reduction of at least 70 points in the CDAI score; CDAI, Crohn's Disease Activity Index; qd, once daily; bid, twice daily; q2w, once every other week; q4w, once every 4 weeks.

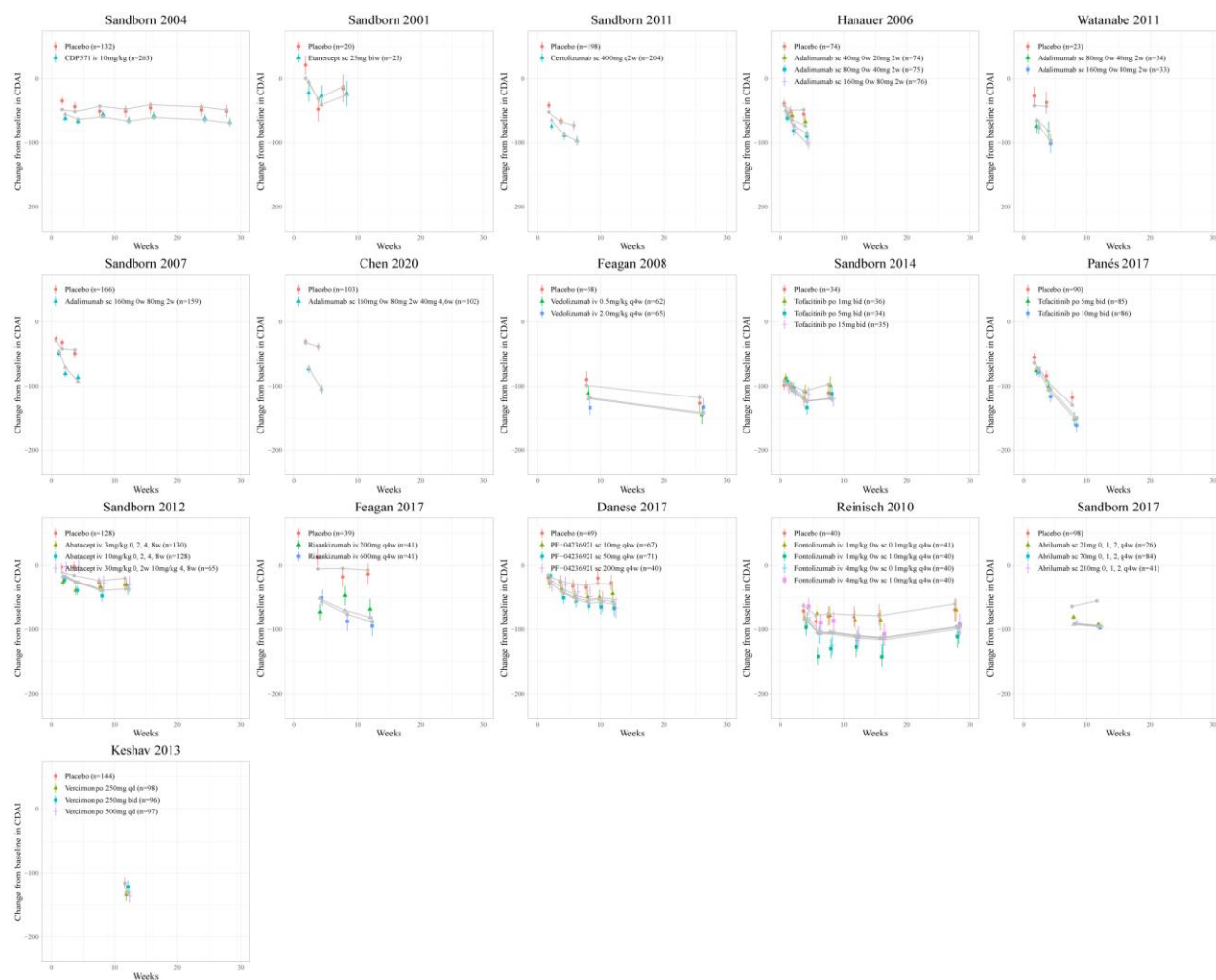
Parameters and model fitted time-course plots Δ CDAI model

Supplementary Table 5 Parameter estimates for Δ CDAI model.

Parameter	Route (regimen)	Estimate	95%CI
E_{max}			
Natalizumab	i.v. (300 mg q4w)	-51.36	(-70.89, -31.83)
CDP571	i.v. (10 mg/kg q8w)	-18.26	(-33.68, -2.85)
Etanercept	s.c. (25 mg/kg biw)	-15.93	(-84.16, 52.30)
Certolizumab pegol	s.c. (400 mg q2w) s.c. (400 mg 0, 2, 4, q4w)	-31.53	(-45.48, -17.59)
Adalimumab (E_{max}) ^a	s.c. (40, 80, 160 mg 0w followed by 20, 40, 80 mg 2w) s.c. (160 mg 0w followed by 80 mg 2w followed by 40 mg 4, 6w)	-151.24	(-322.11, 19.64)
Adalimumab (ED_{50}) ^a	NA	112.23	(9.02, 1.40×10 ³)
Vedolizumab	i.v. (0.5, 2 mg/kg q4w)	-22.38	(-49.72, 4.97)
Tofacitinib	p.o. (1, 5, 10, 15 mg bid)	-26.23	(-49.46, -2.99)
Filgotinib	p.o. (200 mg qd)	-32.16	(-69.00, 4.68)
Abatacept	i.v. (3, 10 mg/kg 0, 2, 4, 10w) i.v. (30 mg/kg 0, 2w followed by 10 mg/kg 4, 10w)	-20.19	(-43.15, 2.76)
Risankizumab	i.v. (200, 600 mg q4w)	-81.85	(-122.85, -40.86)
PF-04236921	s.c. (10, 50, 200 mg q4w)	-31.11	(-60.23, -1.99)
Brazikumab	i.v.-s.c. (700 mg 0, 4w)	-39.99	(-85.67, 5.70)
Fontolizumab	i.v. (4, 10 mg/kg q4w) i.v.-s.c. (1, 4 mg/kg 0w followed by 0.1, 1 mg/kg q4w)	-41.00	(-66.47, -15.52)
Abrilumab	s.c. (21, 70, 210 mg 0, 2, 4, q4w)	-35.63	(-41.90, -29.36)
Vercimon	p.o. (250, 500 mg qd) p.o. (250 mg bid)	-17.62	(-50.29, 15.06)
$k_{general}$			
Rate constant for the onset of all drugs	NA	0.22	(0.14, 0.34)
Covariate			
Baseline CDAI	NA	-2.05	(-4.93, 0.83)

Δ CDAI, change from baseline in CDAI; CDAI, Crohn's Disease Activity Index; 95%CI, 95% confidence interval; E_{max} , maximum drug efficacy; $k_{general}$, rate constant for the onset of all drugs except for infliximab; NA, not available; qd, once daily; bid, twice daily; biw, twice weekly; q2w, once every 2 weeks; q4w, once every 4 weeks.

^a The dose-response relationship is E_{max} model, which means that the E_{max} of any dose of the drug = drug (E_{max}) * dose / (drug (ED_{50}) * dose).



Supplementary Figure 6 Model fitted time-course plots of CDAI change from baseline. Color symbols and vertical bars are observed mean and calculated weight of time points; gray symbols and lines are the model predictions. CDAI, Crohn's Disease Activity Index; qd, once every day; bid, twice every day; biw, twice weekly; q4w, once every 4 weeks; q6w, once every 6 weeks.

Parameters and model fitted time-course plots Δ CRP model

Supplementary Table 6 Parameter estimates for Δ CRP model.

Parameter	Route (regimen)	Estimate	95%CI
E_{max}			
Infliximab	i.v. (5 mg/kg)	-0.61	(-0.98, -0.24)
Natalizumab	i.v. (300 mg q4w)	-0.89	(-1.12, -0.65)
CDP571	i.v. (10 mg/kg)	-0.15	(-0.28, -0.02)
Certolizumab pegol (slope) ^b	s.c. (400 mg q2w) s.c. (100, 200, 400 mg q4w) s.c. (400 mg 0, 2, 4, q4w)	1.12×10 ⁻²	(-1.70×10 ⁻² , -5.47×10 ⁻⁴)
Adalimumab	s.c. (40, 80, 160 mg 0w followed by 20, 40, 80 mg 2w) s.c. (160 mg 0w followed by 80 mg 2w followed by 40 mg 4, 6w)	-0.47	(-0.67, -0.27)
Vedolizumab	i.v. (300 mg 0, 2, 6w)	0.03	(-0.45, 0.52)
Ustekinumab	s.c. (90 mg)	-0.22	(-0.54, 0.10)
Semapimod	i.v. (60 mg for 3d)	-0.07	(-1.80, 1.66)
Tofacitinib	p.o. (1, 5, 10, 15 mg bid)	-0.07	(-0.10, -0.04)
Abatacept	i.v. (3, 10 mg/kg 0, 2, 4, 10w) i.v. (30 mg/kg 0, 2w followed by 10 mg/kg 4, 10w)	0.59	(0.32, 0.87)
PF-04236921 (E _{max}) ^a	s.c. (10, 50, 200 mg q4w)	-7.47	(-12.76, -2.18)
PF-04236921 (ED50) ^a	NA	93.69	(41.26, 241.86)
Upadacitinib (slope) ^b	p.o. (3, 6, 12, 24 mg bid) p.o. (24 mg qd)	-0.22	(-0.43, -0.01)
Fontolizumab	i.v. (4, 10 mg/kg q4w) i.v.-s.c. (1, 4 mg/kg 0w followed by 0.1, 1 mg/kg q4w)	-0.13	(-0.28, 0.03)
Vercimon	p.o. (250, 500 mg qd) p.o. (250, 500 mg bid)	0.10	(-0.05, 0.25)
Laquinimod	p.o. (0.5, 1, 1.5, 2 mg qd)	0.25	(-0.01, 0.50)
Risankizumab	i.v. (200, 600 mg q4w)	4.60×10 ⁻³	(5.70×10 ⁻² , 4.78×10 ⁻²)
Ontamalimab	s.c. (22.5, 75, 225 mg q4w)	-0.05	(-0.12, 0.02)
Covariate			
Age	NA	-7.69	(-11.11, -4.26)
Disease duration	NA	4.95	(3.60, 6.29)
Baseline CRP	NA	-0.87	(-1.24, -0.50)

Δ CRP, change from baseline in CRP; CRP, C-reactive protein; 95%CI, 95% confidence interval; E_{max}, maximum drug efficacy; NA, not available; qd, once daily; bid, twice daily; q2w, once every 2 weeks; q4w, once every 4 weeks.

^a The dose-response relationship is E_{max} model, which means that the E_{max} of any dose of the drug = drug (E_{max}) * dose / (drug (ED50) * dose).

^b *The dose-response relationship is linear, which means that the Emax of any dose of the drug = drug (slope) * dose.*



Supplementary Figure 7 Model fitted time-course plots of CRP change from baseline. Color symbols and vertical bars are observed mean and calculated weight of time points; gray symbols and lines are the model predictions. CRP, C-reactive protein; qd, once daily; bid, twice daily; q2w, once every 2 weeks; q4w, once every 4 weeks.

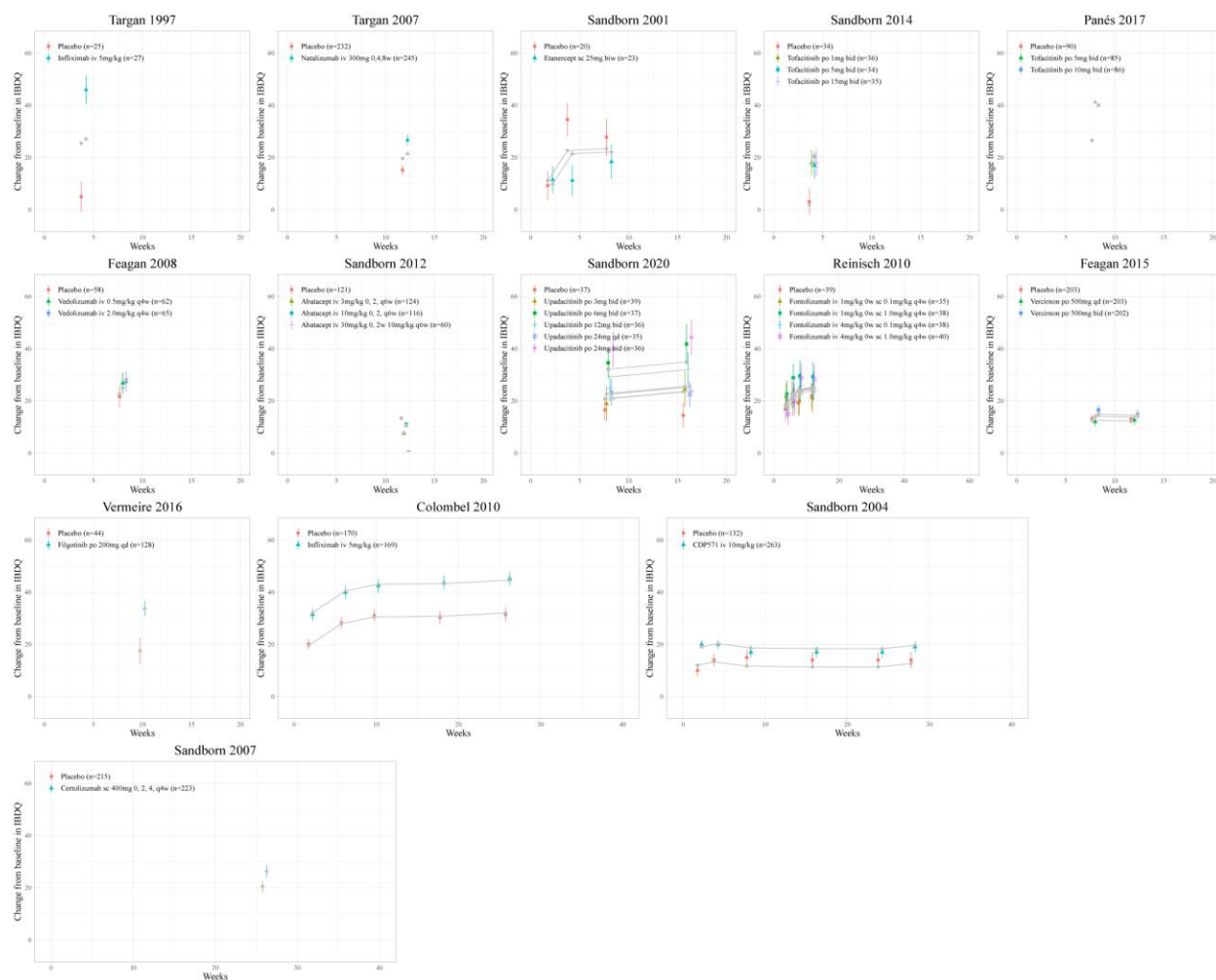
Parameters and model fitted time-course plots Δ IBDQ model

Supplementary Table 7 Parameter estimates for Δ IBDQ model.

Parameter	Route (regimen)	Estimate	95%CI
E_{max}			
Infliximab	i.v. (5, 10, 20 mg/kg) i.v. (5 mg/kg 0, 2, 6, q8w)	15.72	(7.59, 23.85)
Natalizumab	i.v. (3mg/kg) i.v. (3, 6 mg/kg q4w)	2.72	(0.66, 4.79)
CDP571	i.v. (10 mg/kg q8w)	3.93	(0.55, 7.31)
Etanercept	s.c. (25 mg biw)	-1.51	(-26.40, 23.38)
Certolizumab pegol	s.c. (400 mg 0, 2, 4, q4w)	0.31	(-0.19, 0.82)
Adalimumab (slope) ^a	s.c. (40, 80, 160 mg 0w followed by 20, 40, 80 mg 2w)	0.10	(0.05, 0.15)
Vedolizumab	i.v. (0.5, 2 mg/kg q4w)	0.97	(-1.80, 3.75)
Semapimod	i.v. (60 mg for 1, 3d)	-1.30	(-27.19, 24.60)
Apilimod	p.o. (50, 100 mg qd)	-8.26	(-41.19, 24.68)
Filgotinib	p.o. (200mg qd)	6.74	(-0.05, 13.54)
Tofacitinib	p.o. (1, 5, 10, 15 mg bid)	52.74	(39.23, 66.25)
Abatacept	i.v. (3, 10 mg/kg 0, 2, 4, 10w) i.v. (30 mg/kg 0, 2w followed by 10 mg/kg 4, 10w)	-3.54	(-4.35, -2.72)
Risankizumab (slope) ^a	i.v. (200, 600 mg q4w)	0.05	(0.01, 0.10)
Upadacitinib	p.o. (3, 6, 12, 24 mg bid) p.o. (24 mg qd)	4.70	(-1.57, 10.97)
Fontolizumab	i.v.-s.c. (1, 4 mg/kg 0w followed by 0.1, 1 mg/kg q4w)	-0.34	(-4.02, 3.35)
Vercimon	p.o. (500 mg qd) p.o. (500 mg bid)	3.54	(-5.84, 12.93)
Covariate			
Disease duration	NA	-8.98	(-10.60, -7.36)

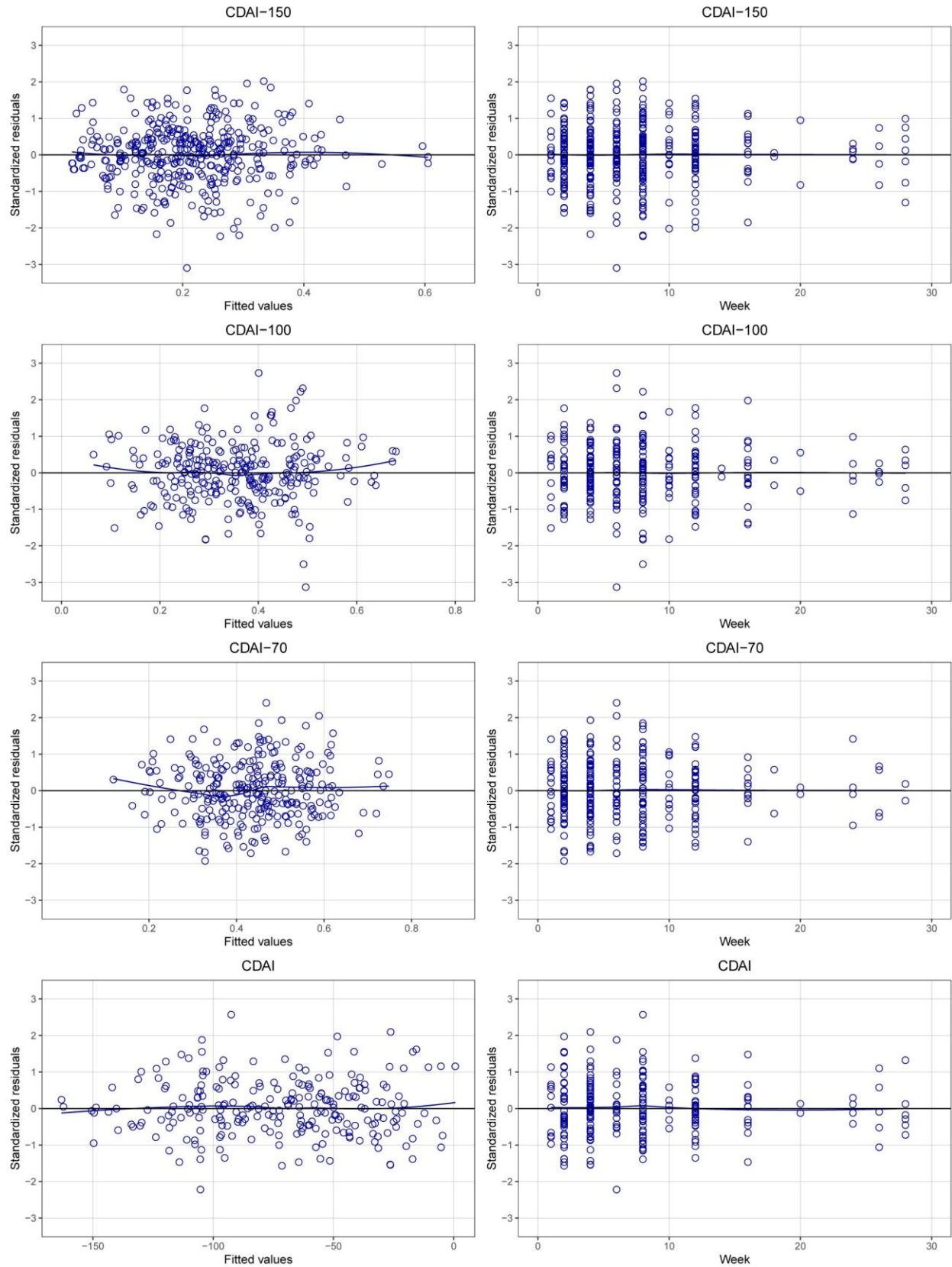
Δ IBDQ, change from baseline in IBDQ; IBDQ, inflammatory bowel disease questionnaire;
95%CI, 95% confidence interval; E_{max}, maximum drug efficacy; NA, not available; qd, once
daily; bid, twice daily; q4w, once every 4 weeks; q8w, once every 8 weeks.

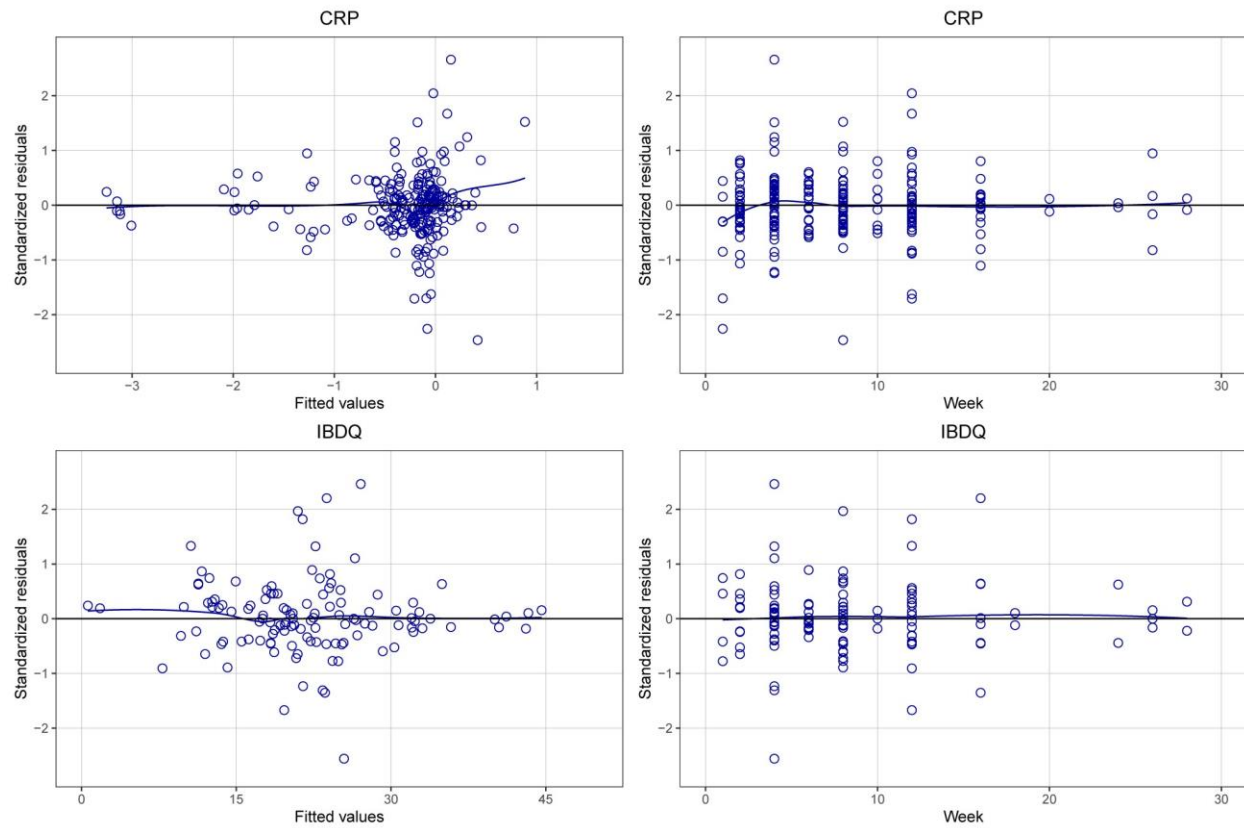
^a The dose-response relationship is linear, which means that the E_{max} of any dose of the drug =
drug (slope) * dose.



Supplementary Figure 8 Model fitted time-course plots of IBDQ change from baseline. Color symbols and vertical bars are observed mean and calculated weight of time points; gray symbols and lines are the model predictions. IBDQ, inflammatory bowel disease questionnaire; biw, twice weekly; q4w, once every 4 weeks.

Diagnostic Plots





Supplementary Figure 9 Diagnostic Plots

Model Code

Code for CDAI150 model

```
cdai150.14 <- function(group,week,CLASS,FLAG,methodFlag,DOSE,group,week,
                        male,age,dur,CDAI,CRP,eo,eminf,emnat,emcdp,
                        emeta,emcer,emone,emved,emust,emapi,emand,
                        emtof,emfil,emmedi,emupa,emfon,emabr,emver,
                        emlaq,emont,k,kada,kris,kpf1,eCDAI,eCRP)
{
  emrel = 1
  emrel = emrel*(CDAI/mean(CDAI150$CDAI,na.rm = T))**eCDAI
  emrel = emrel*(CRP/mean(CDAI150$CRP,na.rm = T))**eCRP
  etime = 1*(CLASS!=5) + (1-exp(-exp(k)*week))*(CLASS==5)
  emrel = emrel*etime
  efinf = 0 + eminf*(FLAG==2)
  efinf = efinf*emrel
  efnat = 0 + emnat*(FLAG==3)
  efnat = efnat*emrel
  efcdp = 0 + emcdp*(FLAG==4)
  efcdp = efcdp*emrel
  efeta = 0 + emeta*(FLAG==5)
  efeta = efeta*emrel
  efcer = 0 + emcer*(FLAG==6)
  efcer = efcer*emrel
  efada = 0 + (kada*DOSE)*(FLAG==7)
  efada = efada*emrel
  efone = 0 + emone*(FLAG==8)
  efone = efone*emrel
  efved = 0 + emved*(FLAG==9)
```

```

efved = efved*emrel
efust = 0 + emust*(FLAG==10)
efust = efust*emrel
efapi = 0 + emapi*(FLAG==11)
efapi = efapi*emrel
efand = 0 + emand*(FLAG==12)
efand = efand*emrel
eftof = 0 + emtof*(FLAG==13)
eftof = eftof*emrel
effil = 0 + emfil*(FLAG==14)
effil = effil*emrel
efris = 0 + (kris*DOSE)*(FLAG==16)
efris = efris*emrel
efpf1 = 0 + (kpf1*DOSE)*(FLAG==17)
efpf1 = efpf1*emrel
efmedi = 0 + emmedi*(FLAG==18)
efmedi = efmedi*emrel
efupa = 0 + emupa*(FLAG==19)
efupa = efupa*emrel
effon = 0 + emfon*(FLAG==20)
effon = effon*emrel
efabr = 0 + emabr*(FLAG==21)
efabr = efabr*emrel
efver = 0 + emver*(FLAG==22)
efver = efver*emrel
eflaq = 0 + emlaq*(FLAG==23)
eflaq = eflaq*emrel
efont = 0 + emont*(FLAG==24)

```

```

efont = efont*emrel

emax = 0 + eo + efinf + efnat + efcdp + efeta + efcer + efada + efone + efved + efust + efapi +
efand + eftof + effil + efris + efpf1 + efmedi + efupa + effon + efabr + efver + eflaq + efont

yp = exp(emax)/(1+exp(emax))

yp
}

#Note: group.week (each time point in each trial), CLASS (class number of the drug. Placebo is
defined as 0), FLAG (number of each treatment), methodFLAG (number of each route of
administration), group (number of each treatment in each trial)

ncdai150.14 <-
gnls(cdai150~cdai150.14(group.week,CLASS,FLAG,methodFlag,DOSE,group,week,male,age,d
ur,CDAI,

        CRP, eo, eminf, emnat, emcdp, emeta, emcer, emone, emved,

        emust, emapi, emand, emtof, emfil, emmedi,

        emupa, emfon, emabr, emver, emlaq, emont, k, kada, kris,

        kpf1, eCDAI, eCRP

),

data = CDAI150,

params = list(eo~-1+I(group.week),

        eminf~1, emnat~1, emcdp~1, emeta~1, emcer~1,

        emone~1, emved~1, emust~1, emapi~1,

        emand~1, emtof~1, emfil~1,

        emmedi~1, emupa~1, emfon~1, emabr~1,

        emver~1, emlaq~1, emont~1, k~1, kada~1, kris~1,

        kpf1~1, eCDAI~1, eCRP~1),

start = list(coef(n10), 0.6),

correlation = corARMA(form = ~tp1|trialNO/armNO, p=2),

weights=varPower(0.5, form=~fitted.)*(1-fitted.)/no, fixed = 0.5),

verbose=T

)

```

Code for CDAI-100 model

```
cdai100.23 <- function(trialNO,armNO,week,FLAG,DOSE,group.week,methodFlag,  
  cdai100,no,tp1,male,age,dur,smok,CDAI,CRP,Regimen,  
  eo,eminf,emnat,emcer,emada,emone,emved,emust,emapi,  
  emtof,emfil,empf1,emmedi,emfon,emver,  
  emlaq,emont,ledada,kupa,eCDAI,eCRP  
)  
{  
  emrel = 1  
  emtime = 1  
  emrel = emrel*(CDAI/mean(CDAI100$CDAI,na.rm = T))**eCDAI  
  emrel = emrel*(CRP/mean(CDAI100$CRP,na.rm = T))**eCRP  
  emrel = emrel*emtime  
  efinf = 0 + eminf*(FLAG==2)  
  efinf = efinf*emrel  
  efnat = 0 + emnat*(FLAG==3)  
  efnat = efnat*emrel  
  efcer = 0 + emcer*(FLAG==4)  
  efcer = efcer*emrel  
  efada = 0 + ((emada*DOSE)/(DOSE+exp(ledada)))*(FLAG==5)  
  efada = efada*emrel  
  efone = 0 + emone*(FLAG==6)  
  efone = efone*emrel  
  efved = 0 + emved*(FLAG==7)  
  efved = efved*emrel  
  efust = 0 + emust*(FLAG==8)  
  efust = efust*emrel  
  efapi = 0 + emapi*(FLAG==9)
```

```

efapi = efapi*emrel
eftof = 0 + emtof*(FLAG==10)
eftof = eftof*emrel
effil = 0 + emfil*(FLAG==11)
effil = effil*emrel
efpf1 = 0 + empf1*(FLAG==13)
efpf1 = efpf1*emrel
efmedi = 0 + emmedi*(FLAG==14)
efmedi = efmedi*emrel
efupa = 0 + (kupa*DOSE)*(FLAG==15)
efupa = efupa*emrel
effon = 0 + emfon*(FLAG==16)
effon = effon*emrel
efver = 0 + emver*(FLAG==17)
efver = efver*emrel
eflaq = 0 + emlaq*(FLAG==18)
eflaq = eflaq*emrel
efont = 0 + emont*(FLAG==19)
efont = efont*emrel
emax = eo + efinf + efnat + efcfer + efada + efone + efved + efust + efapi +
      eftof + effil + efpf1 + efmedi + efupa + effon + efver + eflaq + efont
yp = exp(emax)/(1+exp(emax))
yp
}

```

```

ncdai100.23 <-
gnls(cdai100~cdai100.23(trialNO,armNO,week,FLAG,DOSE,group.week,methodFlag,
                        cdai100,no,tp1,male,age,dur,smok,CDAI,CRP,Regimen,

```

```

        eo,eminf,emnat,emcer,emada,emone,emved,emust,emapi,
        emtof,emfil,empf1,emmedi,emfon,emver,
        emlaq,emont,ledada,kupa,eCDAI,eCRP
    ),
    data = CDAI100,
    params = list(eo~-1+I(group.week),
        eminf~1,emnat~1,emcer~1,emada~1,emone~1,emved~1,emust~1,
        emapi~1,emtof~1,emfil~1,empf1~1,emmedi~1,
        emfon~1,emver~1,emlaq~1,emont~1,ledada~1,kupa~1,eCDAI~1,
        eCRP~1
    ),
    start = c(coef(n17),0.3),
    weights=varPower(0.5,form=~fitted.)*(1-fitted.)/no,fixed = 0.5),
    correlation = corCompSymm(form = ~tp1|group),
    verbose = T
)

```

Code for CDAI-70 model

```
cdai70.16<-function(FLAG,group.week,DOSE,Regimen,methodFlag,male,age,dur,CDAI,CRP,
                    eo,eminf,emnat,emcdp,emeta,emcer,emada,emved,emust,
                    emsem,emtof,empf1,emmedi,emupa,emver,emlaq,
                    emont,ledupa,eCDAI,eCRP
)
{
  emrel = 1
  emrel = emrel*(CDAI/mean(CDAI70$CDAI,na.rm = T))**eCDAI
  emrel = emrel*(CRP/mean(CDAI70$CRP,na.rm = T))**eCRP
  efinf = 0 + eminf*(FLAG==2)
  efinf = efinf*emrel
  efnat = 0 + emnat*(FLAG==3)
  efnat = efnat*emrel
  efcdp = 0 + emcdp*(FLAG==4)
  efcdp = efcdp*emrel
  efeta = 0 + emeta*(FLAG==5)
  efeta = efeta*emrel
  efcer = 0 + emcer*(FLAG==6)
  efcer = efcer*emrel
  efada = 0 + emada*(FLAG==7)
  efada = efada*emrel
  efved = 0 + emved*(FLAG==8)
  efved = efved*emrel
  efust = 0 + emust*(FLAG==9)
  efust = efust*emrel
  efsem = 0 + emsem*(FLAG==10)
  efsem = efsem*emrel
```

```

eftof = 0 + emtof*(FLAG==11)
eftof = eftof*emrel
efpf1 = 0 + empf1*(FLAG==13)
efpf1 = efpf1*emrel
efmedi = 0 + emmedi*(FLAG==14)
efmedi = efmedi*emrel
efupa = 0 + ((emupa*DOSE)/(DOSE+exp(ledupa)))*(FLAG==15)
efupa = efupa*emrel
efver = 0 + emver*(FLAG==16)
efver = efver*emrel
eflaq = 0 + emlaq*(FLAG==17)
eflaq = eflaq*emrel
efont = 0 + emont*(FLAG==18)
efont = efont*emrel
# total effect
emax = 0 + eo + efinf + efnat + efcdp + efeta + efcer + efada + efved +
  efust + efsem + eftof + efpf1 + efmedi + efupa + efver + eflaq +
  efont
yp =exp(emax)/(1+exp(emax))
yp
}

ncdai70.16<-gnls(cdai70~
cdai70.16(FLAG,group,week,DOSE,Regimen,methodFlag,male,age,dur,CDAI,CRP,
          eo,eminf,emnat,emcdp,emeta,emcer,emada,
          emved,emust,emsem,emtof,empf1,
          emmedi,emupa,emver,emlaq,emont,ledupa,
          eCDAI,eCRP
),

```

```

data=CDAI70,
params=list(eo~-1+I(group.week),
            eminf~1,emnat~1,emcdp~1,emeta~1,emcer~1,emada~1,emved~1,
            emust~1,emsem~1,emtof~1,empf1~1,emmedi~1,emupa~1,
            emver~1,emlaq~1,emont~1,ledupa~1,eCDAI~1,eCRP~1
),
start = c(coef(n13)),
correlation = corAR1(form = ~tp|group),
weights=varPower(0.5,form=~fitted.)*(1-fitted.)/no,fixed = 0.5),
verbose=T
)

```

Code for Δ CDAI model

```
cdai27 <- function(trialNO,armNO,week,no,FLAG,DOSE,methodFlag,cdai,SD,group,week,
  tp1,male,age,dur,CDAI,CRP,
  eo,emnat,emcdp,emeta,emcer,emada,emved,emtof,
  emfil,emaba,emris,empf,emmedi,emfon,
  emabr,emver,k,edada,emCDAI
)
{
  emrel = 1
  emrel = emrel*(CDAI/306.285)**emCDAI
  emtime = 1*(1-exp(-exp(k)*week))
  emrel = emrel*emtime
  efnat = 0 + emnat*(FLAG==3)
  efnat = efnat*emrel
  efcdp = 0 + emcdp*(FLAG==4)
  efcdp = efcdp*emrel
  efeta = 0 + emeta*(FLAG==5)
  efeta = efeta*emrel
  efcer = 0 + emcer*(FLAG==6)
  efcer = efcer*emrel
  efada = 0 + ((emada*(DOSE))/(exp(edada)+DOSE))*(FLAG==7)
  efada = efada*emrel
  efved = 0 + emved*(FLAG==8)
  efved = efved*emrel
  eftof = 0 + emtof*(FLAG==10)
  eftof = eftof*emrel
  effil = 0 + emfil*(FLAG==11)
  effil = effil*emrel
}
```

```

efaba = 0 + emaba*(FLAG==13)
efaba = efaba*emrel
efris = 0 + emris*(FLAG==14)
efris = efris*emrel
efpf = 0 + empf*(FLAG==15)
efpf = efpf*emrel
efmedi = 0 + emmedi*(FLAG==16)
efmedi = efmedi*emrel
effon = 0 + emfon*(FLAG==17)
effon = effon*emrel
efabr = 0 + emabr*(FLAG==18)
efabr = efabr*emrel
efver = 0 + emver*(FLAG==19)
efver = efver*emrel
emax = eo + efnat + efcdp + efeta + efcer + efada + efved +
      eftof + effil + efaba + efris + efpf + efmedi +
      effon + efabr + efver
yp = emax
yp
}

ncdai27 <-
gnls(cdai~cdai27(trialNO,armNO,week,no,FLAG,DOSE,methodFlag,cdai,SD,group.week,
               tp1,male,age,dur,CDAI,CRP,
               eo,emnat,emcdp,emeta,emcer,emada,emved,emtof,
               emfil,emaba,emris,empf,emmedi,emfon,emabr,
               emver,k,edada,emCDAI
               ),
data = CDAI,

```

```

params = list(eo~-1+I(group.week),
              emnat~1,emcdp~1,emeta~1,emcer~1,emada~1,emved~1,
              emtof~1,emfil~1,emaba~1,emris~1,empf~1,
              emmedi~1,emfon~1,emabr~1,emver~1,k~1,
              edada~1,emCDAI~1
              ),
start = c(coef(n8),-2),
correlation = corAR1(form = ~tp1|group),
weights = varFixed(~(SD^2/no)),
verbose = T
)

```

Code for Δ CRP model

```
crp26 <- function(trialNO,armNO,week,FLAG,group.week,methodFlag,crp,SD,
                  DOSE,no,tp1,male,age,dur,CRP,CDAI,eo,eminf,emnat,emcdp,
                  kcer,emada,emved,emust,emsem,emtof,emaba,empf1,kupa,emfon,
                  emver,emlaq,emris,emont,ledpf1,eage,edur,eCRP)
{
  emrel = 1
  emrel = emrel*(age/mean(age,na.rm = T))**eage
  emrel = emrel*(dur/mean(dur,na.rm = T))**edur
  emrel = emrel*(CRP/mean(CRP,na.rm = T))**eCRP
  emtime = 1
  emrel = emrel*emtime
  efinf = 0 + eminf*(FLAG==2)
  efinf = efinf*emrel
  efnat = 0 + emnat*(FLAG==3)
  efnat = efnat*emrel
  efcdp = 0 + emcdp*(FLAG==4)
  efcdp = efcdp*emrel
  efcer = 0 + (kcer*DOSE)*(FLAG==5)
  efcer = efcer*emrel
  efada = 0 + emada*(FLAG==6)
  efada = efada*emrel
  efved = 0 + emved*(FLAG==7)
```

efved = efved*emrel

efust = 0 + emust*(FLAG==8)

efust = efust*emrel

efsem = 0 + emsem*(FLAG==9)

efsem = efsem*emrel

eftof = 0 + emtof*(FLAG==10)

eftof = eftof*emrel

efaba = 0 + emaba*(FLAG==11)

efaba = efaba*emrel

efpf1 = 0 + ((empf1*DOSE)/(DOSE+exp(ledpf1)))*(FLAG==12)

efpf1 = efpf1*emrel

efupa = 0 + (kupa*DOSE)*(FLAG==13)

efupa = efupa*emrel

effon = 0 + emfon*(FLAG==14)

effon = effon*emrel

efver = 0 + emver*(FLAG==15)

efver = efver*emrel

eflaq = 0 + emlaq*(FLAG==16)

eflaq = eflaq*emrel

efris = 0 + emris*(FLAG==17)

efris = efris*emrel

efont = 0 + emont*(FLAG==18)

efont = efont*emrel

```

yp = eo + efinf + efnat + efcdp + efcfer + efada + efved + efust + efsem +
    eftof + efaba + efpf1 + efupa + effon + efver + eflaq + efris + efont
yp
}

ncrp26 <- gnls(crp~crp26(trialNO,armNO,week,FLAG,group.week,methodFlag,crp,SD,
    DOSE,no,tp1,male,age,dur,CRP,CDAI,eo,eminf,emnat,emcdp,
    kcer,emada,emved,emust,emsem,emtof,emaba,empf1,kupa,emfon,
    emver,emlaq,emris,emont,ledpf1,eage,edur,eCRP),
    data = CRP,
    params = list(eo~-1+I(group.week),
        eminf~1,emnat~1,emcdp~1,kcer~1,emada~1,
        emved~1,emust~1,emsem~1,emtof~1,emaba~1,
        empf1~1,kupa~1,emfon~1,emver~1,emlaq~1,
        emris~1,emont~1,ledpf1~1,eage~1,edur~1,
        eCRP~1),
    start = c(coef(n22),-1),
    correlation = corARMA(form = ~tp1|trialNO/armNO,p=2),
    weights = varFixed(~(SD^2)/no),
    verbose = T
)

```

Code for Δ IBDQ model

```
ibdq23 <- function(trialNO,armNO,DOSE,methodFlag,FLAG,week,no,tp1,group.week,  
  ibdq,SD,male,age,dur,CDAI,CRP,IBDQ,eo,eminf,emnat,emcdp,  
  emeta,emcer,kada,emved,emsem,emapi,emtof,emfil,  
  emaba,kris,emupa,emfon,emver,edur  
)  
{  
  emrel = 1  
  emrel = emrel*(dur/mean(dur,na.rm = T))**edur  
  emtime = 1  
  emrel = emrel*emtime  
  efinf = 0 + eminf*(FLAG==2)  
  efinf = efinf*emrel  
  efnat = 0 + emnat*(FLAG==3)  
  efnat = efnat*emrel  
  efcdp = 0 + emcdp*(FLAG==4)  
  efcdp = efcdp*emrel  
  efeta = 0 + emeta*(FLAG==5)  
  efeta = efeta*emrel  
  efcer = 0 + emcer*(FLAG==6)  
  efcer = efcer*emrel  
  efada = 0 + (kada*DOSE)*(FLAG==7)  
  efada = efada*emrel
```

efved = 0 + emved*(FLAG==8)

efved = efved*emrel

efsem = 0 + emsem*(FLAG==10)

efsem = efsem*emrel

efapi = 0 + emapi*(FLAG==11)

efapi = efapi*emrel

eftof = 0 + emtof*(FLAG==12)

eftof = eftof*emrel

effil = 0 + emfil*(FLAG==13)

effil = effil*emrel

efaba = 0 + emaba*(FLAG==14)

efaba = efaba*emrel

efris = 0 + (kris*DOSE)*(FLAG==15)

efris = efris*emrel

efupa = 0 + emupa*(FLAG==16)

efupa = efupa*emrel

effon = 0 + emfon*(FLAG==17)

effon = effon*emrel

efver = 0 + emver*(FLAG==18)

efver = efver*emrel

emax = eo + efinf + efnat + efcdp + efeta + efcfer + efada+ efved +

efsem + efapi + eftof + effil + efaba + efris + efupa +

effon + efver

```

    emax
  }

nibdq23 <- gnls(ibdq~ibdq23(trialNO,armNO,DOSE,methodFlag,FLAG,week,no,tp1,
group.week,
               ibdq,SD,male,age,dur,CDAI,CRP,IBDQ,eo,eminf,emnat,emcdp,
               emeta,emcer,kada,emved,emsem,emapi,emtof,emfil,
               emaba,kris,emupa,emfon,emver,edur),
data = IBDQ,
params = list(eo~-1+I(group.week),eminf~1,emnat~1,emcdp~1,
              emeta~1,emcer~1,kada~1,emved~1,
              emsem~1,emapi~1,emtof~1,emfil~1,emaba~1,
              kris~1,emupa~1,emfon~1,emver~1,edur~1),
start = c(coef(n22)),
correlation = corARMA(form = ~tp1|group,p=1),
weights = varFixed(~(SD^2)/no),
verbose = T

)

```