Supplementary Materials

Comparation of Time-Course, Dose-Effect, Influencing Factors and Adverse Events of Biologics in the Treatment of Adult Patients with Moderate to Severe Plaque Psoriasis

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References and Time Points of Included Studies

Supplementary Table S1. Time points for studies included in the model-based meta-analysis.

No.	Study	Patients	Drug	Regimen	Time points (week)		
					PASI75	PASI90	PASI100
1	K.A. Papp(1) 2016	AMAGINE-1 661	Brodalumab	140mg; 210mg	2, 4, 6, 8, 10, 12	2, 4, 6, 8, 10, 12	4, 6, 8, 10, 12
2	Lebwohl M(2) 2015	AMAGINE-2 1831	Brodalumab Ustekinumab	Bro:140mg/210mg Ust:45mg weight ≤100 kg 90 mg weight >100 kg	2, 4, 6, 8, 10, 12	2, 4, 6, 8, 10, 12	4, 6, 8, 10, 12
3	Lebwohl M(2) 2015	AMAGINE-3 1881	Brodalumab Ustekinumab	Bro:140mg/210mg Ust:45mg weight ≤100 kg 90 mg weight >100 kg	2, 4, 6, 8, 10, 12	2, 4, 6, 8, 10, 12	4, 6, 8, 10, 12
4	Nakagawa(3) 2016	151	Brodalumab	70mg; 140mg; 210mg	2, 4, 6, 8, 10, 12	2, 4, 6, 8, 10, 12	4, 6, 8, 10, 12
5	Seong Jun Seo(4)	62	Brodalumab	210mg	2, 4, 6, 8, 10, 12	2, 4, 6, 8, 10, 12	4, 6, 8, 10, 12

	2021						
6	Kim A.Papp(5) 2018	250	Bimekizumab	64mg; (LD320mg)160mg; 160mg; 320mg; 480mg,	4, 8, 12	4, 8, 12	4, 8, 12
7	Kristian Reich(6) 2021	567	Bimekizumab Ustekinumab	Bim: 320mg; Ust:45mg weight ≤100 kg 90 mg weight >100 kg	4, 8, 12, 16	4, 8, 12, 16	4, 8, 12, 16
8	Gordon(7) 2021	435	Bimekizumab	320mg	2, 4, 8, 12, 16	2, 4, 8, 12, 16	2, 4, 8, 12, 16
9	Gottlieb(8) 2018	CIMPASI-1 234	Certolizumab	400mg 0, 2, 4w followed by 200mg; 400mg	4, 8, 12, 16	4, 8, 12, 16	/
10	Gottlieb(8) 2018	CIMPASI-2 226	Certolizumab	400mg 0, 2, 4w followed by 200mg; 400mg	4, 8, 12, 16	4, 8, 12, 16	/
11	Mark Lebwohl(9) 2018	559	Certolizumab Etanercept	Cer: 400mg 0, 2, 4w followed by 200mg; 400mg	4, 8, 12, 16	4, 8, 12, 16	/

				Eta: 50mg			
12	Umezawa(10) 2021	127	Certolizumab	400mg 0, 2, 4w followed by 200mg; 400mg	4, 8, 12, 16	4, 8, 12, 16	/
13	OHTSUKI(11) 2018	192	Guselkumab	50mg; 100mg	2, 4, 8, 12, 16	2, 4, 8, 12, 16	4, 8, 12, 16
14	Gordon(12) 2015	293	Guselkumab Adalimumab	Gus: 5mg; 15mg; 50mg; 100mg; 200mg; Ada:(LD80mg)40mg	4, 8, 12, 16	4, 8, 12, 16	4, 8, 12, 16
15	K.B. Gordon(13) 2016	UNCOVER-1 1296	Ixekizumab	(LD160mg)80mg, q2w; (LD160mg)80mg, q4w	2, 4, 8, 12	2, 4, 8, 12	4, 8, 12
16	Griffiths(14) 2015	UNCOVER-2 1224	Etanercept Ixekizumab	Eta: 50mg; Ixe: (LD160mg)80mg, q2w; (LD160mg)80mg, q4w	2, 4, 8, 12	2, 4, 8, 12	2, 4, 8, 12
17	Kristian Reich(15) 2018	UNCOVER-3	Etanercept Ixekizumab	Eta: 50mg; Ixe: (LD160mg)80mg,	2, 4, 8, 12	2, 4, 8, 12	2, 4, 8, 12

		1346		q2w; (LD160mg)80mg, q4w			
18	Leonardi(16) 2012	141	Ixekizumab	10mg; 25mg; 75mg; 150mg	2, 4, 6, 8, 12	2, 4, 6, 8, 12	4, 6, 8, 12
19	K. Reich(17) 2019	205	Mirikizumab	30mg; 100mg; 300mg	4, 8, 12, 16	4, 8, 12, 16	4, 8, 12, 16
20	OHTSUKI(18) 2019	171	Risankizumab	75mg; 150mg	16	4, 8, 12, 16	4, 8, 12, 16
21	Blauvelt(19) 2020	507	Risankizumab	150mg	4, 8, 12, 16	4, 8, 12, 16	4, 8, 12, 16
22	Gordon(20) 2018	UltlMMa-1 506	Risankizumab Ustekinumab	Ris:150mg Ust:45mg weight ≤100 kg 90 mg weight >100 kg	12	4, 8, 12, 16	4, 8, 12, 16
23	Gordon(20) 2018	UltlMMa-2 491	Risankizumab Ustekinumab	Ris:150mg Ust:45mg weight ≤100 kg	12	4, 8, 12, 16	4, 8, 12, 16

				90 mg weight >100 kg			
24	Sigurgeirsson(21) 2021	214	Secukinumab	2*150mg; 300mg	2, 3, 4, 8, 12	2, 3, 4, 8, 12	4, 8, 12
25	Sigurgeirsson(22) 2022	122	Secukinumab	2*150mg; 300mg	4, 12	4, 12	4,12
26	P. Rich(23) 2012	271	Secukinumab	75m; 150mg; 300mg	2, 4, 8, 12	2, 4, 8, 12	/
27	Langley(24) 2014	ERASURE 734	Secukinumab	150mg; 300mg	2, 3, 4, 8, 12	4, 8, 12	4, 8, 12
28	Lin Cai(25) 2020	441	Secukinumab	150mg; 300mg	4, 8, 12	4, 8, 12	/
29	K.A. Papp(26) 2012	125	Secukinumab	25mg, once or q4w; 75mg; 150mg	2, 4, 8, 12	8, 12, 16	/
30	A. Blauvelt(27) 2015	177	Secukinumab	150mg; 300mg	2, 3, 4, 8, 12	3, 4, 8, 12	4, 8, 12
31	C. Paul(28) 2015	181	Secukinumab	150mg; 300mg	2, 3, 4, 8, 12	2, 3, 4, 8, 12	4, 8, 12

32	Langley(24) 2014	FIXTURE 1297	Secukinumab Etanercept	Sec:150mg; 300mg; Eta:50mg	4, 8, 12	4, 8, 12	4, 8, 12
33	Kim A Papp(29) 2021	313	Sonelokimab Secukinumab	Son:30mg; 60mg; 120mg 0,2,4,8w; 120mg q2w; Sec:300mg	12	4, 8, 12	4, 8, 12
34	K. Papp(30) 2015	350	Tildrakizumab	5mg; 25mg; 100mg; 200mg	2, 4, 6, 8, 12, 16	16	16
35	Kristian Reich(31) 2017	reSURFACE 1 772	Tildrakizumab	100mg; 200mg	4, 8, 12	12	12
36	Kristian Reich(31) 2017	reSURFACE 2 1090	Tildrakizumab Etanercept	Til:100mg; 200mg Eta:50mg	4, 8, 12	12	12
37	Leonardi(32) 2008	PHOENIX1 766	Ustekinumab	45mg; 90mg	2, 4, 8, 12	2, 4, 8, 12	12
38	Kim A Papp(33) 2008	PHOENIX2 1230	Ustekinumab	45mg; 90mg	2, 4, 8, 12	4, 8, 12	12

39	IGARASHI(34) 2012	157	Ustekinumab	45mg; 90mg	2, 4, 8, 12	2, 4, 8, 12	/
40	Tsen-Fang Tsai(35) 2011	119	Ustekinumab	45mg weight ≤100 kg 90 mg weight >100 kg	4, 8, 12	12	12
41	Zhang(36) 2022	187	Vunakizumab	40mg; 80mg; 160; 240mg	2, 4, 6, 8, 12, 16, 20	2, 4, 6, 8, 12, 16, 20	4, 8, 12, 16, 20
42	Andrew Blauvelt(37) 2017	VOYAGE1 837	Guselkumab Adalimumab	Gus:100mg; Ada: (LD80mg)40mg	2, 4, 8, 12, 16	2, 4, 8, 12, 16	4, 8, 12, 16
43	Kristian Reich(38) 2017	VOYAGE2 992	Guselkumab Adalimumab	Gus:100mg; Ada: (LD80mg)40mg	2, 4, 8, 12, 16	2, 4, 8, 12, 16	4, 8, 12, 16
44	Hideshi Torii(39) 2010	54	Infliximab	5mg/kg	2, 6, 10, 14	2, 6, 10, 14	/
45	Alice B. Gottlieb(40) 2004	249	Infliximab	3mg/kg; 5mg/kg	2, 4, 6, 8, 10	10	/
46	Kristian Reich(41)	353	Infliximab	5mg/kg	2, 6, 10, 14,	2, 6, 10, 14,	/

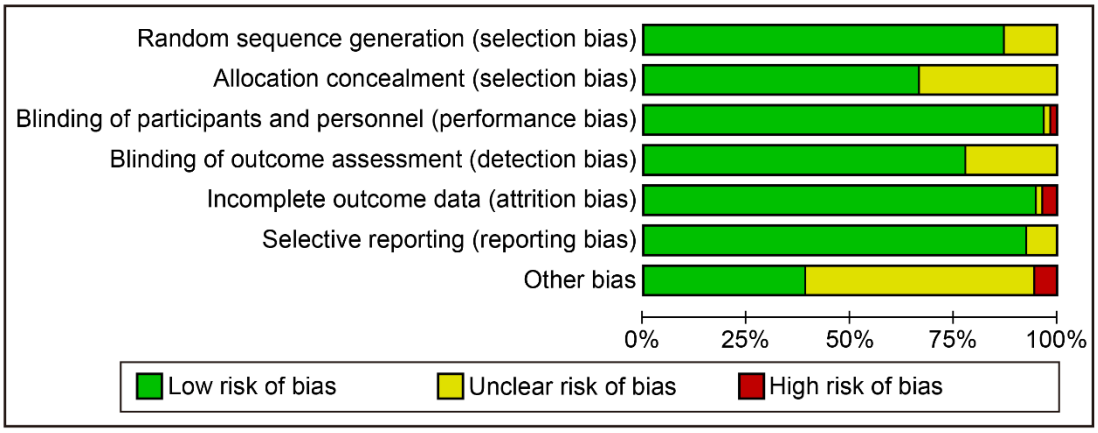
	2005				22,24	22,24	
47	Krupashankar(42) 2014	223	Itolizumab	0.4mg/kg 0, 1, 2, 3, 4w then 1.6mg/kg q2w; 1.6mg/kg q2w	2, 3, 4, 6, 8,10, 12	/	/
48	L. Cai(43) 2016	425	Adalimumab	Ada: (LD80mg)40mg	3, 7, 12	3, 7, 12	3, 7, 12
49	ASAHINA(44) 2010	169	Adalimumab	40mg; 80mg; 80mg 0w followed by 40mg	4, 8, 12, 16	4, 8, 12, 16	/
50	Alan Menter(45) 2008	1212	Adalimumab	80mg 0w followed by 40mg	4, 8, 12, 16	4, 12, 16	4, 12, 16
51	A.B. Gottlieb(46) 2011	347	Etanercept Briakinumab	Eta:50mg Bri:200mg 0,4w_100mg 8w	4, 8, 12	4, 8, 12	4, 8, 12
52	B.E. Strober(47) 2011	350	Etanercept Briakinumab	Eta:50mg Bri:200mg 0,4w_100mg 8w	4, 8, 12	4, 8, 12	4, 8, 12
53	Alice B.	112	Etanercept	25mg	2, 4, 8, 12, 16,	12, 24	/

	Gottlieb(48) 2003				20, 24		
54	K.A.Papp(49) 2005	583	Etanercept	25mg; 50mg	2, 4, 8, 12	12	/

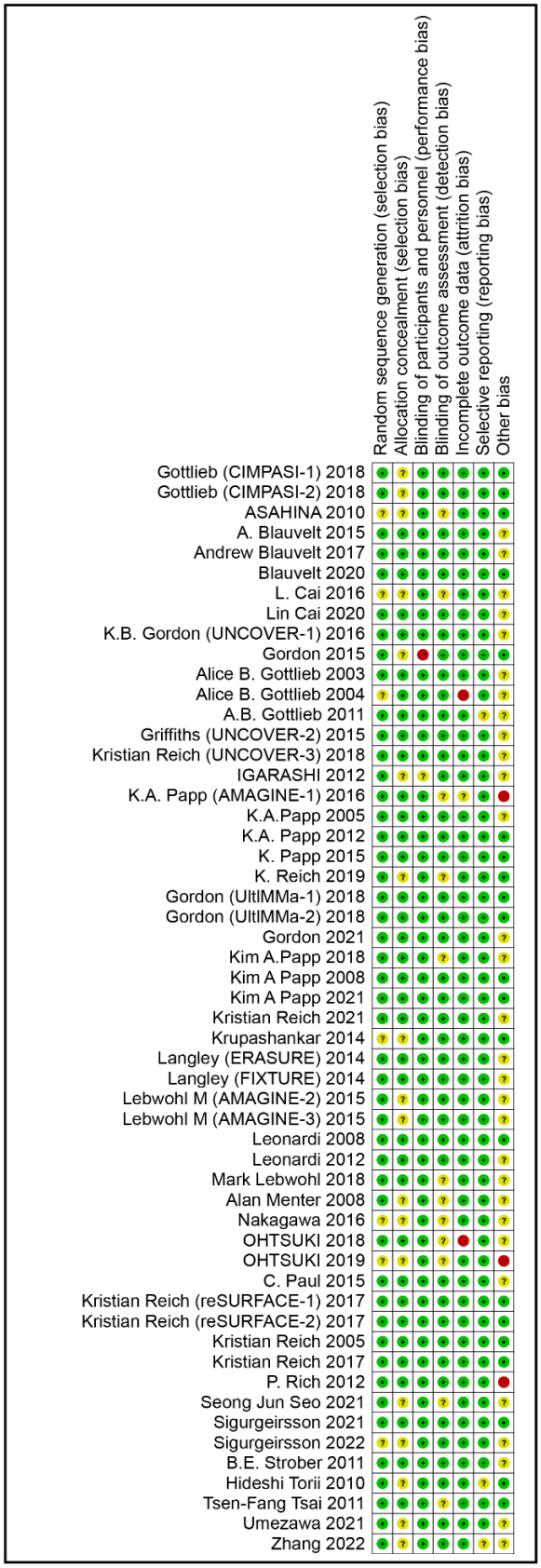
PASI, Psoriasis Area and Severity Index score; PASI75, PASI90 and PASI100, the proportion of patients whose PASI decreased by ≥75%, 90% and 100% compared with baseline, respectively; LD, Loading dose; w, week; q2w, once every 2 weeks; q4w, once every 4 weeks.

Risk of Bias Assessment

The risk of bias in the included studies was independently assessed by Weiqi Gao, Boran Yu and Ya Yan using the Cochrane Risk of Bias Tool. The evaluation items included random sequence generation, allocation concealment, blinding of participants and personnel, blinding in the outcome assessment, incomplete outcome data, selective reporting, and other biases. Disagreements were resolved through discussion with a third investigator (Libo Zhao).



Supplementary Figure S1. Risk of bias assessment. Overall risk of bias, using Cochrane's risk of bias assessment tool.



Supplementary Figure S2. Risk of bias assessment. Study-level risk of bias, using Cochrane's risk of bias assessment tool.

Model Development

1.Development of basic model

After a graphical exploration of the data, the longitudinal model of PASI75, PASI90 and PASI100 were characterized using a hierarchical regression model with the maximum likelihood estimation method. In this study, we assumed that the efficacy of the drug group consists of the placebo response and pure drug efficacy. Here, pure drug efficacy is the relative efficacy of the drug, which is the efficacy after subtracting the corresponding placebo response. The model could be commonly described as follows:

$$E_{i,j,t} = E_{placebo,i,t} + E_{drug,i,j,t} \qquad (1)$$

$$E_{drug,i,j,t} = function(drug, dose, regimen, time, \theta, X_{ij}) \qquad (2)$$

In formula 1, $E_{i,j,t}$ represents the efficacy in the *j*th treatment arm of the *i*th trial at *t* time, which is the sum of $E_{placebo,i,t}$ (the placebo effects of the *i*th trial at *t* time) and $E_{drug,i,j,t}$ (the drug effects in the *j*th treatment arm of the *i*th trial at *t* time). For outcomes measured as probabilities, a logit translation was performed to restrict the treatment effect to a range of 0–1. $E_{drug,i,j,t}$ in formula 2 is a function dependent on the type of drug, dose, regimen, time, fixed-effect model parameters θ, and covariates *X*.

2.Development of the time course relationship part in model

At first, the drug effects were set not to alter over time. Then, during model development, if the model fit improved, a time variable was added to create a non-linear model to describe the time-varying drug effects. The formula was listed as follows:

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

In formula 3, $E_{max drug}$ represents the maximum efficacy of each treatment and *k* represents the rate constant describing the onset of the drug effect.

3.Development of dose-response relationship part in model

During the development of the model, 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 that match different doses, routes, and regimens of a drug. For drugs with a dose range, a dose-response relationship was estimated by the simple fixed-effect, linear, E_{max} and log-linear model. Functions of these models are listed as follows:

Simple fixed-effect model: $f = E_0 + E_{max}$ (4)

linear model: $f = E_0 + \delta \cdot \text{Dose}$ (5)

E_{max} model: $f = E_0 + \frac{Emaxdrug \cdot \text{Dose}}{ED50 + Dose}$ (6)

log-linear model: $f = E_0 + (E_{maxdrug} + \beta \cdot \log(\text{Dose - constant}))$ (7)

In which, E_0 represented the placebo efficacy, while δ was the slope parameter of linear model. $E_{maxdrug}$ represented the maximum efficacy of the drug. β was the slope parameter of log-linear model.

4.Model for PASI75, PASI90 and PASI100

$$N_{\text{effect } i,j,t} \sim \text{binomial}\ (P_{i,j,t}, N_{i,j}) \quad (8)$$

$$P_{i,j,t} = g\ (E_{placebo,i,t} + E_{drug\ i,j,t}) \quad (9)$$

For ratio outcomes, efficacy of a treatment arm was considered as $P_{i,j,t}$ (the probability of patients achieving endpoints at *t* time in *j*th treatment arm of *i*th trial), from a binomial distribution of $N_{\text{effect } i,j,t}$ (the number of patients achieving endpoint at *t* time in *j*th treatment arm of *i*th trial) with probability ($P_{i,j,t}$) and sample size ($N_{i,j}$). *g* was a logit translate of the efficacy of treatment, which was a sum of $E_{placebo,i,t}$ (placebo effect of *i*th trial at *t* time) and $E_{drug\ i,j,t}$ (drug effect of *j*th treatment arm in *i*th trial at *t*

time), to limit the probability to a range of 0-1.

For PASI75, PASI90, PASI100, the weight was based on the standard error of observed values and was generated by the following equation (formula 10) with *P* and *N*, avoiding the possible deviations in the final model caused by the extreme outcome values, and ensuring that more larger sample size outcomes had a greater impact.

$$Weight = \sqrt{\frac{P \cdot (1-P)}{N}} \qquad (10)$$

5.Covariate

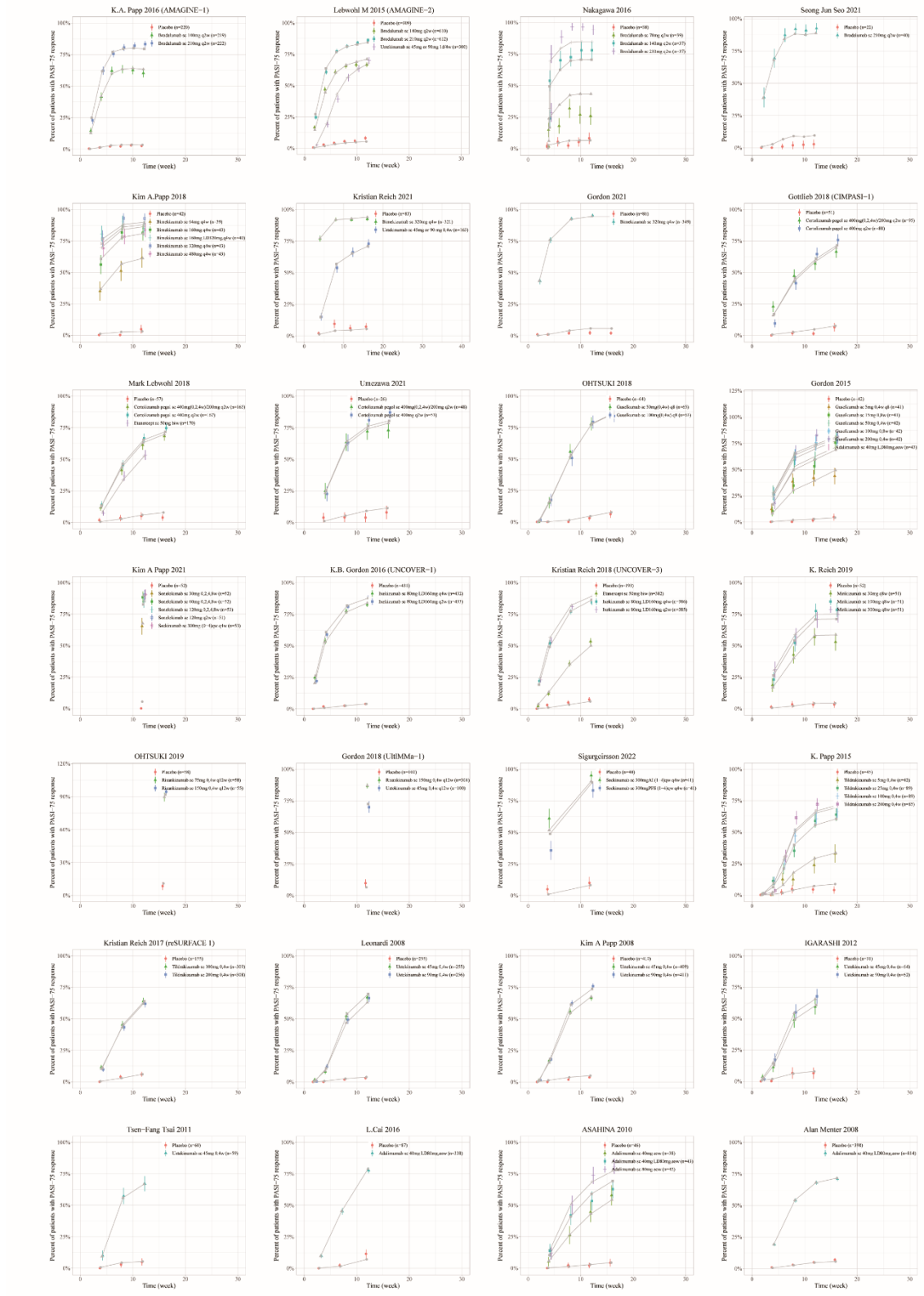
Baseline characteristics, including percentage of male, age (year), weight (kg), disease duration (year), percentage of prior biological therapy and baseline PASI, were set as the covariates in the model. Covariates were investigated for their possible impact on the treatment efficacies with the following equation (formula 11), where θ was the parameter quantifying the covariate effects.

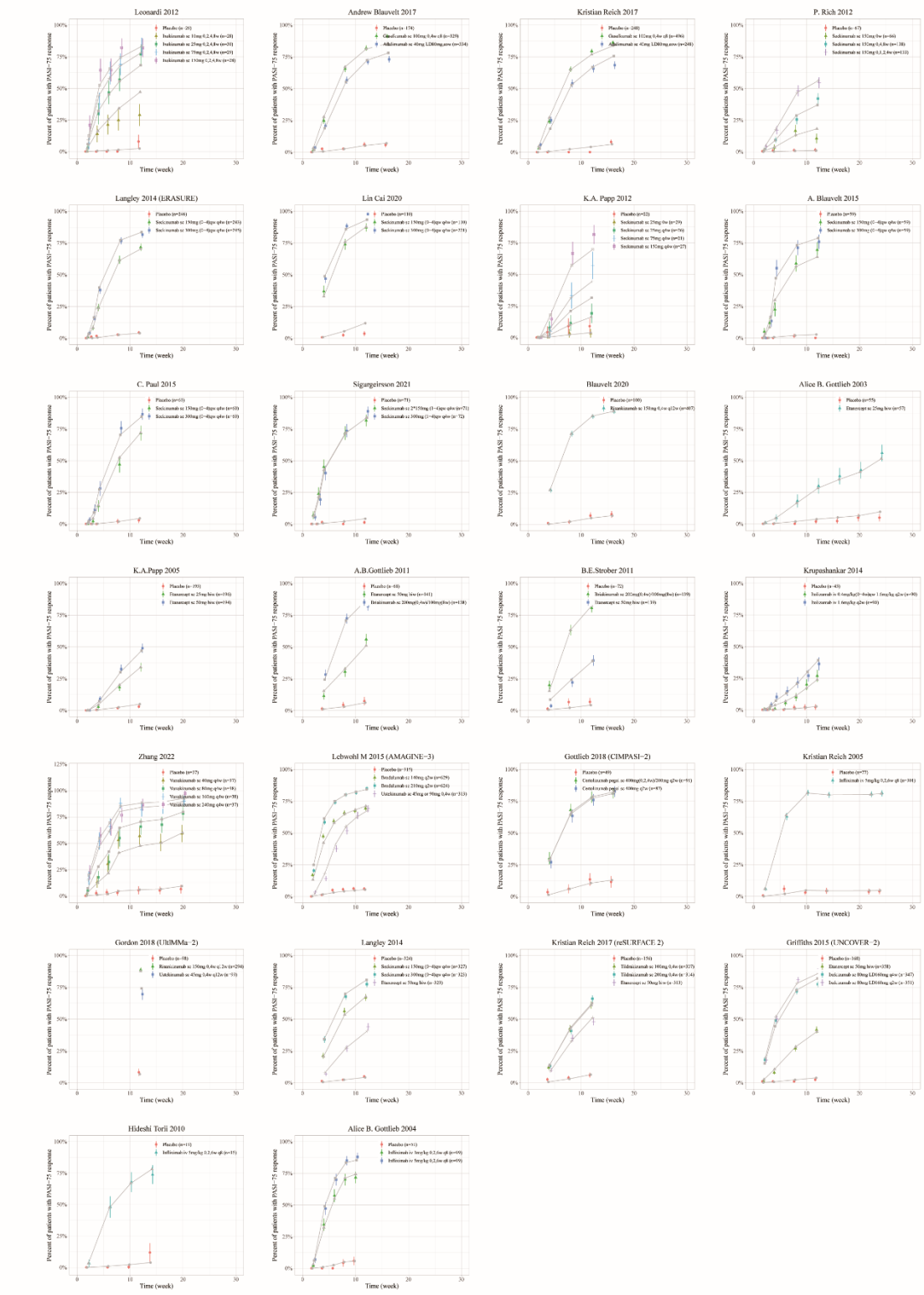
$$\text{Effect}_{\text{Covariate}} = \frac{\text{Covariate}\theta}{\text{mean(Covariate)}} \qquad (11)$$

Model development and iteration were based on the data and guided by successful convergence of the minimization routine. Model selection was based on the Akaike information criterion and the log-likelihood ratio at an acceptance *p*-value of 0.05.

Final Models

1.Model fitted time-course plots of response rate for PASI75





Supplementary Figure S3. Model fitted time-course plots of response rate for PASI75. Color symbols and vertical bars are observed mean and calculated weight of time points; gray symbols and lines are the model predictions. PASI, Psoriasis Area and Severity

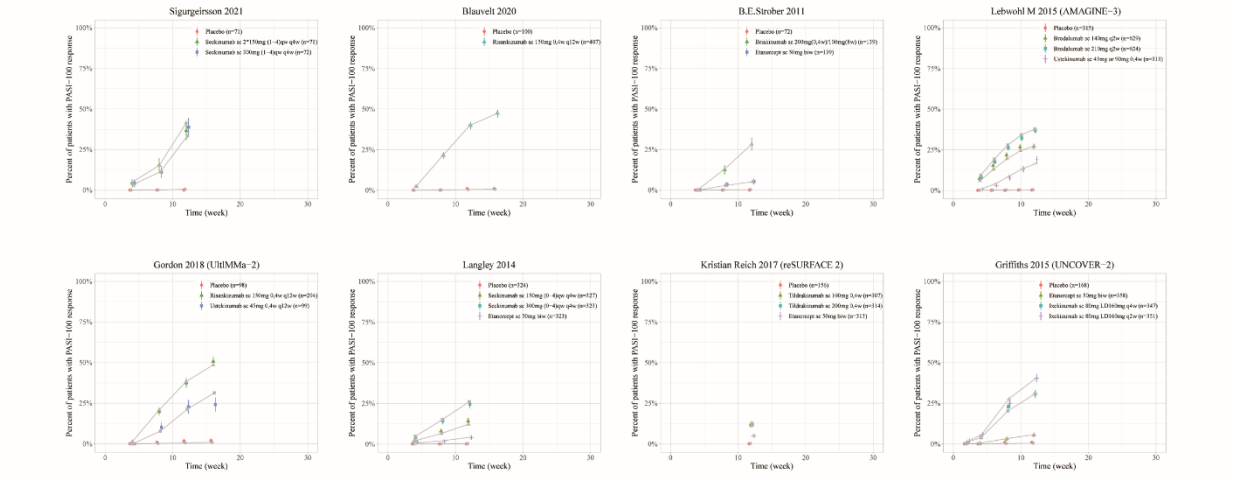
Index score; PASI75, the proportion of patients achieving ≥75% reduction from baseline PASI score; s.c., subcutaneous injection; i.v., intravenous injection; w, week; eow, every other week; biw, twice weekly; q2w, once every 2 weeks; q4w, once every 4 weeks.

2.Model fitted time-course plots of response rate for PASI90

Supplementary Figure S4. Model fitted time-course plots of response rate for PASI90. Color symbols and vertical bars are observed mean and calculated weight of time points; gray symbols and lines are the model predictions. PASI, Psoriasis Area and Severity Index score; PASI90, the proportion of patients achieving ≥ 90% reduction from

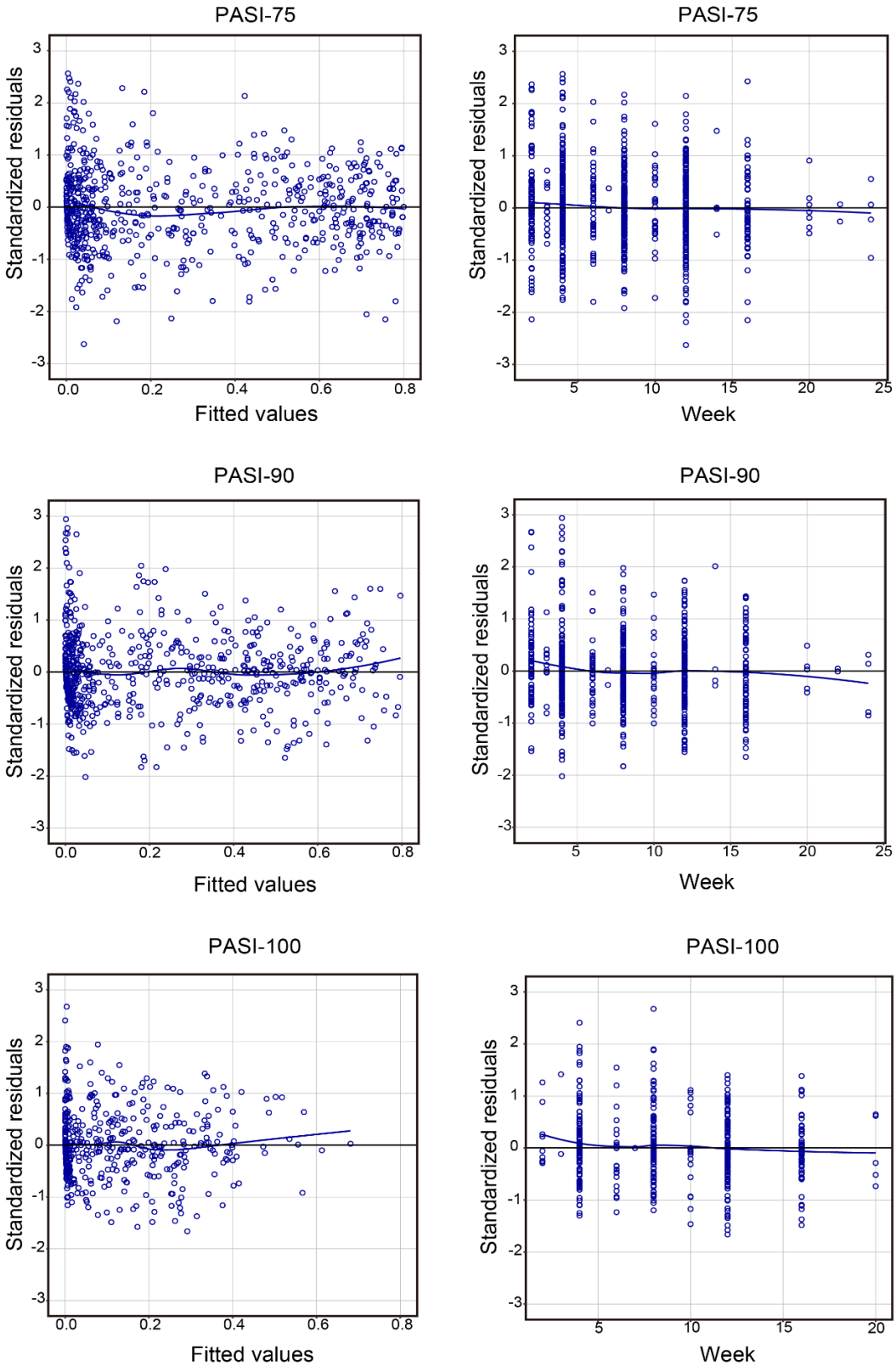
baseline PASI score; s.c., subcutaneous injection; i.v., intravenous injection; w, week; eow, every other week; biw, twice weekly; q2w, once every 2 weeks; q4w, once every 4 weeks.

3.Model fitted time-course plots of response rate for PASI100



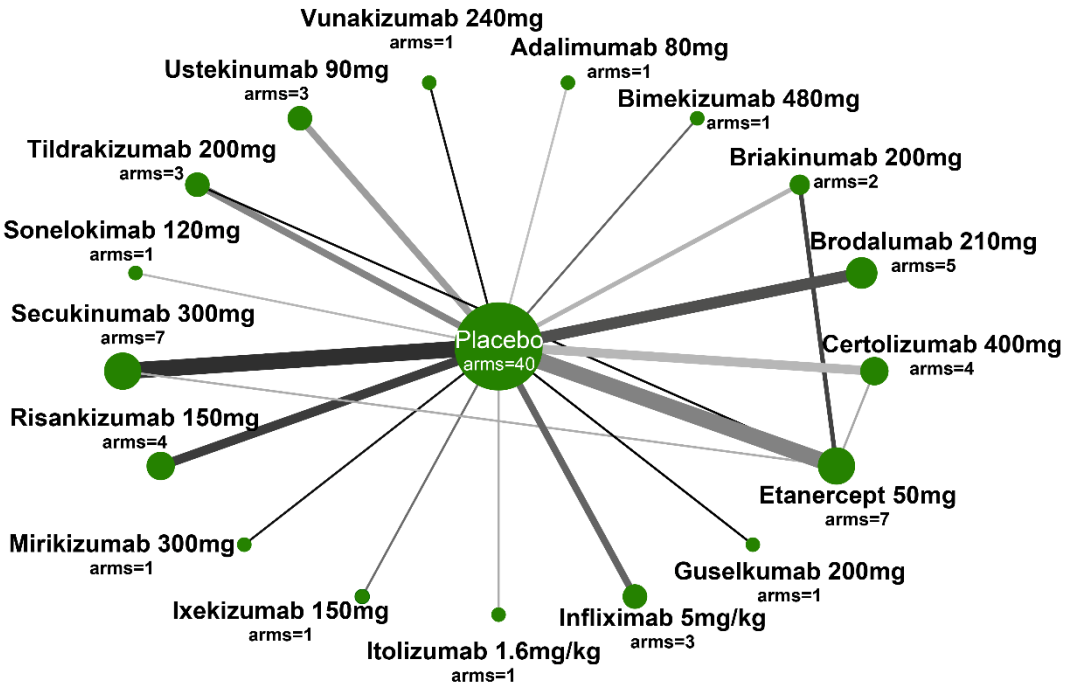
Supplementary Figure S5. Model fitted time-course plots of response rate for PASI100. Color symbols and vertical bars are observed mean and calculated weight of time points; gray symbols and lines are the model predictions. PASI, Psoriasis Area and Severity Index score; PASI100, the proportion of patients achieving ≥ 100% reduction from baseline PASI score; s.c., subcutaneous injection; i.v., intravenous injection; w, week; eow, every other week; biw, twice weekly; q2w, once every 2 weeks; q4w, once every 4 weeks.

Diagnostic Plots



Supplementary Figure S6. Diagnostic Plots

Network plot



Supplementary Figure S7. Network plot presenting the trial data contributing evidence comparing Incidence rate of adverse events. Width of the lines is proportional to the number of arms comparing every pair of treatments, size of every circle is proportional to the number of randomly assigned participants.

Model Code

Code for PASI75 model

```
pasi75.27 <-
function(trialno,armno,week,CLASS,FLAG,DOSE,groupweek,methodFlag,
PASI75,no,tp1,male,age,we,dur,Priorb,baline,Regimen,eo,embro,emust,embim,emeta,
embri,emada,emcer,emgus,eminf,emito,emixe,emmir,emris,emsec,emson,emtil,emvu
n,k,ledbro,ledgus,ledbim,ledixe,ledinf,ledvun,ledito,ledsec,ledtil,ledada,ledeta,ledmir,
ledust,sadc,sadr,sads,ePriorb)
{
   emrel = 1
   emtime = 1*(CLASS!=2) + (1-exp(-exp(k)*week))*(CLASS==2)
   emrel = emrel*(Priorb/mean(All75$Priorb,na.rm = T))**ePriorb
   emrel = emrel*emtime
   efbro = 0 + ((embro*DOSE)/(DOSE+ledbro))*(FLAG==2)
   efbro = efbro*emrel
   efust = 0 + ((emust*DOSE)/(DOSE+ledust))*(FLAG==3)
   efust = efust*emrel
   efbim = 0 + ((embim*DOSE)/(DOSE+ledbim))*(FLAG==4)
   efbim = efbim*emrel
   efeta = 0 + ((emeta*DOSE)/(DOSE+ledeta))*(FLAG==5)
   efeta = efeta*emrel
   efbri = 0 + embri*(FLAG==6)
```

efbri = efbri*emrel

efada = 0 + ((emada*DOSE)/(DOSE+ledada))*(FLAG==7)

efada = efada*emrel

efcer = 0 + (emcer+sadc*log(abs(DOSE-20)))*(FLAG==8)

efcer = efcer*emrel

efgus = 0 + ((emgus*DOSE)/(DOSE+ledgus))*(FLAG==9)

efgus = efgus*emrel

efinf = 0 + ((eminf*DOSE)/(DOSE+ledinf))*(FLAG==10)

efinf = efinf*emrel

efito = 0 + ((emito*DOSE)/(DOSE+ledito))*(FLAG==11)

efito = efito*emrel

efixe = 0 + ((emixe*DOSE)/(DOSE+ledixe))*(FLAG==12)

efixe = efixe*emrel

efmir = 0 + ((emmir*DOSE)/(DOSE+ledmir))*(FLAG==13)

efmir = efmir*emrel

efris = 0 + (emris+sadr*log(abs(DOSE-20)))*(FLAG==14)

efris = efris*emrel

efsec = 0 + ((emsec*DOSE)/(DOSE+ledsec))*(FLAG==15)

efsec = efsec*emrel

efson = 0 + (emson+sads*log(abs(DOSE-20)))*(FLAG==16)

efson = efson*emrel

eftil = 0 + ((emtil*DOSE)/(DOSE+ledtil))*(FLAG==17)

```
    eftil = eftil*emrel
    efvun = 0 + ((emvun*DOSE)/(DOSE+ledvun))*(FLAG==18)
    efvun = efvun*emrel
    emax = eo + efbro + efust + efbim + efeta + efbri + efada + efcer + efgus +
    efinf + efito + efixe + efmir + efris + efsec + efson + eftil + efvun
    yp = exp(emax)/(1+exp(emax))
    yp
}
n27 <-
gnls(PASI75~pasi75.27(trialno,armno,week,CLASS,FLAG,DOSE,groupweek,metho
dFlag,PASI75,no,tp1,male,age,we,dur,Priorb,baline,Regimen,eo,embro,emust,embim,
emeta,embri,emada,emcer,emgus,eminf,emito,emixe,emmir,emris,emsec,emson,emtil,
emvun,k,ledbro,ledgus,ledbim,ledixe,ledinf,ledvun,ledito,ledsec,ledtil,ledada,ledeta,le
dmir,ledust,sadc,sadr,sads,ePriorb),data = PASI75data,
params = list(eo~-1+I(groupweek),
embro~1,emust~1,embim~1,emeta~1,embri~1,emada~1,emcer~1,emgus~1,eminf~1,e
mito~1,emixe~1,emmir~1,emris~1,emsec~1,emson~1,emtil~1,emvun~1,k~1,ledbro~
1,ledgus~1,ledbim~1,ledixe~1,ledinf~1,ledvun~1,ledito~1,ledsec~1,ledtil~1,ledada~1
,ledeta~1,ledmir~1,ledust~1,sadc~1,sadr~1,sads~1,ePriorb~1),
start = c(coef(n26),0.57),
weights=varPower(0.5,form=~fitted(.)*(1-fitted(.))/no,fixed = 0.5),
verbose = T)
```

Code for PASI90 model

```
pasi90.28 <-
function(trialno,armno,week,CLASS,FLAG,DOSE,groupweek,methodFlag,PASI90,n
o,tp1,male,age,we,dur,Priorb,baline,Regimen,eo,embro,emust,embim,emeta,embri,em
ada,emcer,emgus,eminf,emixe,emmir,emris,emsec,emson,emtil,emvun,k,ledbro,ledgu
s,ledbim,ledixe,ledvun,ledsec,ledtil,ledada,ledeta,ledmir,ledust,sadc,ledinf,sadr,sads,e
age,ePriorb,ewe)
{
   emrel = 1
   emtime = 1*(CLASS!=2) + (1-exp(-exp(k)*week))*(CLASS==2)
   emrel = emrel*(age/mean(All90$age,na.rm = T))**eage
   emrel = emrel*(Priorb/mean(All90$Priorb,na.rm = T))**ePriorb
   emrel = emrel*(we/mean(All90$we,na.rm = T))**ewe
   emrel = emrel*emtime
   efbro = 0 + ((embro*DOSE)/(DOSE+ledbro))*(FLAG==2)
   efbro = efbro*emrel
   efust = 0 + ((emust*DOSE)/(DOSE+ledust))*(FLAG==3)
   efust = efust*emrel
   efbim = 0 + ((embim*DOSE)/(DOSE+ledbim))*(FLAG==4)
   efbim = efbim*emrel
   efeta = 0 + ((emeta*DOSE)/(DOSE+ledeta))*(FLAG==5)
   efeta = efeta*emrel
```

efbri = 0 + embri*(FLAG==6)

efbri = efbri*emrel

efada = 0 + ((emada*DOSE)/(DOSE+ledada))*(FLAG==7)

efada = efada*emrel

efcer = 0 + (emcer+sadc*log(abs(DOSE-20)))*(FLAG==8)

efcer = efcer*emrel

efgus = 0 + ((emgus*DOSE)/(DOSE+ledgus))*(FLAG==9)

efgus = efgus*emrel

efinf = 0 + ((eminf*DOSE)/(DOSE+ledinf))*(FLAG==10)

efinf = efinf*emrel

efixe = 0 + ((emixe*DOSE)/(DOSE+ledixe))*(FLAG==12)

efixe = efixe*emrel

efmir = 0 + ((emmir*DOSE)/(DOSE+ledmir))*(FLAG==13)

efmir = efmir*emrel

efris = 0 + (emris+sadr*log(abs(DOSE-20)))*(FLAG==14)

efris = efris*emrel

efsec = 0 + ((emsec*DOSE)/(DOSE+ledsec))*(FLAG==15)

efsec = efsec*emrel

efson = 0 + (emson+sads*log(abs(DOSE-20)))*(FLAG==16)

efson = efson*emrel

eftil = 0 + ((emtil*DOSE)/(DOSE+ledtil))*(FLAG==17)

eftil = eftil*emrel

```
    efvun = 0 + ((emvun*DOSE)/(DOSE+ledvun))*(FLAG==18)
    efvun = efvun*emrel
    emax = eo + efbro + efust + efbim + efeta + efbri + efada + efcer + efgus +
    efinf + efixe + efmir + efris + efsec + efson + eftil + efvun
    yp = exp(emax)/(1+exp(emax))
    yp
}
n28 <-
gnls(PASI90~pasi90.28(trialno,armno,week,CLASS,FLAG,DOSE,groupweek,metho
dFlag,PASI90,no,tp1,male,age,we,dur,Priorb,baline,Regimen,eo,embro,emust,embim,
emeta,embri,emada,emcer,emgus,eminf,emixe,emmir,emris,emsec,emson,emtil,emvu
n,k,ledbro,ledgus,ledbim,ledixe,ledvun,ledsec,ledtil,ledada,ledeta,ledmir,ledust,sadc,l
edinf,sadr,sads,eage,ePriorb,ewe), data = PASI90data,
params = list(eo~-1+I(groupweek),
embro~1,emust~1,embim~1,emeta~1,embri~1,emada~1,emcer~1,emgus~1,eminf~1,e
mixe~1,emmir~1,emris~1,emsec~1,emson~1,emtil~1,emvun~1,k~1,ledbro~1,ledgus~
1,ledbim~1,ledixe~1,ledvun~1,ledsec~1,ledtil~1,ledada~1,ledeta~1,ledmir~1,ledust~
1,sadc~1,ledinf~1,sadr~1,sads~1,eage~1,ePriorb~1,ewe~1),
start = c(coef(n27),0.040),
weights=varPower(0.5,form=~fitted(.)*(1-fitted(.))/no,fixed = 0.5),
verbose = T
)
```

Code for PASI100 model

```
pasi100.24 <-
function(trialno,armno,week,CLASS,FLAG,DOSE,groupweek,methodFlag,PASI100,
no,tp1,Regimen,male,age,we,dur,Priorb,baline,eo,embro,emust,embim,emeta,embri,e
mada,emgus,emixe,emmir,emris,emsec,emson,emtil,emvun,k,ledbro,ledgus,ledbim,le
dixe,ledvun,ledsec,ledtil,ledmir,ledust,sadr,sads,eage,ewe,edur)
{
   emrel = 1
   emtime = 1*(CLASS!=2) + (1-exp(-exp(k)*week))*(CLASS==2)
   emrel = emrel*(age/mean(All100$age,na.rm = T))**eage
   emrel = emrel*(we/mean(All100$we,na.rm = T))**ewe
   emrel = emrel*(dur/mean(All100$dur,na.rm = T))**edur
   emrel = emrel*emtime
   efbro = 0 + ((embro*DOSE)/(DOSE+ledbro))*(FLAG==2)
   efbro = efbro*emrel
   efust = 0 + ((emust*DOSE)/(DOSE+ledust))*(FLAG==3)
   efust = efust*emrel
   efbim = 0 + ((embim*DOSE)/(DOSE+ledbim))*(FLAG==4)
   efbim = efbim*emrel
   efeta = 0 + emeta*(FLAG==5)
   efeta = efeta*emrel
   efbri = 0 + embri*(FLAG==6)
```

```
efbri = efbri*emrel

efada = 0 + emada*(FLAG==7)

efada = efada*emrel

efgus = 0 + ((emgus*DOSE)/(DOSE+ledgus))*(FLAG==9)

efgus = efgus*emrel

efixe = 0 + ((emixe*DOSE)/(DOSE+ledixe))*(FLAG==12)

efixe = efixe*emrel

efmir = 0 + ((emmir*DOSE)/(DOSE+ledmir))*(FLAG==13)

efmir = efmir*emrel

efris = 0 + (emris+sadr*log(abs(DOSE-20)))*(FLAG==14)

efris = efris*emrel

efsec = 0 + ((emsec*DOSE)/(DOSE+ledsec))*(FLAG==15)

efsec = efsec*emrel

efson = 0 + (emson+sads*log(abs(DOSE-20)))*(FLAG==16)

efson = efson*emrel

eftil = 0 + ((emtil*DOSE)/(DOSE+ledtil))*(FLAG==17)

eftil = eftil*emrel

efvun = 0 + ((emvun*DOSE)/(DOSE+ledvun))*(FLAG==18)

efvun = efvun*emrel

emax = eo + efbro + efust + efbim + efeta + efbri + efada + efgus +

efixe + efmir + efris + efsec + efson + eftil + efvun

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

```
   yp
}
n24 <-
gnls(PASI100~pasi100.24(trialno,armno,week,CLASS,FLAG,DOSE,groupweek,meth
odFlag,PASI100,no,tp1,Regimen,male,age,we,dur,Priorb,baline,eo,embro,emust,embi
m,emeta,embri,emada,emgus,emixe,emmir,emris,emsec,emson,emtil,emvun,k,ledbro,
ledgus,ledbim,ledixe,ledvun,ledsec,ledtil,ledmir,ledust,sadr,sads,eage,ewe,edur),
data = PASI100data,
params = list(eo~-1+I(groupweek),
embro~1,emust~1,embim~1,emeta~1,embri~1,emada~1,emgus~1,emixe~1,emmir~1,
emris~1,emsec~1,emson~1,emtil~1,emvun~1,k~1,ledbro~1,ledgus~1,ledbim~1,
                    ledixe~1,ledvun~1,ledsec~1,ledtil~1,ledmir~1,ledust~1,sadr~1,
                    sads~1,eage~1,ewe~1,edur~1),
start = c(coef(n23),-0.69),
weights=varPower(0.5,form=~fitted(.)*(1-fitted(.))/no,fixed = 0.5),
verbose = T
)
```

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