

Supplementary 1

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Search strategy

PubMed

Query

("asthma" OR "status asthmaticus") AND "children" AND ("Beclometasone dipropionate " OR "Budesonide" OR "Ciclesonide" OR "Fluticasone furoate" OR "Fluticasone propionate" OR "Mometasone furoate" OR "Triamcinolone acetonide")

Article type

Clinical Trial, Randomized Controlled Trial

Results

530

Date

2-March-2022

Embase

Query

#1 'asthma'/exp OR asthma

#2 'children'/exp OR children

#3 'beclometasone dipropionate'/exp OR 'beclometasone dipropionate' OR (('beclometasone'/exp OR beclometasone) AND dipropionate)

#4 'budesonide'/exp OR budesonide

#5 'ciclesonide'/exp OR ciclesonide

#6 'fluticasone furoate'/exp OR 'fluticasone furoate' OR (('fluticasone'/exp OR fluticasone) AND furoate)

#7 'fluticasone propionate'/exp OR 'fluticasone propionate' OR (('fluticasone'/exp OR fluticasone) AND ('propionate'/exp OR propionate))

#8 'mometasone furoate'/exp OR 'mometasone furoate' OR (('mometasone'/exp OR mometasone) AND furoate)

#9 'triamcinolone acetonide'/exp OR 'triamcinolone acetonide' OR (('triamcinolone'/exp OR triamcinolone) AND ('acetonide'/exp OR acetonide))

#10 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

#11 #1 AND #2 AND #10

#12 #1 AND #2 AND #10 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)

Results

1310

Date

2-March-2022

Detailed data included in the analysis at each time point

We showed the measured data of FEV₁ at each time point in VPC, but the measured data of the secondary outcome at each point were not shown. Table S1, S2 lists the data collected at each time point in different studies.

Table S1. FEV₁ collected at each time point in different studies

Study	Arm	Time (week)	FEV ₁ %change
vonberg 2007	CIC 400	0	0
		2	10.59
		4	14.12
		8	15.23
		12	15.49
	BUD 160	0	0
		2	11.39
		4	11.39
		8	13.29
		12	15.82
Pedersen 2009	CIC 80	0	0
		4	11.78
		8	14.56
		12	16.08
	CIC 160	0	0
		4	13.41
		8	15.94
		12	16.51

Table S1. (Continued)

Study	Arm	Time (week)	FEV ₁ %change
Escribano 2006	BUD (CFC/ no spacer)	0	0
		2	6.17
		4	13.33
		8	14.53
		12	18.43
	BUD (CFC/ spacer)	0	0
		2	6.79
		4	7.94
		8	9.18
		12	11.55
	BUD (HFA/ no spacer)	0	0
		2	11.48
		4	8.91
		8	11.39
		12	17.64
	BUD (HFA/ spacer)	0	0
		2	7.23
		4	6.63
		8	12.16
		12	16.1
pearlman 2017	BUD	0	0
		12	10.49

Table S2. Symptom-free days % collected at each time point in different studies

Study	Arm	Time (week)	Symptom-free days %
H.G.M 2002	FP	0	14.0208
		3	42.27
		6	56.1869
		9	61.0682
		12	66.1573
Nayak 2002	BDP 80	0	25.6
		2	11.2
		4	17.4
		6	22.6
		8	27.3
		10	26.7
		12	29.4
	BDP 160	0	27.1
		2	13.1
		4	22.6
		6	27.1
		8	29.2
		10	30.9
		12	32.1
Pedersen 2009	CIC 80	12	83.788
	CIC 160	12	80.034
	FP	12	89.42
Płoszczuk 2018	FP	0	31.01
		12	76.78

Base model selection

The selection of base model is mainly based on the lower objective function value (OFV) and the standard error (SE) should be lower than 30%. The details of base model selection process are listed in Table S3.

Table S3. Base model selection process

ID	Model	Inter-study variability	Formulation	Residual error	OFV	Note
1	Sigmoid $E_{\max}$	ET_{50} , $E_{\max}$, Hill	Exponential	Additive	69.491	Error, BSV ($E_{\max}$)=0.003, BSV (Hill)=0.003
2	Sigmoid $E_{\max}$	ET_{50} , $E_{\max}$, Hill	Additive	Additive	-	Failed
3	Sigmoid $E_{\max}$	ET_{50}	Exponential	Additive	69.488	ET_{50} SE%=61.5, Hill SE%=38.4
4	Sigmoid $E_{\max}$	ET_{50}	Additive*	Additive	-	Failed
5	$E_{\max}$	$E_{\max}$, ET_{50}	Additive	Additive	74.758	BSV ($E_{\max}$)=0.005 BSV ($E_{\max}$): SE%=1010.3
6	$E_{\max}$	$E_{\max}$, ET_{50}	Exponential	Additive	-	Error, BSV ($E_{\max}$)=0.003
7	$E_{\max}$	ET_{50}	Additive	Additive	74.758	
8	$E_{\max}$	ET_{50}	Exponential	Additive	71.561	$E_{\max}$ SE%=2.8, ET_{50} SE%=24.7, BSV (ET_{50}) SE%=21.7

Because the standard errors of model parameter in Sigmoid $E_{\max}$ model were higher than 30% (model 3), the simplified $E_{\max}$ model was chosen as the base model. Because the estimated value of inter-study variability (ISV) of $E_{\max}$ is close to 0, in order to stabilize the model, only the ISV of ET_{50} is retained in the base model.

Covariate model selection

Each covariate was screened in a stepwise manner based on differences in the objective function value (OFV) between hierarchical models. Differences in the OFV of 3.84 (χ^2 , $\alpha = 0.05$, $df = 1$) and 6.63 (χ^2 , $\alpha = 0.01$, $df = 1$) during the forward inclusion and backward deletion steps, respectively, were considered statistically significant. The details of covariate model selection process is listed in Table S4.

Table S4. Covariate model selection process

Model ID	Covariate	Model type	OFV	Δ OFV
Forward inclusion 1				
1		Base model	71.561	-
2	Drug type on ET ₅₀	Binary model	66.166	-5.395
3	Baseline on ET ₅₀	Additive model	69.254	-2.307
4	Baseline on ET ₅₀	Power model	68.174	-3.387
5	Male rate on ET ₅₀	Additive model	71.454	-0.107
6	Male rate on ET ₅₀	Power model	70.144	-1.417
7	Age on ET ₅₀	Additive model	69.726	-1.835
8	Age on ET ₅₀	Power model	70.783	-0.778
9	Daily dose on ET ₅₀	Additive model	70.485	-1.076
10	Daily dose on ET ₅₀	Power model	68.932	-2.629
Forward inclusion 2				
11	Baseline on ET ₅₀	Additive model	63.128	-3.038
12	Baseline on ET ₅₀	Power model	66.046	-0.12
13	Male rate on ET ₅₀	Additive model	65.09	-1.076
14	Male rate on ET ₅₀	Power model	63.645	-2.521
15	Age on ET ₅₀	Additive model	66.068	-0.098
16	Age on ET ₅₀	Power model	66.165	-0.001
17	Daily dose on ET ₅₀	Additive model*	-	-
18	Daily dose on ET ₅₀	Power model	64.385	-1.781
*For model 17, we cannot run it successfully.				
Since only one covariable is included, the backward deletion steps are not performed.				

Dose-response relationship

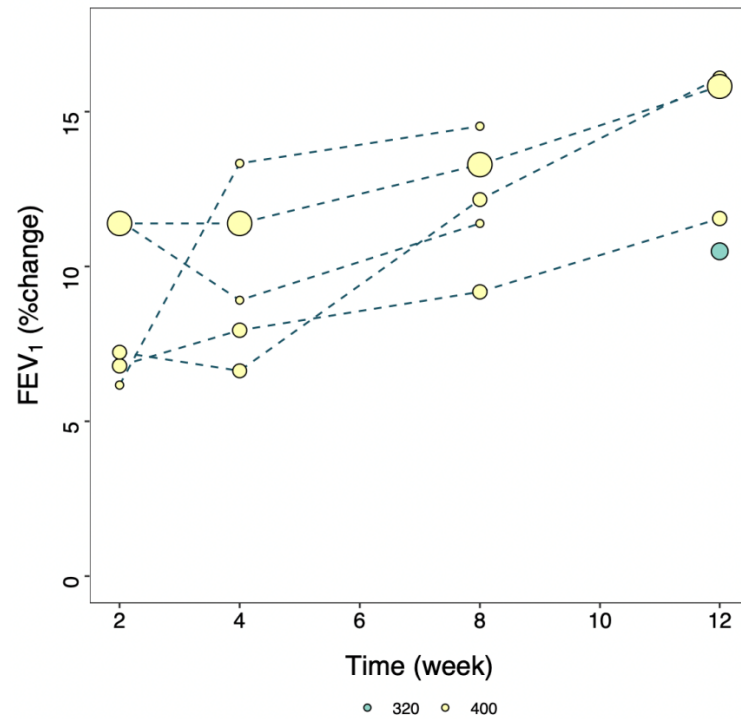


Figure S1.A. The dose-response relationship of BUD

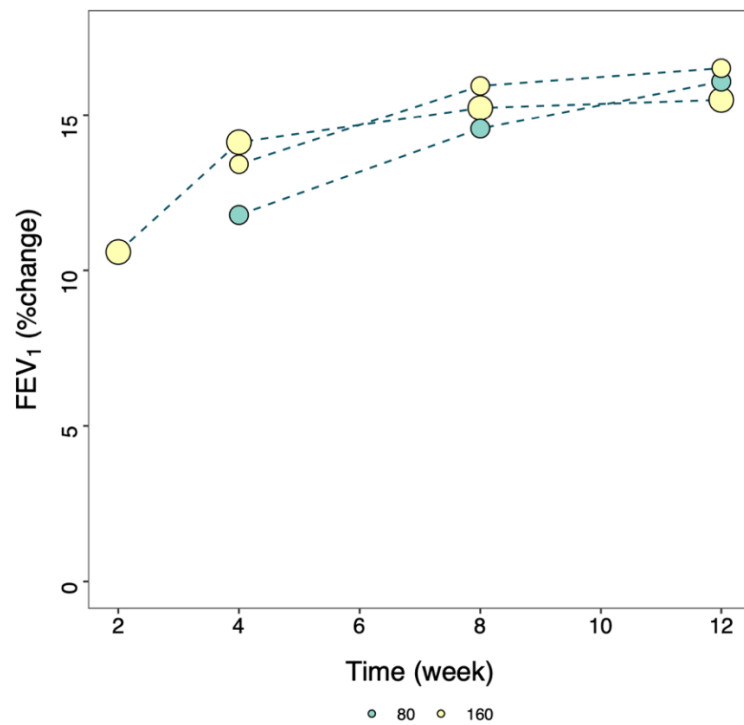


Figure S1.B. The dose-response relationship of CIC