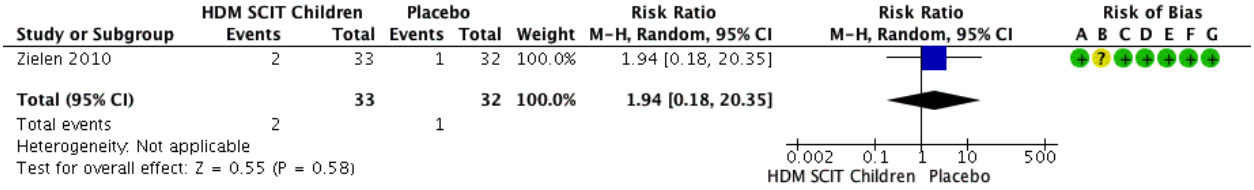
1. Should HDM SCIT versus no HDM SCIT be used for treatment in **paediatric** patients with asthma?

1.1. FOREST PLOTS

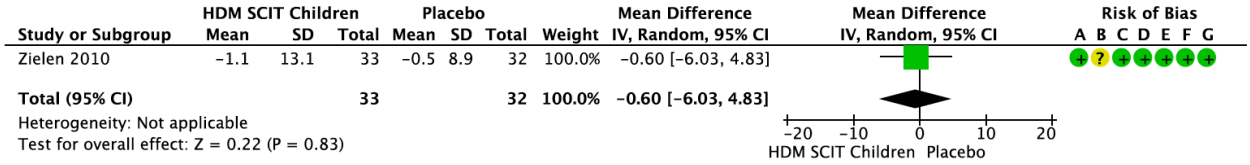
1.1.1. Critical outcomes

1.1.1.1. Asthma exacerbations - assessed as number of patients required a course of oral prednisolone



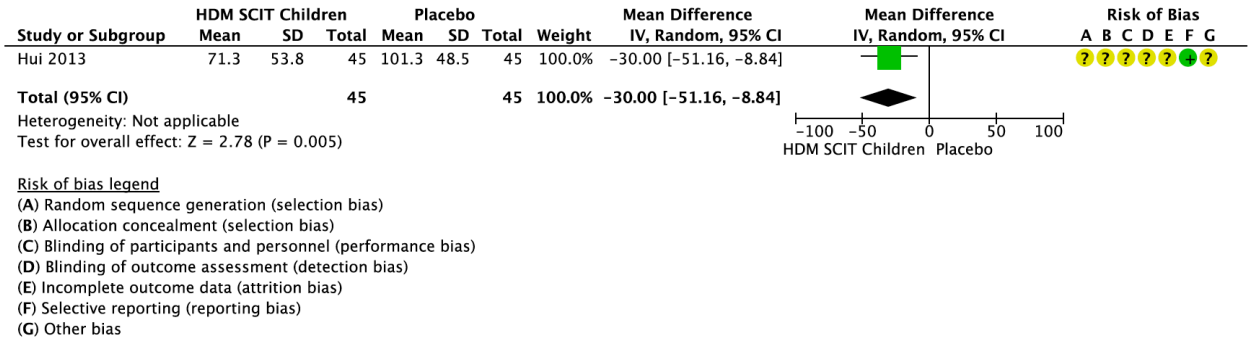
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

1.1.1.2. Asthma control - assessed as score of daytime asthma symptoms [symptom score: 0 (none)–5 (severe)]

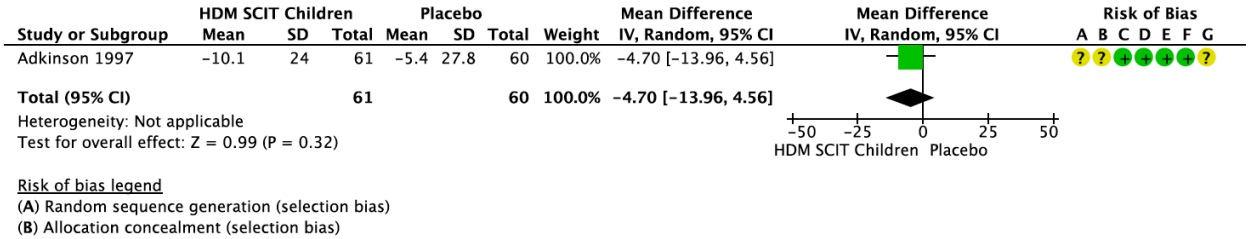


Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

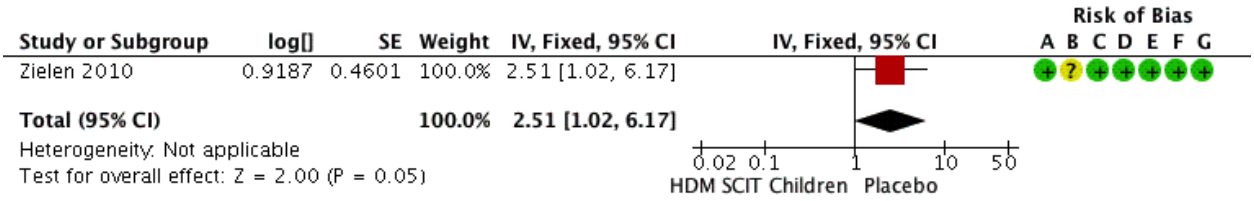
1.1.1.3. Steroid sparing effect (inhaled steroids) – assessed as ICS doses (μg) at 3 years



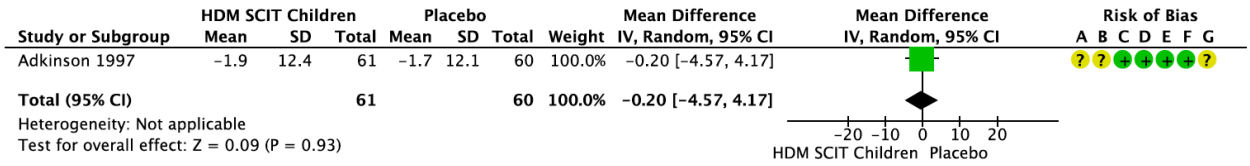
1.1.1.4. Steroid sparing effect (inhaled steroids) – assessed as no. of days using inhaled corticosteroids in previous 60 days



1.1.1.5. Steroid sparing effect (inhaled steroids) – assessed as ICS doses by proportional odds model



1.1.1.6. Steroid sparing effect (oral steroids) – assessed as no. of days using oral corticosteroids in previous 60 days

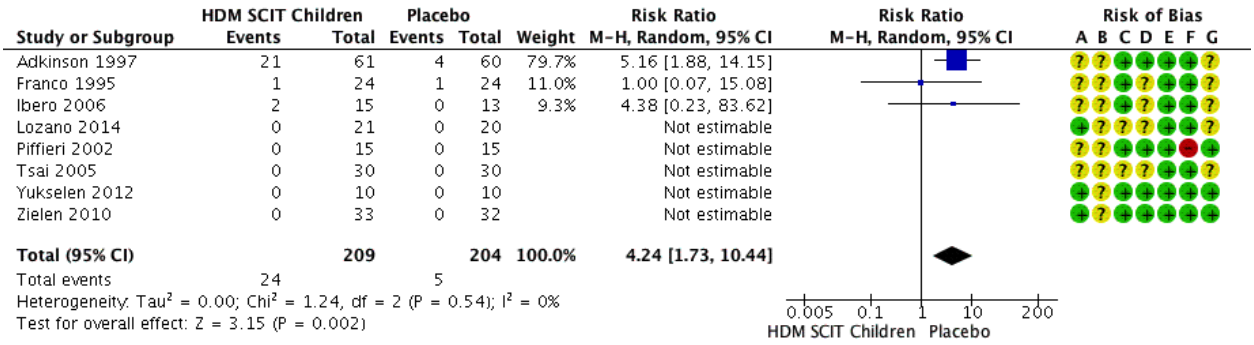


Study or Subgroup	HDM SCIT Children Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Adkinson 1997	-1.9	12.4	61	-1.7	12.1	60	100.0%	-0.20 [-4.57, 4.17]
Total (95% CI)			**61**			**60**	**100.0%**	**-0.20 [-4.57, 4.17]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.09 (P = 0.93)

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

1.1.1.7. Safety (systemic reactions) – assessed as number of patients with at least one reaction



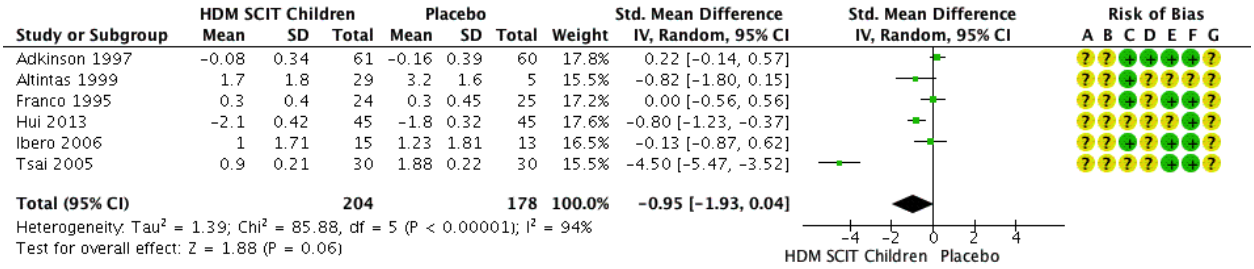
Study or Subgroup	HDM SCIT Children Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Adkinson 1997	21	61	4	60	79.7%	5.16 [1.88, 14.15]
Franco 1995	1	24	1	24	11.0%	1.00 [0.07, 15.08]
Ibero 2006	2	15	0	13	9.3%	4.38 [0.23, 83.62]
Lozano 2014	0	21	0	20		Not estimable
Piffieri 2002	0	15	0	15		Not estimable
Tsai 2005	0	30	0	30		Not estimable
Yukselen 2012	0	10	0	10		Not estimable
Zielen 2010	0	33	0	32		Not estimable
Total (95% CI)		**209**		**204**	**100.0%**	**4.24 [1.73, 10.44]**
Total events	24		5			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.24$, df = 2 (P = 0.54); $I^2 = 0\%$
Test for overall effect: Z = 3.15 (P = 0.002)

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

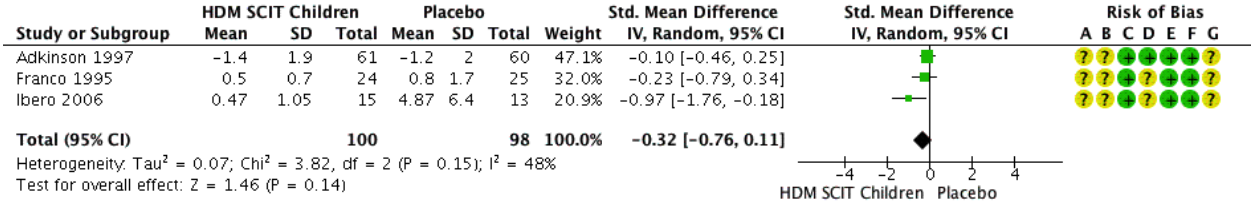
1.1.2. Important but no critical outcomes

1.1.2.1. Symptom score



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

1.1.2.2. Medication score



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

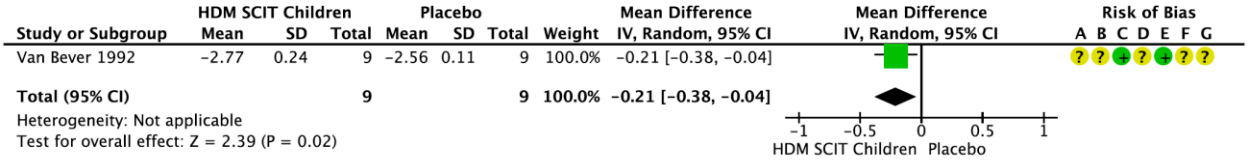
1.1.2.3. Quality of Life

We found no evidence.

1.1.2.4. Lung function: Small airways assessed as percentage or absolute improvement of MEF 25, MEF 50, MEF 75

We found no evidence

1.1.2.5. Lung function: Allergen specific bronchial provocation (ASBP) – assessed as PD20 FEV1 to allergen challenge

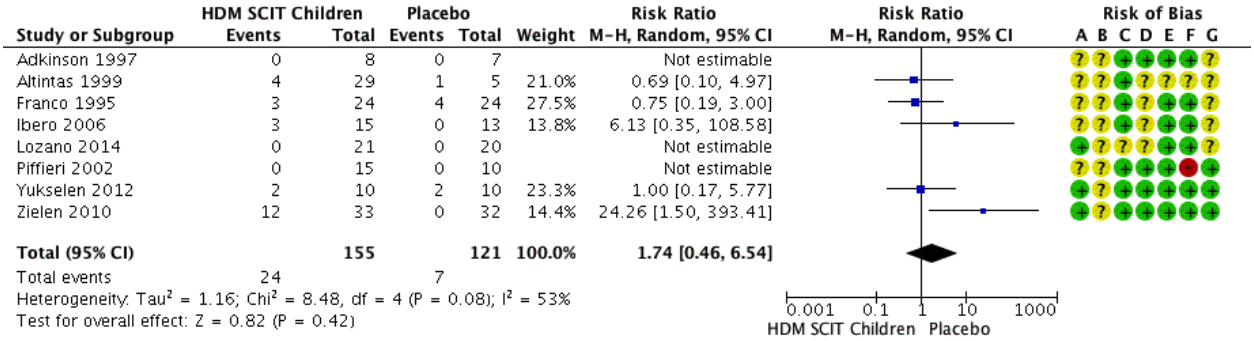


Study or Subgroup	HDM SCIT Children Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Van Bever 1992	-2.77	0.24	9	-2.56	0.11	9	100.0%	-0.21 [-0.38, -0.04]
Total (95% CI)			**9**			**9**	**100.0%**	**-0.21 [-0.38, -0.04]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.39 (P = 0.02)

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

1.1.1.1. Safety (local reactions)



Study or Subgroup	HDM SCIT Children Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Adkinson 1997	0	8	0	7		Not estimable
Altintas 1999	4	29	1	5	21.0%	0.69 [0.10, 4.97]
Franco 1995	3	24	4	24	27.5%	0.75 [0.19, 3.00]
Ibero 2006	3	15	0	13	13.8%	6.13 [0.35, 108.58]
Lozano 2014	0	21	0	20		Not estimable
Piffieri 2002	0	15	0	10		Not estimable
Yukselen 2012	2	10	2	10	23.3%	1.00 [0.17, 5.77]
Zielen 2010	12	33	0	32	14.4%	24.26 [1.50, 393.41]
Total (95% CI)		**155**		**121**	**100.0%**	**1.74 [0.46, 6.54]**
Total events	24		7			

Heterogeneity: $Tau^2 = 1.16$; $Chi^2 = 8.48$, df = 4 (P = 0.08); $I^2 = 53\%$
Test for overall effect: Z = 0.82 (P = 0.42)

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

1.2. EVIDENCE PROFILE

Author(s): Juan J. Yepes-Nuñez
Date: October 2018
Question: HDM SCIT compared to no HDM SCIT for treatment in paediatric patients with asthma
Setting: Outpatients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HDM SCIT	no HDM SCIT	Relative (95% CI)	Absolute (95% CI)		
Asthma exacerbations assessed as number of patients required a course of oral prednisolone (follow up: 2 years)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	2/33 (6.1%)	1/32 (3.1%)	**RR 1.94** (0.18 to 20.35)	**29 more per 1,000** (from 26 fewer to 605 more)	⨁⨁◯◯ LOW	CRITICAL
Asthma control assessed as score of daytime asthma symptoms [symptom score: 0 (none)–5 (severe)] (follow up: 2 years)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	33	32	-	MD **0.6 SD lower** (6.03 lower to 4.83 higher)	⨁⨁◯◯ LOW	CRITICAL
Corticosteroid use (inhaled steroids) assessed as ICS doses (ug) (follow up: 3 years)												
1	randomised trials	serious [c]	not serious	not serious [d]	serious [e]	none	45	45	-	MD **30 lower** (51.16 lower to 8.84 lower)	⨁⨁◯◯ LOW	CRITICAL
Corticosteroid use (inhaled steroids) assessed as number of days on which inhaled corticosteroid was used in previous 60 days (follow up: 2.5 years)												
1	randomised trials	not serious [f]	not serious	not serious	very serious [b]	none	61	60	-	MD **4.7 lower** (13.96 lower to 4.56 higher)	⨁⨁◯◯ LOW	CRITICAL
Corticosteroid use (inhaled steroids) assessed as ICS doses by proportional odds model (follow up: 2 years)												
1	randomised trials	not serious	not serious	not serious	very serious [e]	none	-/33	-/32	**2.51** (1.02 to 6.17)	**-- per 1,000** (from -- to --)	⨁⨁◯◯ LOW	CRITICAL
Corticosteroid use (oral steroids) assessed as number of days on which oral corticosteroid was used in previous 60 days (follow up: 2.5 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HDM SCIT	no HDM SCIT	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious [f]	not serious	not serious	very serious [a]	none	61	60	-	MD **0.2 lower** (4.57 lower to 4.17 higher)	⨁⨁◯◯ LOW	CRITICAL
Systemic adverse events assessed as number of patients with at least one reaction (follow up: from 4 months to 3 years)												
9	randomised trials	not serious [g]	not serious	not serious [h]	serious [e]	none	24/217 (11.1%)	5/211 (2.4%)	**RR 4.24** (1.73 to 10.44)	**77 more per 1,000** (from 17 more to 224 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Symptom scores (follow up: from 4 months to 3 years)												
6	randomised trials	not serious [f]	serious [i]	not serious [h]	very serious [a]	none	204	178	-	SMD **0.95 lower** (1.93 lower to 0.04 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Medication scores (follow up: from 4 months to 2.5 years)												
3	randomised trials	not serious [f]	not serious	not serious [h]	very serious [a]	none	100	98	-	SMD **0.32 lower** (0.76 lower to 0.11 higher)	⨁⨁◯◯ LOW	IMPORTANT
Asthma QoL - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Lung function: Small airways assessed as percentage or absolute improvement of MEF 25, MEF 50, MEF 75 - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Lung function: Allergen specific bronchial provocation tests (ABPT) assessed as PD20 FEV1 to allergen challenge (follow up: 1 year)												
1	randomised trials	not serious [j]	not serious	not serious	very serious [e]	none	9	9	-	MD **0.21 lower** (0.38 lower to 0.04 lower)	⨁⨁◯◯ LOW	IMPORTANT
Local adverse events (follow up: from 4 months to 3 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HDM SCIT	no HDM SCIT	Relative (95% CI)	Absolute (95% CI)		
8	randomised trials	not serious [k]	not serious	not serious [h]	very serious [l]	none	24/155 (15.5%)	7/121 (5.8%)	**RR 1.74** (0.46 to 6.54)	**43 more per 1,000** (from 31 fewer to 320 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **SMD:** Standardised mean difference

Explanations

a. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 3 events in total; and no optimal information size criterion met.
b. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, and no optimal information size criterion met.
c. Serious risk of bias. We could not obtain information for allocation concealment, blinding participants and outcome assessment as well as incomplete outcome data. Thus, we are not confident that the treatment effect was certain.
d. The study used a surrogate outcome to assess HDM SCIT efficacy
e. Very serious imprecision due to no optimal information size criterion met.
f. Allocation concealment and random sequence generation were unclear in all studies included.
g. Allocation concealment was unclear in all studies reported systemic reactions.
h. Patients across studies received different HDM SCIT extracts. Allergen extracts are different between each AIT company and batch.
i. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.0001; I-square 94%).
j. Random sequence generation, allocation concealment, blinding of outcome assessment, selective reporting and other bias were unclear in all studies included.
k. Allocation concealment was unclear in all studies reported local reactions.
l. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 31 events in total. No optimal information size criterion met.

References

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1.3. SOF TABLE

Summary of findings:

HDM SCIT compared to no HDM SCIT for treatment in paediatric patients with asthma

Patient or population: paediatric patients with asthma
Setting: Outpatients
Intervention: HDM SCIT
Comparison: no HDM SCIT

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no HDM SCIT	**Risk with HDM SCIT**				
Asthma exacerbations assessed as number of patients required a course of oral prednisolone (follow up: 2 years)	31 per 1,000	**61 per 1,000** (6 to 636)	**RR 1.94** (0.18 to 20.35)	65 (1 RCT)	⨁⨁◯◯ LOW [a]	
Asthma control assessed as score of daytime asthma symptoms [symptom score: 0 (none)–5 (severe)] (follow up: 2 years)	The mean asthma control assessed as score of daytime asthma symptoms [symptom score: 0 (none)–5 (severe)] (follow up: 2 years) was **0** SD	The mean asthma control assessed as score of daytime asthma symptoms [symptom score: 0 (none)–5 (severe)] (follow up: 2 years) in the intervention group was 0.6 SD lower (6.03 lower to 4.83 higher)	-	65 (1 RCT)	⨁⨁◯◯ LOW [b]	
Corticosteroid use (inhaled steroids) assessed as ICS doses (ug) (follow up: 3 years)	The mean corticosteroid use (inhaled steroids) assessed as ICS doses (ug) (follow up: 3 years) was **0**	The mean corticosteroid use (inhaled steroids) assessed as ICS doses (ug) (follow up: 3 years) in the intervention group was 30 lower (51.16 lower to 8.84 lower)	-	90 (1 RCT)	⨁⨁◯◯ LOW [c,d,e]	

Summary of findings:

HDM SCIT compared to no HDM SCIT for treatment in paediatric patients with asthma

Patient or population: paediatric patients with asthma
Setting: Outpatients
Intervention: HDM SCIT
Comparison: no HDM SCIT

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no HDM SCIT	**Risk with HDM SCIT**				
Corticosteroid use (inhaled steroids) assessed as number of days on which inhaled corticosteroid was used in previous 60 days (follow up: 2.5 years)	The mean corticosteroid use (inhaled steroids) assessed as number of days on which inhaled corticosteroid was used in previous 60 days (follow up: 2.5 years) was **0**	The mean corticosteroid use (inhaled steroids) assessed as number of days on which inhaled corticosteroid was used in previous 60 days (follow up: 2.5 years) in the intervention group was 4.7 lower (13.96 lower to 4.56 higher)	-	121 (1 RCT)	⨁⨁◯◯ LOW [b,f]	
Corticosteroid use (inhaled steroids) assessed as ICS doses by proportional odds model (follow up: 2 years)	0 per 1,000	**0 per 1,000** (0 to 0)	**2.51** (1.02 to 6.17)	65 (1 RCT)	⨁⨁◯◯ LOW [e]	
Corticosteroid use (oral steroids) assessed as number of days on which oral corticosteroid was used in previous 60 days (follow up: 2.5 years)	The mean corticosteroid use (oral steroids) assessed as number of days on which oral corticosteroid was used in previous 60 days (follow up: 2.5 years) was **0**	The mean corticosteroid use (oral steroids) assessed as number of days on which oral corticosteroid was used in previous 60 days (follow up: 2.5 years) in the intervention group was 0.2 lower (4.57 lower to 4.17 higher)	-	121 (1 RCT)	⨁⨁◯◯ LOW [a,f]	

Summary of findings:

HDM SCIT compared to no HDM SCIT for treatment in paediatric patients with asthma

Patient or population: paediatric patients with asthma
Setting: Outpatients
Intervention: HDM SCIT
Comparison: no HDM SCIT

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no HDM SCIT	**Risk with HDM SCIT**				
Systemic adverse events assessed as number of patients with at least one reaction (follow up: from 4 months to 3 years)	24 per 1,000	**100 per 1,000** (41 to 247)	**RR 4.24** (1.73 to 10.44)	428 (9 RCTs)	⨁⨁⨁◯ MODERATE [e,g,h]	
Symptom scores (follow up: from 4 months to 3 years)	-	-	-	382 (6 RCTs)	⨁◯◯◯ VERY LOW [a,f,h,i]	
Medication scores (follow up: from 4 months to 2.5 years)	-	-	-	198 (3 RCTs)	⨁⨁◯◯ LOW [a,f,h]	
Asthma QoL - not reported	-	see_comment	-	-	-	
Lung function: Small airways assessed as percentage or absolute improvement of MEF 25, MEF 50, MEF 75 - not reported	-	-	-	-	-	

Summary of findings:

HDM SCIT compared to no HDM SCIT for treatment in paediatric patients with asthma

Patient or population: paediatric patients with asthma
Setting: Outpatients
Intervention: HDM SCIT
Comparison: no HDM SCIT

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no HDM SCIT	**Risk with HDM SCIT**				
Lung function: Allergen specific bronchial provocation tests (ABPT) assessed as PD20 FEV1 to allergen challenge (follow up: 1 year)	The mean lung function: Allergen specific bronchial provocation tests (ABPT) assessed as PD20 FEV1 to allergen challenge (follow up: 1 year) was **0**	The mean lung function: Allergen specific bronchial provocation tests (ABPT) assessed as PD20 FEV1 to allergen challenge (follow up: 1 year) in the intervention group was 0.21 lower (0.38 lower to 0.04 lower)	-	18 (1 RCT)	⨁⨁◯◯ LOW [e,j]	
Local adverse events (follow up: from 4 months to 3 years)	58 per 1,000	**101 per 1,000** (27 to 378)	**RR 1.74** (0.46 to 6.54)	276 (8 RCTs)	⨁⨁◯◯ LOW [h,k,l]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **SMD:** Standardised mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 3 events in total; and no optimal information size criterion met.
b. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, and no optimal information size criterion met.
c. Serious risk of bias. We could not obtain information for allocation concealment, blinding participants and outcome assessment as well as incomplete outcome data. Thus, we are not confident that the treatment effect was certain.
d. The study used a surrogate outcome to assess HDM SCIT efficacy
e. Very serious imprecision due to no optimal information size criterion met.

f. Allocation concealment and random sequence generation were unclear in all studies included.
g. Allocation concealment was unclear in all studies reported systemic reactions.
h. Patients across studies received different HDM SCIT extracts. Allergen extracts are different between each AIT company and batch.
i. Serious inconsistency. Unexplained inconsistency, with point estimates widely different and confidence intervals not overlapping (P-value chi-square <0.0001; I-square 94%).
j. Random sequence generation, allocation concealment, blinding of outcome assessment, selective reporting and other bias were unclear in all studies included.
k. Allocation concealment was unclear in all studies reported local reactions.
l. Very serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference, including only 31 events in total. No optimal information size criterion met.