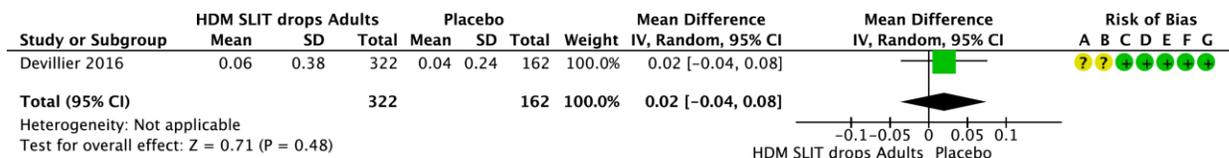


1. Should HDM SLIT drops versus no SLIT drops be used for treatment in **adult** patients with asthma?

1.1. FOREST PLOTS

1.1.1. Critical outcomes

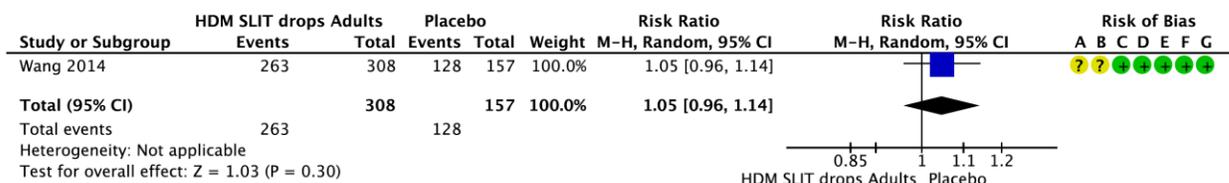
1.1.1.1. Asthma exacerbations – assessed as number of asthma exacerbations standardized over a year



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

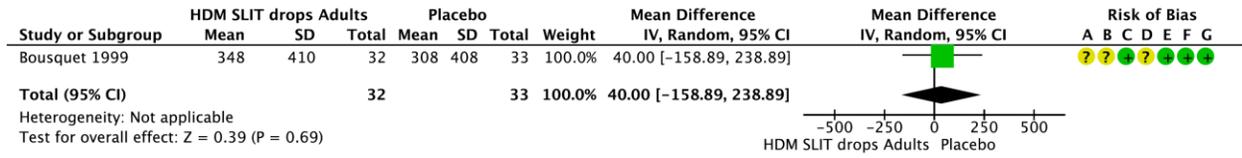
1.1.1.2. Asthma control – assessed as proportion of patients with well controlled asthma (defined by GINA)



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

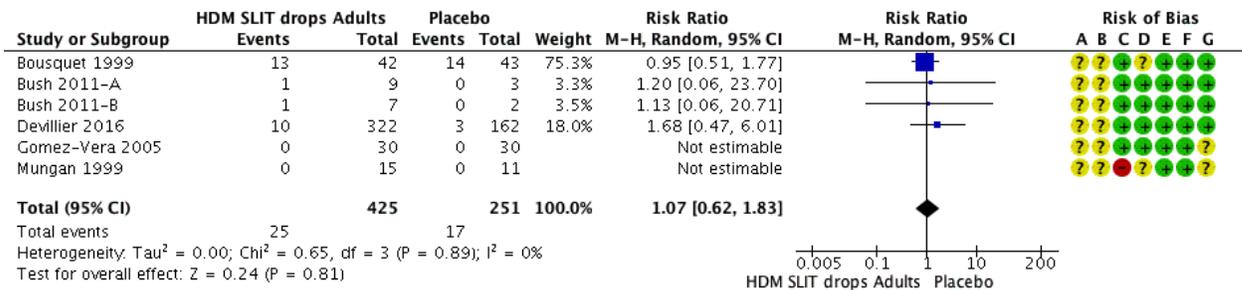
1.1.1.3. Steroid sparing effect (inhaled steroids) – assessed as micrograms of beclomethasone per day



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

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

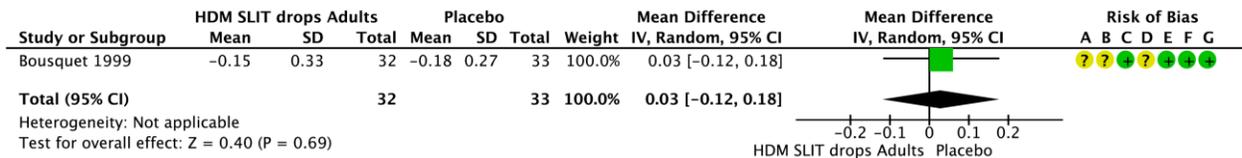


Risk of bias legend

- (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

We found no evidence

1.1.2.3. Quality of Life

We found no evidence

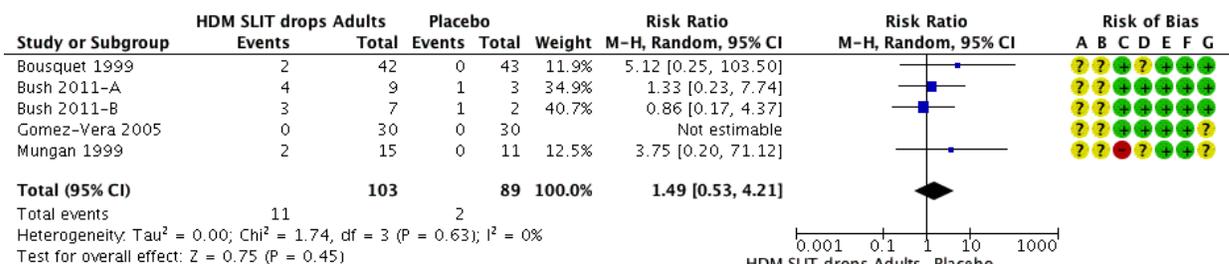
1.1.2.4. Lung function: Small airways assessed as percentage or absolute improvement of MEF 25, MEF 50, MEF 75

We found no evidence

1.1.2.5. Lung function: Allergen specific bronchial provocation (ASBP)

We found no evidence

1.1.2.6. Safety (local reactions)



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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HDM SLIT drops	no HDM SLIT drops	Relative (95% CI)	Absolute (95% CI)		
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) - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Local adverse events (follow up: 6 months to 2 years)												
4	randomised trials	not serious ^a	not serious	not serious	very serious ^a	none	11/103 (10.7%)	2/89 (2.2%)	RR 1.49 (0.53 to 4.21)	11 more per 1,000 (from 11 fewer to 72 more)	 LOW	IMPORTANT

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

Explanations

- 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 met.
- Serious indirectness. The study used a surrogate outcome to assess HDM SLIT efficacy.
- Patients across studies received different HDM SLIT extracts. Allergen extracts are different between each AIT company and batch.
- Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference.
- One out of four studies rated as high risk of bias due to lack of reporting blinding of participants and personnel

References

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1.3. SOF TABLE

Summary of findings:

HDM SLIT drops compared to no HDM SLIT drops for treatment in adult patients with asthma

Patient or population: adult patients with asthma

Setting: Outpatients

Intervention: HDM SLIT drops

Comparison: no HDM SLIT drops

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no HDM SLIT drops	Risk with HDM SLIT drops				
Asthma exacerbations - assessed as number of asthma exacerbations standardized (follow up: 1 year)	The mean asthma exacerbations - assessed as number of asthma exacerbations standardized (follow up: 1 year) was 0	The mean asthma exacerbations - assessed as number of asthma exacerbations standardized (follow up: 1 year) in the intervention group was 0.02 higher (0.04 lower to 0.08 higher)	-	484 (1 RCT)	⊕⊕○○ LOW ^a	
Asthma control - assessed as proportion of patients with well controlled asthma (defined by GINA) (follow up: 1 year)	815 per 1,000	856 per 1,000 (783 to 929)	RR 1.05 (0.96 to 1.14)	465 (1 RCT)	⊕⊕○○ LOW ^a	
Corticosteroid use (inhaled steroids) - assessed as micrograms of beclomethasone per day (follow up: 2 years)	The mean corticosteroid use (inhaled steroids) - assessed as micrograms of beclomethasone per day (follow up: 2 years) was 0	The mean corticosteroid use (inhaled steroids) - assessed as micrograms of beclomethasone per day (follow up: 2 years) in the intervention group was 40 higher (158.89 lower to 238.89 higher)	-	65 (1 RCT)	⊕○○○ VERY LOW ^{a,b}	

Summary of findings:

HDM SLIT drops compared to no HDM SLIT drops for treatment in adult patients with asthma

Patient or population: adult patients with asthma

Setting: Outpatients

Intervention: HDM SLIT drops

Comparison: no HDM SLIT drops

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no HDM SLIT drops	Risk with HDM SLIT drops				
Systemic adverse events - number of patients with at least one reaction (follow up: from 6 months to 2 years)	68 per 1,000	72 per 1,000 (42 to 124)	RR 1.07 (0.62 to 1.83)	676 (5 RCTs)	⊕⊕⊕○ MODERATE ^{c,d}	
Symptom scores (follow up: 2 years)	The mean symptom scores (follow up: 2 years) was 0	The mean symptom scores (follow up: 2 years) in the intervention group was 0.03 higher (0.12 lower to 0.18 higher)	-	65 (1 RCT)	⊕⊕○○ LOW ^a	
Medication scores - not reported	-	see_comment	-	-	-	
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	-	see_comment	-	-	-	
Lung function: Allergen specific bronchial provocation tests (ABPT) - not reported	-	see_comment	-	-	-	
Local adverse events (follow up: from 6 months to 2 years)	22 per 1,000	33 per 1,000 (12 to 95)	RR 1.49 (0.53 to 4.21)	192 (4 RCTs)	⊕⊕○○ LOW ^{a,e}	

Summary of findings:

HDM SLIT drops compared to no HDM SLIT drops for treatment in adult patients with asthma

Patient or population: adult patients with asthma

Setting: Outpatients

Intervention: HDM SLIT drops

Comparison: no HDM SLIT drops

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no HDM SLIT drops	Risk with HDM SLIT drops				

*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; MD: Mean difference; RR: Risk ratio; 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

- 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 met.
- Serious indirectness. The study used a surrogate outcome to assess HDM SLIT efficacy.
- Patients across studies received different HDM SLIT extracts. Allergen extracts are different between each AIT company and batch.
- Serious imprecision. 95% CI is consistent with the possibility for important benefit and large harm exceeding a minimal important difference.
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