

## Original Article

# Extrafine HFA-beclomethasone dipropionate versus budesonide for asthma: a meta-analysis

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**Abstract:** The small-particle inhaled corticosteroid might be a new available way to treat uncontrolled asthma. To evaluate the efficacy and safety of extrafine hydrofluoroalkane-beclomethasone dipropionate (HFA-BDP) versus budesonide (BUD) in patients with asthma, a meta-analysis was performed. A systematic search was made of PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Clinicaltrials.gov and Ovid, and a hand search of leading respiratory journals. Randomised controlled trials (RCTs) on treatment of asthma for 4 or more weeks with extrafine HFA-BDP, compared with BUD, were reviewed. Five studies involving 949 asthmatic patients met the inclusion criteria. There was no significant difference in FEV<sub>1</sub> (SMD=-0.03L, 95% CI -0.15 to 0.10L, I<sup>2</sup>=0%, P=0.70), morning PEF (WMD=0.88 L/min, 95% CI -5.96 to 7.72 L/min, I<sup>2</sup>=0%, P=0.80), evening PEF (WMD=6.32 L/min, 95% CI -1.17 to 13.81 L/min, I<sup>2</sup>=33%, P=0.10) and use of rescue medication (WMD=-0.13, 95% CI -0.31 to 0.06, I<sup>2</sup>=41%, P=0.18) between extrafine HFA-BDP at half of the daily dose and BUD group. Individual studies reported no significant differences in asthma exacerbations and 7-point Asthma Control Questionnaire score (ACQ-7). There were no significant difference in total number of adverse events (OR=1.04, 95% CI 0.78 to 1.38, I<sup>2</sup>=0%, P=0.81) between the two groups. Our meta-analysis demonstrated that extrafine HFA-BDP at half of daily dose is equivalent to BUD in improving lung function and use of rescue medication, without increasing adverse events in patients with asthma. Long-term trials are required to assess the efficacy and safety of extrafine HFA-BDP.

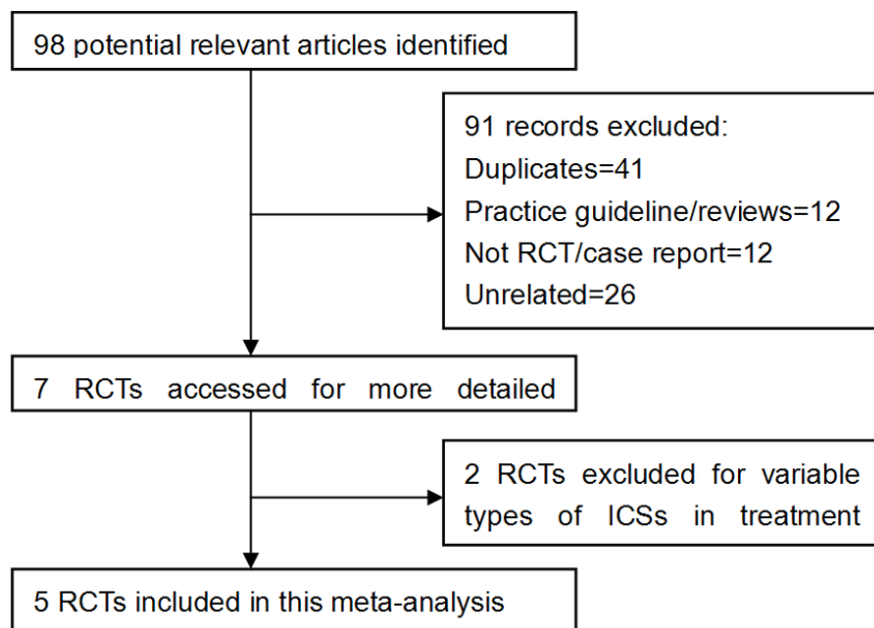
**Keywords:** Asthma, extrafine, beclomethasone, budesonide, meta-analysis

## Introduction

Asthma is a common chronic respiratory disease characterized by airway obstruction and inflammation [1]. Inhaled corticosteroids (ICSs) are recommended by various guidelines as first-line treatment for asthma for their broad anti-inflammatory effects [2, 3]. However, a great proportion of patients with asthma are suffering recurring symptoms and exacerbations, even after administration of high doses of ICSs combined with long-acting  $\beta_2$  agonists (LABAs), antileukotrienes, theophyllines, anti-IgE and immunosuppressants [4, 5]. Furthermore, high-dose ICSs has been associated with a variety of systemic and upper airway side effects [6, 7]. In recent years, increasing evidence shows that the airway inflammation occurs throughout the entire respiratory tract,

including the large, intermediate, and small airways [8]. The small airways (<2 mm) contribute significantly to the clinical expression and severity of asthma [9]. Current devices generate drug aerosols in particles <5  $\mu\text{m}$  and it is shown that particles of 4-5  $\mu\text{m}$  deposit primarily in the large airways [10]. Unfortunately, the conventional ICSs were unable to reach the small airways due to their large particle sizes [11]. The small-particle ICS might be a new available way to treat uncontrolled asthma.

In 1987, the Montreal Protocol required the eventual banning of all chlorofluorocarbons (CFC), including those used in metered-dose inhalers (MDIs) [12]. The traditional MDIs had to be reformulated with the new hydrofluoroalkane-134a (HFA) propellants. This new technology presented the opportunity to produce



**Figure 1.** Flow chart showing strategy for identification of relevant studies.

small-particle ICSs. By now, three such ICSs, beclomethasone dipropionate (BDP), ciclesonide (CIC) and flunisolide have been developed to treat asthma [13]. Among them, HFA-BDP is the only available small-particle ICS in China. Compared with larger particles, extrafine HFA-BDP with a mass median aerodynamic diameters (MMAD) of 1~2  $\mu\text{m}$  have a lower oropharyngeal deposition (20-30% vs >80%) and a higher lung deposition (50-60% vs 10-20%) [12, 14]. It will be very important to establish relative benefits and risks between extrafine HFA-BDP and conventional ICSs. Previous studies demonstrated that extrafine HFA-BDP achieved equivalent asthma control at half of the daily dose, when compared with the CFC-BDP [15-17]. Fluticasone (FP), which is a more potent corticosteroid than BDP, was considered equally effective as extrafine HFA-BDP at the same doses [18]. Budesonide (BUD) is recommended as first-line treatment of asthma by many international guidelines [2, 3]. However, little has been known about its relative efficacy and risk when compared with extrafine HFA-BDP. Recently, an real-world study showed that a new fixed combination of beclomethasone and formoterol in hydrofluoroalkane Modulite pressurised metered-dose inhaler achieved better asthma control and quality of life compared to budesonide/formoterol [19].

The aim of the present meta-analysis was to evaluate the efficacy and safety of extrafine HFA-BDP versus BUD in patients with asthma.

### Materials and methods

#### Data sources

We searched PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Clinicaltrials.gov and Ovid for relevant trials published from January 1980 to October 2014. The structured search strategies used the following search terms: (“beclomethasone OR beclometasone OR BDP”) AND (“budesonide OR BUD”) AND (“extrafine or ultrafine or small particle or small molecule or HFA or hydrofluoroalkane”) AND (“asthma”). These searches were supplemented by hand searching of leading respiratory journals and conference abstracts.

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#### Study selection

Studies included in the meta-analysis met the following criteria: (1) RCTs comparing extrafine HFA-BDP with BUD (administered via dry powder inhaler or MDI with or without spacers) in patients with asthma; (2) more than 12 years of age; (3) duration of at least 4 weeks; (4) a diagnosis of asthma without other lung diseases; (5) human studies; and (6) English language.

#### Quality and risk of bias assessment

The methodological quality of each study was assessed by the Jadad Scale (5 points), which scores trials according to randomization, double blinding, and withdrawals [20]. The studies were considered of high quality with a Jadad score  $\geq 3$  points.

The risk of bias was assessed according to guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

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**Table 1.** Characteristics of participants of included studies

Study/year/region	Participants, n/male, %	Age, year, mean ± SD	Treatment duration	Inclusion criteria	Exclusion criteria
Papi et al. [23]/2007/Europe	219/42.1%	43.4±12.3 VS 46.0±11.1	12 wk	18-65 years; moderate to severe persistent asthma; FEV <sub>1</sub> 50-80% of predicted normal values; had asthma symptoms not adequately controlled at a daily dose ≤1000 µg of BDP-equivalent	COPD or smokers; severe exacerbation or RTI ≤8 weeks; three or more courses of oral corticosteroids or hospitalisation due to asthma ≤6 months; treatment with LABAs, anticholinergics or antihistamines ≤2 weeks, and/or with topical or intra-nasal corticosteroids or leukotriene antagonists or change of ICS dose ≤4 weeks
Hauber et al. [24]/2006/Canada	17/41.2%	36.8±2.9 VS 34.9±2.9	4 wk	mildly asthmatic patients who were only using SABA	Patients with respiratory infection in the previous three months
Molimard et al. [25]/2005/France	311/50.2%	42.4±14.1 VS 42.9±13.8	12 wk	18-60 years; moderate to severe asthma; not controlled on BDP ≤1000 µg/d; nocturnal discomfort during previous 5 days or asthma requiring 2 puffs/d beta-agonist in last 7 days	COPD; upper or lower RTI ≤4 weeks; exacerbation of asthma leading to hospitalisation or systemic steroids treatment in 4 weeks prior to inclusion
Worth et al. [26]/2001/Europe	209/44.5%	49.2±14.3 VS 47.8±13.8	8 wk	18-75 years; moderate to severe asthma (PEF 50-80%); inhaled corticosteroid at an equivalent dosage to BUD 500-1000 µg/d and a SABA on an "as needed" basis in the previous 4 weeks	Significant diseases other than asthma; acute upper or lower RTI ≤2 weeks; systemic steroids treatment ≤8 weeks; current use of nasal steroid ≥400 µg BDP or equivalent, or varying doses of nasal steroid
Reichel et al. [27]/2001/Europe	193/52.3%	46.2±14.0 VS 46.4±13.5	6 wk	18-75 years; had asthma for at least four weeks before study (PEF 50-90%); not controlled on BUD 400 µg/d and "as required" SABA therapy	Significant respiratory diseases other than asthma or oral candidiasis; RTI ≤2 weeks; systemic steroids treatment ≤4 weeks; alcohol or substance abuse ≤2 years; current use of nasal steroid ≥400 µg BDP or equivalent

SABA, short acting β agonist; COPD, chronic obstructive pulmonary disease; RTI, respiratory tract infection; LABA, long acting β agonist.

**Table 2.** Studies included in the present analysis

Study/year/region	Study design	End Point	Treatment Groups; inhaler	Control groups; inhaler	Jadad Score
Papi et al. [23]/2007/Europe	Multicenter, double-bind parallel group RCT	Lung function; symptoms; exacerbations; safety and tolerability	HFA-BDP 400 µg/d, formoterol 24 µg/d; MDI	Budesonide 800 µg/d, formoterol 24 µg/d; DPI	4
Hauber et al. [24]/2006/Canada	Double-bind, crossover group RCT	Lung function; Inflammatory cell changes; Changes of inflammatory gene expression	HFA-BDP 400 µg/d; MDI	Budesonide 800 µg/d; DPI	3
Molimard et al. [25]/2005/France	Multicenter, open-label, parallel group RCT	FEV <sub>1</sub> ; ACQ; rescue medication usage; adverse events	HFA-BDP 800 µg/d; MDI	Budesonide 1600 µg/d; DPI	2
Worth et al. [26]/2001/Europe	Multicenter, open-label, parallel group RCT	Lung function; symptoms; rescue medication usage; Eosinophil Count and Serum ECP Levels; safety and tolerability	HFA-BDP 800 µg/d; MDI	Budesonide 1600 µg/d; DPI	2
Reichel et al. [27]/2001/Europe	Multicenter, open-label, parallel group RCT	Lung function; symptoms; rescue medication usage; safety and tolerability	HFA-BDP 400 µg/d; MDI	Budesonide 800 µg/d; DPI	2

	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
Hauber et al, 2006	?	?	+	+	?	?	+
Molimard et al, 2005	?	+	-	-	+	+	+
Papi et al, 2007	?	?	+	+	+	+	+
Reichel et al, 2001	?	?	-	-	+	+	+
Worth et al, 2001	?	?	-	-	+	+	+

+ High risk    ? Unclear    - High risk

Figure 2. Summary of the risk of bias in the included studies.

Randomization sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias for included RCTs were assessed. Each potential source of bias was graded low, high or unclear risk. Potential publication bias was evaluated by visual examination of funnel plot.

Data extraction

Data extraction was based on reported statistics (means, SD and SE) for the intention to

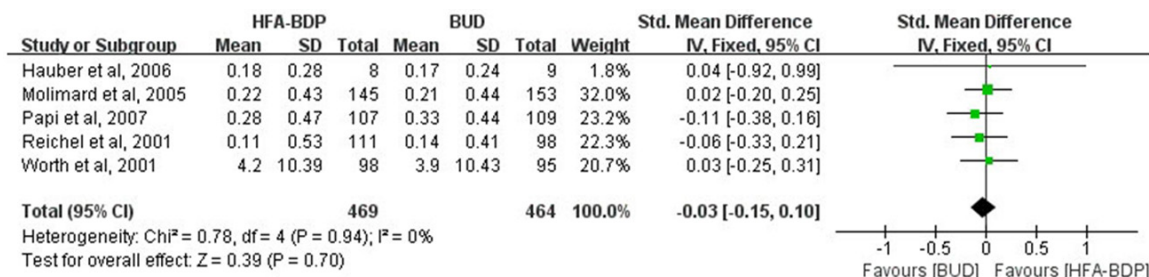
treat population. Two authors (Xin Chen and Yingbo Kang) independently extracted data from the selected studies. If disagreement arose, all the authors conferred till a consensus was arrived at. Authors of a publication were contacted if only its abstract was available or data were missing. Primary outcomes were changes from baseline in forced expiratory volume in 1 second (FEV<sub>1</sub>), morning and evening peak expiratory flow (PEF). Secondary outcomes included rescue bronchodilator use, acute exacerbations, symptoms, 7-point Asthma Control Questionnaire (ACQ-7) score and adverse events.

Statistical analysis

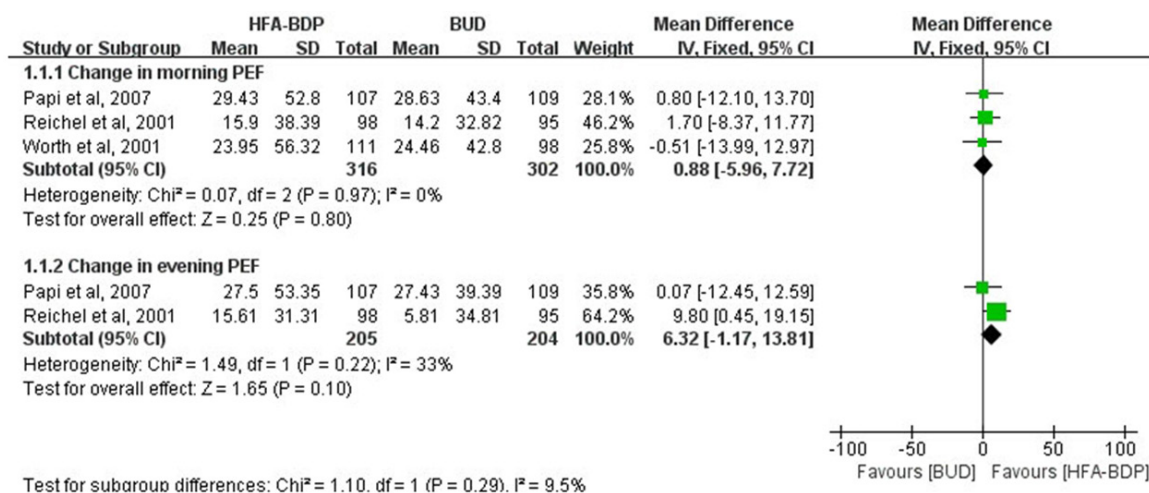
All statistical analyses were conducted by using Review Manager 5.2 (The Cochrane Collaboration, Software Update, Oxford, UK). For dichotomous outcomes, we combined data as odd ratios (OR) with 95% confidence interval (CI). For continuous outcomes, we combined data as weighted mean

difference (WMD) if outcome data were reported on the same scale or standardized mean difference (SMD) for different scales with 95% CIs. Heterogeneity across RCTs was tested by using the Chi-square-based Q-statistic test and I<sup>2</sup> test, with p-value ≤0.10 indicating significant heterogeneity and thresholds of I<sup>2</sup> value for low (0%~49%), moderate (50%~74%) and high (>75%) degree of heterogeneity. Data with low heterogeneity (P>0.1, I<sup>2</sup><50%) were processed by fixed effect model. Otherwise random effect models were used.

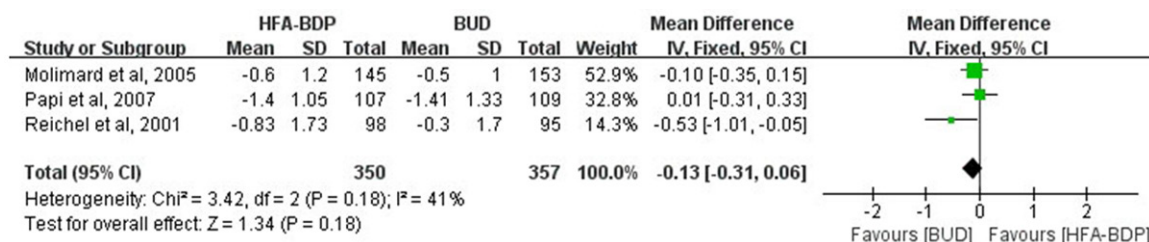
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**Figure 3.** Effects of HFA-BDP versus BUD on  $\text{FEV}_{1,1}$ . HFA-BDP, hydrofluoroalkane-beclomethasone dipropionate; BUD, budesonide;  $\text{FEV}_{1,1}$ , forced expiratory volume in 1 second.



**Figure 4.** Effects of HFA-BDP versus BUD on morning and evening PEF. HFA-BDP, hydrofluoroalkane-beclomethasone dipropionate; BUD, budesonide; PEF, peak inspiratory flow.



**Figure 5.** Effects of HFA-BDP versus BUD on rescue medication use. HFA-BDP, hydrofluoroalkane-beclomethasone dipropionate; BUD, budesonide.

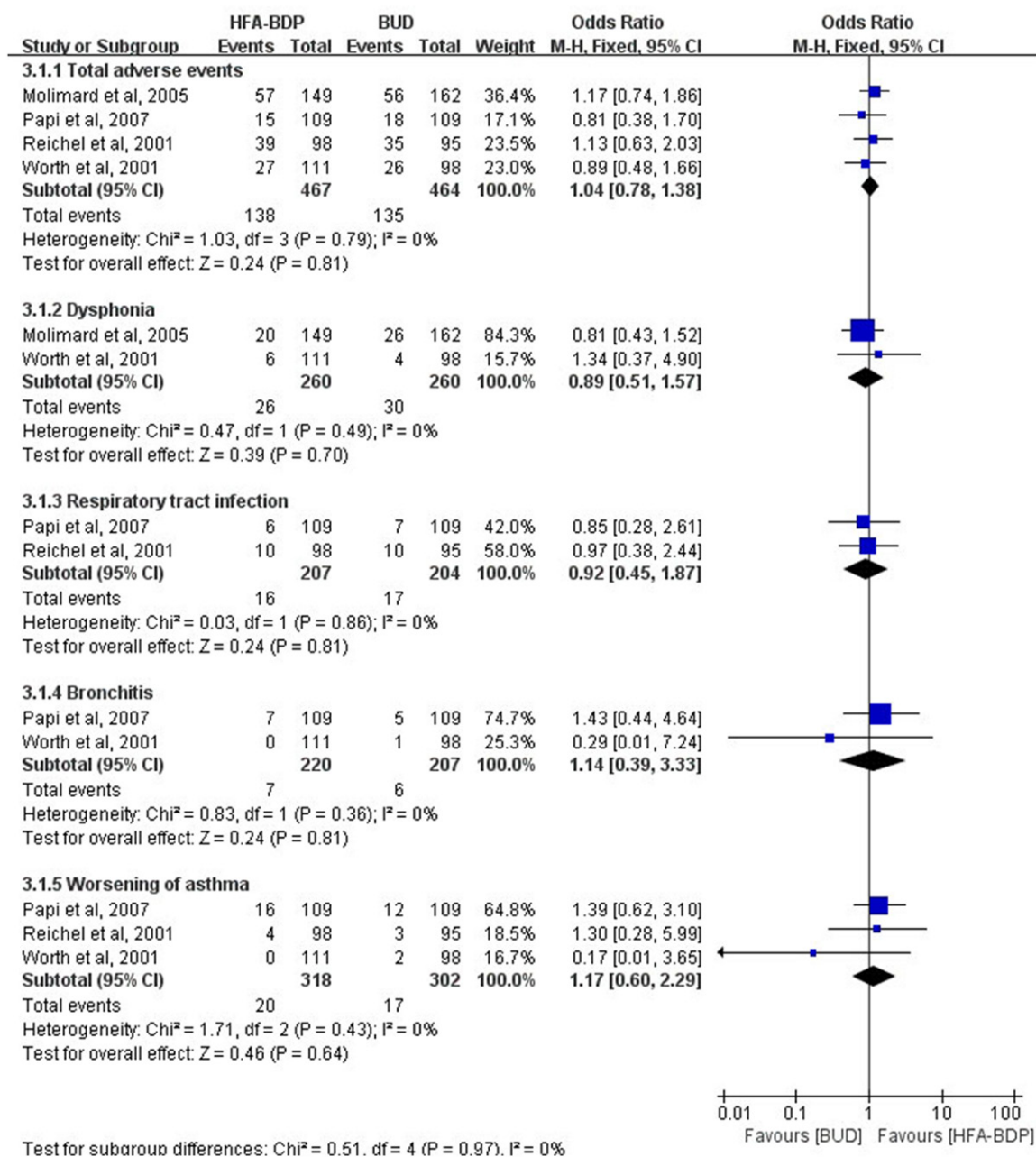
## Results

### Search results

The progress of searching and selecting trials is presented in **Figure 1**. Of the 98 potentially eligible articles that were screened, we excluded 91 that were either not relevant or had duplicate data. Seven full-text articles were reviewed for detail evaluation. Two trials were further excluded because the types of ICSS in treat-

ment groups were variable [21, 22]. Five articles involving 949 participants with asthma, including 5 RCTs (4 parallel RCTs and 1 cross-over RCT) that met our inclusion criteria were selected for the present meta-analysis [23-27]. Characteristics of the trials we included are shown in **Tables 1, 2**. In all included trials, BUD was delivered via dry powder inhaler (DPI), and the relative effects of extrafine HFA-BDP versus BUD were compared at a dose ratio of 1:2.

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**Figure 6.** Effects of HFA-BDP versus BUD on adverse events. HFA-BDP, hydrofluoroalkane-beclomethasone dipropionate; BUD, budesonide.

### Study quality and bias assessment

The methodological quality of all included studies was shown in **Table 2**. A summary of our judgments for risk of bias is given in **Figure 2**. Three studies had a low score of 2 points, and two studies scored 3 and 4 points, respectively. Among 5 studies, two studies used double-blind designs, no study described the randomi-

sation methods, and only one study described allocation concealment. Publication bias was not estimated for limited studies.

### Primary outcomes

**Change in FEV<sub>1</sub>:** All five studies reported FEV<sub>1</sub>. Four studies reported FEV<sub>1</sub> in absolute, and only one reported FEV<sub>1</sub>% pred. The pooled anal-

ysis showed that there was no significant difference in FEV<sub>1</sub> in absolute between HFA-BDP and BUD groups (SMD=-0.03 L, 95% CI -0.15 to 0.10 L, I<sup>2</sup>=0%, P=0.70) (**Figure 3**).

### *Change in morning and evening PEF*

Three included studies took changes in morning PEF values as end points. The results of each study showed no significant difference in morning PEF between patients treated with HFA-BDP and BUD. The overall analysis showed no significant difference between HFA-BDP and BUD groups (WMD=0.88 L/min, 95% CI -5.96 to 7.72 L/min, I<sup>2</sup>=0%, P=0.80) (**Figure 4**). Two studies reported evening PEF. No significant differences were observed in evening PEF between the two groups (WMD=6.32 L/min, 95% CI -1.17 to 13.81 L/min, I<sup>2</sup>=33%, P=0.10) (**Figure 4**).

### *Secondary outcomes*

**Rescue medication usage:** The mean number of puffs of rescue medication during the whole day were reported in four studies. No significant differences in rescue medication usage were noticed between extrafine HFA-BDP and BUD groups (WMD=-0.13, 95% CI -0.31 to 0.06, I<sup>2</sup>=41%, P=0.18) (**Figure 5**).

### *Acute exacerbations*

Only one study by Papi et al reported data about acute exacerbations [23]. The results showed that there were no significant differences in rate of acute exacerbations (17/107 vs 12/109) and the time to the first exacerbation (P=0.342) between the two groups. There were no obvious difference in the numbers of requiring oral steroid therapy between the two groups (2/107 vs 2/109).

### *Symptoms*

Of the trials included, three studies reported the symptoms of asthma. However, there was insufficient data of symptoms to perform the cumulative analysis. One trial by Reichel et al reported no significant difference in the percent of days free from symptoms between the two groups [27]. Another trial by Papi et al reported no significant difference in both daytime (WMD=-0.07, 95% CI -0.29 to 0.15, P=0.53) and nighttime symptom score (WMD=

-0.07, 95% CI -0.28 to 0.14, P=0.52) between the two groups [23]. An RCT by Worth et al showed that the HFA-BDP group had a significantly greater improvements in wheeze (26.48 vs 8.29%, P=0.01), shortness of breath (22.68 vs 11.25%, P=0.02), chest tightness (20.71 vs 6.25%, P<0.01), and daily symptoms (25.36 vs 12.22%, P=0.03) than those of BUD group [26].

### *Asthma control*

Only one study by Molimard et al reported the ACQ score (ACQ-7). Although there was a trend in favor of HFA-BDP, there was no significant difference in the ACQ-7 scales between the two groups (MD=-0.20, 95% CI -0.42 to 0.02, P=0.07) [25].

### *Adverse events*

The incidence of adverse events was evaluated in four included studies. The overall cumulative incidence of adverse events was 29.6% in the HFA-BDP group and 29.1% in the BUD group. The overall analysis showed no significant difference in the total number of adverse events between extrafine HFA-BDP and BUD groups (OR=1.04, 95% CI 0.78 to 1.38, I<sup>2</sup>=0%, P=0.81). No serious adverse events was observed in both the two groups. The subgroup analysis showed that there was no statistical significant difference in dysphonia (OR=0.89, 95% CI 0.51 to 1.57, I<sup>2</sup>=0%, P=0.70), respiratory tract infections (OR=0.92, 95% CI 0.45 to 1.87, I<sup>2</sup>=0%, P=0.81), bronchitis (OR=1.14, 95% CI 0.39 to 3.33, I<sup>2</sup>=0%, P=0.81) and worsening of asthma (OR=1.17, 95% CI 0.60 to 2.29, I<sup>2</sup>=0%, P=0.64) between the two groups (**Figure 6**).

## **Discussion**

To our knowledge, this is the first meta-analysis to evaluate the relative efficacy and safety of extrafine HFA-BDP versus BUD in patients with asthma. This meta-analysis has assembled data from 5 clinical trials recruiting 949 adults largely with moderate to severe asthma. The relative efficacy of extrafine HFA-BDP versus BUD was evaluated by its impact on lung function and other clinical outcomes, including rescue medication use, acute exacerbations, symptoms and asthma control.

Overall the relative efficiency of these two drugs were similar on results where data were avail-

able. Lung function evaluation indicated that no significant difference was shown between groups for the change in FEV<sub>1</sub> and am PEF. Change in pm PEF was similar, but did not exclude the possibility of a meaningful benefit for extrafine HFA-BDP (upper CI limit 13.81 L/min). No significant differences were observed between groups in terms of the use of rescue medications. However, Data on other outcomes that could be pooled were sparse. Exacerbation rate, an important feature of asthma control, was monitored only in Papi et al [23]. because of the short treatment duration of most studies. Though Papi et al concluded that no difference was found in the rate of asthma exacerbations and in time to first exacerbation between groups, equivalence could not conclusively determined by one outcome alone. This meta-analysis shows that extrafine HFA-BDP at half of daily dose is equivalent to BUD in improving lung function and use of rescue medication in patients with asthma.

There was no obvious difference in the total numbers of adverse events between the two groups in this analysis. Oropharyngeal candidiasis, dysphonia, cough and perioral dermatitis were most concerning local adverse events of ICS. These adverse events were reported in a very small part of the included patients, which were of mild to moderate severity according to the statements in the relevant articles. Subgroup analysis did not found any difference either. Previous studies showed that small-particle ICS deposit less amounts in the oropharynx than large-particle ICS, it results in lower incidence of inhalation route disorders such as cough and dysphonia [28]. However, the local oropharyngeal adverse effects in these two groups were equally low, possibly being related to the absence of studies over 3 months in duration. With regard to systemic safety, there is concern that improved pulmonary deposition would increase systemic exposure of HFA-BDP, although administered at lower daily doses. So far, few studies investigated the effect of HFA-BDP versus BUD on growth and hypothalamic pituitary adrenal axis (HPA) function for patients with asthma. In one of these included studies, Worth et al found an obvious decrease of corrected urine cortisol/creatinine (UCC) ratio in BUD group versus HFA-BDP group (-4.88 vs -0.36, P<0.05), it indicated less effect of extrafine HFA-BDP on the HPA axis function

[26]. Further studies are required to answer the questions.

We are very interested in the efficacy of extrafine HFA-BDP versus BUD on small airway function in patients with asthma, because a major advantage of small particle ICSs is that they are able to reach the small airways [13]. So far, there is no golden standard test to assess small airway function [29-31]. Several methods had been reported available to reflect small airway function more accurately than spirometry, such as late-phase sputum, residual volume (RV), peripheral airway resistance, alveolar nitric oxide (NO) concentrations and air trapping et al [32-35]. However, we didn't perform cumulative analysis of small airway function, because the small airway function were not directly measured in most of included studies. Even so, we can still get some information from individual studies. A trial by Hauber et al demonstrated extrafine HFA-BDP, instead of BUD, significantly reduced the percentage of eosinophilic and expression of IL-4 and IL-5 mRNA in late-phase sputum [24]. Another trial by Molimard et al reported that extrafine HFA-BDP (-440 ml) decreased RV more significantly than those of BUD (-90 ml) [25]. The results of such trials indicated that extrafine HFA-BDP has more benefits than BUD in small airways inflammation and air trapping. Further investigations aimed at the effects of extrafine HFA-BDP versus BUD on small airways functions are required.

The main strength of our study was the inclusion of a large pool of patients with mild to severe asthma, allowing us to perform robust analysis of clinically relevant outcomes following the treatment of HFA-BDP versus BUD. The trials included in this analysis used almost identical designs with regard to inclusion criteria. And the clinical characteristics of study populations were quite homogeneous. However, the results should be interpreted with caution because they might have been influenced by other factors. First, only two included studies addressed blinding methods, and few trials addressed the randomisation methods and allocation concealment. It inevitably induce performance bias and detection bias in this meta-analysis. Second, because some of the data currently available are insufficient for a systematic analysis, further investigation into the effects of extrafine HFA-BDP versus BUD on



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exacerbations, symptoms, quality of life and asthma control are required. Third, publication bias was not estimated for limited studies. Fourth, BUD was delivered via DPI in all included trials. The results of this analysis cannot be applied to BUD delivered via other inhalers.

### Conclusion

This meta-analysis suggests that extrafine HFA-BDP at half of equivalent dosage, is non-inferior to BUD in improving lung function, use of rescue medication, and no increase in the number of adverse events. Because of the limitations of this meta-analysis, we suggest that further work should be required to compare extrafine HFA-BDP with that of BUD. Larger, longer, multi-center, well-designed RCTs are expected to validate the efficacy and safety of extrafine HFA-BDP for asthma.

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### Disclosure of conflict of interest

None.

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