National PBM Drug Monograph
Mometasone (Asmanex® Twisthaler® 220mcg)
VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

EXECUTIVE SUMMARY

Mometasone was approved in 2005 making it the sixth orally inhaled corticosteroid approved for prophylactic maintenance therapy of asthma in patients ≥ 12 years of age. Mometasone is available as a dry powder inhaler (DPI) delivered via the Twisthaler® device. Each unit is prefilled to deliver 14 (institutional use), 30, 60 or 120 doses. Each breath-actuated inhalation delivers 200mcg of mometasone.

Mometasone is considered to be a high potency agent with low systemic bioavailability. Mometasone can be doses as 200mcg or 400mcg once daily in the evening or 200mcg bid. The highest recommended dose is 400mcg bid.

There are 10 published randomized clinicals of 8-12 weeks duration comparing mometasone to placebo and or an inhaled steroid comparator in patients with asthma. Among these 10 trials, 8 required that patients must have used daily ICS for at least 30 days prior to screening. Mometasone 200mcg q evening, 200mcg q am (in 1 out of 3 studies), 400mcg daily, 200mcg bid, and 400mcg bid resulted in significantly greater improvement in change in FEV1, the primary outcome measure, compared to placebo. Most secondary outcomes such as change in morning and evening peak flow rate (PEFR), $FEF_{25\%-75\%}$, FVC, symptoms scores, nocturnal awakening, as needed albuterol use, and physician evaluated response to therapy were significantly improved with mometasone compared to placebo.

In general, mometasone 200mcg bid or 400mcg once daily is as effective as fluticasone 250mcg bid. Mometasone 200mcg bid and beclomethasone 168mcg bid are significantly better than placebo; however, numerically, mometasone resulted in greater improvement in FEV1, PEFR, and some symptom scores than beclomethasone (statistical comparison between the 2 agents was not performed). Mometasone 400mcg q am was significantly better than budesonide 400mcg qam for nearly all efficacy parameters (doses probably not equivalent). Mometasone 200-400mcg bid was numerically better than budesonide 400mcg bid for FEV1, physician assessment of improvement, and prn albuterol use (200mcg bid dose only).

There are 2 unpublished randomized double-blind 52-week trials comparing mometasone to placebo in patients with COPD. One study showed that mometasone 800mcg every evening resulted in greater improvement in post-bronchodilator FEV1, symptom scores, and time to exacerbation compared to placebo. The second study showed that mometasone 800mcg q evening or 400mcg bid improved post-bronchodilator, symptom scores (400mcg bid dose only), and reduced the percent of patients having one or more exacerbations.

Mometasone was well tolerated and adverse events were generally mild-moderate in severity. The most commonly reported adverse events were headache, allergic rhinitis, pharyngitis and upper respiratory tract infection. Oral candidiasis occurred more frequently in the groups receiving ICS compared to placebo.

Changes in BMD with mometasone were determined in male and female patients with asthma in two 2-year studies. Compared to placebo, there was a small but statistically significant decrease in lumbar spine BMD with mometasone 200mcg bid. Changes between mometasone 400mcg bid and placebo were not significant. There were no significant changes in total femoral BMD with either dose of mometasone and placebo. Changes in BMD with mometasone versus placebo were determined in patients in the 1-year COPD trial (P00340). At endpoint, changes in lumbar spine BMD were not significant between groups. There was a trend towards greater loss in total femoral BMD with mometasone 400mcg bid compared to placebo.

Changes in HPA-axis with short-term use of recommended doses of mometasone, determined by serum cortisol AUC_{24h} and 10-h or 24-h urinary free cortisol (UFC), were minimal compared to placebo. Mometasone 400mcg once daily x 14 days resulted in a lesser decrease in cortisol AUC_{24h} and UFC_{24h} than

beclomethasone-HFA 200mcg bid or beclomethasone-CFC 400mcg bid. Both mometasone and fluticasone in equivalent doses decreased UFC_{10h} to a similar extent. After 12-weeks and 52-weeks of mometasone treatment in patients with asthma, cosyntropin stimulation test was not significantly impaired. Evaluation of HPA-axis with long-term treatment of mometasone, using more sensitive measures is needed.

INTRODUCTION

Mometasone was approved in 2005 and is the sixth orally inhaled corticosteroid to join beclomethasone, budesonide, flunisolide, fluticasone, and triamcinolone. Mometasone is available as a dry powder inhaler (DPI) delivered via the Twisthaler® device. Mometasone is considered to be a high potency agent with low systemic bioavailability. In-vitro studies show that mometasone is similar in potency to fluticasone and more potent than budesonide, beclomethasone, and triamcinolone.

PHARMACOKINETICS

Pharmacokinetic properties were determined in a cross-over study in 24 healthy subjects following a single IV dose and a single inhaled dose via DPI of mometasone 400mcg[1]; 6 healthy adults after 5 puffs of 200mcg of radiolabeled mometasone[1]; 24 patients with mild-moderate asthma given mometasone 400mcg bid for 15 days[2]; and in 3 separate parallel studies (published in 1 paper) using doses of 200, 400, 800mcg bid and 400, 800, 1600mcg once daily for 28-days.[17]

In the single dose study, only the Cmax and AUC_{tf} (0h to final measurable sampling time) could be calculated for the inhaled dose because the plasma concentrations were too low for reliable estimates of other pharmacokinetic parameters. The Cmax and AUC_{tf} of inhaled mometasone were less than 1% of the values following IV administration.[1] Questions as to the accuracy regarding the <1% bioavailability of mometasone have been raised because the analytical assay used was unable to detect concentrations of mometasone below 50pg/ml in the blood possibly leading to misinterpretation of the data.[3]

Other pharmacokinetic parameters obtained after a single IV dose of mometasone 400mcg were t1/2=4.4h, CL=53.5L/h, Vd=332L. Based on the radiolabeled mometasone study, metabolism occurs in the liver, primarily via CYP 3A4. Several metabolites are formed, but none were considered to be major. Excretion of mometasone is predominantly via the feces (74%) and 8% in the urine.[1]

Table 1: Plasma concentration of mometasone

Study	Subjects	Dose	Cmax (mcg/L)	AUC $_{0h\text{-}tf}$ (mcg/L • hr)
Affrime[1]	healthy adults	MF DPI 400mcg single dose MF IV 400mcg single dose	0.05 6.8	0.09 9.5
Affrime[1]	healthy adults	Radiolabeled MF DPI 200mcg x 5 puffs	0.07	0.279
Affrime[2]	mild-moderate persistent asthma	MF DPI 400mcg single dose MF DPI 400mcg bid x 14 days	0.054 0.151	NR
Affrime[17]	mild-moderate persistent asthma	MF DPI 200mcg bid x 28 days MF DPI 400mcg bid x 28 days MF DPI 800mcg bid x 28 days MF DPI 400mcg qd x 28 days MF DPI 800mcg qd x 28 days MF DPI 1600mcg qd x 28 days	0.02 0.11 0.19 0.07 0.11 0.24	NR 0.46 1.03 NR NR NR

FDA INDICATIONS

For prophylactic maintenance therapy of asthma in patients ≥ 12 years of age

VA FORMULARY ALTERNATIVES

Flunisolide oral inhaler is on the VA national formulary. This is an open class so VISNs may have other agents listed on their VISN formularies.

DOSAGE AND ADMINISTRATION

For patients with asthma who have been previously treated with bronchodilators alone or is on therapy that includes an ICS, the recommended starting dose is 220mcg once daily in the evening. The highest recommended dose is 440mcg daily which can be administered as a single evening dose or in divided doses

of 220mcg bid. For patients receiving chronic oral corticosteroids therapy, the recommended dose of mometasone is 440mcg bid. Prednisone may be tapered by no faster than 2.5mg/day on a weekly basis, beginning after at least 1 week of mometasone therapy. Monitor patient's asthma control, which should include objective measurements of airflow. Patients should also be monitored for signs of adrenal insufficiency. Once prednisone taper is complete, the dosage of mometasone should be reduced to the lowest effective dose.

DEVICE

The Twisthaler® device is prefilled with 14 (institutional use), 30, 60 or 120 doses of mometasone. The amount of drug delivered at the mouthpiece is 200mcg. The device contains a dose counter, allowing patients to see the number of doses remaining. When the cap is removed, the dose is loaded and ready for inhalation and the dose counter will count down by one. When the counter reaches 00 doses remaining, the cap automatically locks, preventing further use.

In vitro tests for dose uniformity have been conducted according to USP, FDA, and European pharmacopeia (EP) standards. The first, middle and last doses were tested using a drawn airflow rate of 60L/min applied for 2 seconds. The delivered doses were within 91-112% of claimed amounts for all 10 meters tested. These tests were repeated varying the airflow rate (28.3, 40, 50, 60, and 70L/min for a duration of 2 seconds) and varying the inspiration time (1, 2, and 3 seconds at a flow rate of 60L/min). When airflow rate was varied, the mean delivered dose ranged from 97% to 108% of the claimed delivery. When inspiration time was varied, the mean delivered dose ranged from 102% to 104% of the claimed delivery. All inhalers tested were well within the specifications set forth by the USP, FDA, and EP.[4]

In an open-label study, patients who were previously using fluticasone MDI were randomized to mometasone or remained on fluticasone, were asked to evaluate the device for ease of use and if they would want to use the particular inhaler in the future. Both groups had a similar proportion of patients who found the inhaler very easy or easy to use (89.9% mometasone; 85.9% fluticasone). More patients in the mometasone group "liked the inhaler a lot" (46.8% vs. 22.4%) whereas more patients in the fluticasone group "liked their inhaler" (44% vs. 28% estimated from graph). The proportion of patients who disliked it or disliked it a lot were similar in both groups.[9]

EFFICACY

Several randomized published clinical trials in asthma of 8-12 weeks duration have been conducted; 4 are dose ranging studies comparing mometasone to placebo[5-8] and 6 compared mometasone to other inhaled steroids (fluticasone, budesonide, beclomethasone) +/- placebo.[9-14] Eight studies required that patients must have used daily ICS for at least 30 days before screening.[7-14] Lastly, 1 trial evaluates use of mometasone in patients receiving chronic oral steroids and is discussed separately.[15]

Some of the comparative trials did not use equipotent doses, used dosing frequencies that are outside the product's labeling, or used unapproved devices; therefore, making some comparisons between products difficult.

All studies used the intent-to-treat principle and performed a power analysis to determine sample size. The primary outcome was change in FEV1 from baseline to endpoint. Secondary outcomes included: change in morning and evening peak flow rate (PEFR), $FEF_{25\%-75\%}$, FVC, symptoms scores, nocturnal awakening, as needed albuterol use, and physician evaluated response to therapy.

Compared to placebo, mometasone in doses of 200mcg q am, 200mcg q pm, 400mcg q am, and 200mcg bid resulted in greater improvement for most measured outcomes in patients who were previously ICS-naïve.[5, 6] In patients who were ICS users prior to the study enrollment, mometasone 200mcg q pm, 400mcg qam or pm, 200mcg bid, and 400mcg bid resulted in greater improvement in measured outcomes compared to placebo.[7, 8, 11, 13, 14]

For trials comparing mometasone to other ICS, it generally can be said that:

- Mometasone 200mcg bid or 400mcg once daily is as effective as fluticasone 250mcg bid.[9, 10]

- Mometasone 200mcg bid and beclomethasone 168mcg bid are significantly better than placebo. Numerically, mometasone resulted in greater improvement in FEV1, PEFR, and some symptom scores than beclomethasone; however, a statistical comparison between the 2 agents was not performed.[13,14]
- Mometasone 400mcg q am was significantly better then budesonide 400mcg qam for nearly all efficacy parameters (doses probably not equivalent). Mometasone 200-400mcg bid was numerically better than budesonide 400mcg bid for FEV1, physician assessment of improvement, and prn albuterol use (200mcg bid dose only).[11, 12]

One study found that there was greater improvement in pulmonary functions and peak flow with administration of mometasone 200mcg once daily in the evening than in the morning.[7] Mometasone 400mcg once daily in the morning [5,7] or evening [8] and mometasone 200mcg bid appear to improve outcomes to a similar extent; although these doses were not statistically compared.

Survival curves (Kaplan-Meier estimates) of time to worsening asthma were analyzed in 5 studies. [5-7, 13, 14] All active treatments had a greater probability of remaining on therapy than placebo. Two studies reported median time to worsening of asthma for placebo to be 40 and 55 days. [13, 14] Median times could not be determined for the active treatments because too few patients met the criteria for asthma worsening. Two studies provided the number of patients who met the criteria for asthma worsening. In Nayak et al., 9, 13, and 26 patients met the criteria for asthma worsening in the MF400mcg daily, MF 200mcg daily and placebo groups respectively.[6] In Nathan et al., 6, 8, 13, and 32 patients met the criteria for asthma worsening in the MF200mcg bid, MF100mcg bid, BDP, and placebo groups respectively.[13]

Table 2: Results of primary outcome in asthma studies

Study	Duration	Baseline FEV1 % predicted	Required prior use of ICS	Dosing	Change in FEV1 (L)¶
Kemp[5]	12-weeks	71-73% predicted	No	MF 200mcg q am (n=79)† MF 400mcg q am (n=74) MF 200mcg bid (n=79) † Placebo (n=74)	0.27 ± 0.06 0.41± 0.06* 0.4 ± 0.05* 0.14 ± 0.06
Nayak[6]	12-weeks	72-73 % predicted	No	MF 200mcg q am (n=72) † MF 400mcg q am (n=77) Placebo (n=87)	0.35 ± 0.05* 0.35 ± 0.04* 0.06 ± 0.05
Noonan[7]	12-weeks	76-81% predicted	Yes	MF 200mcg q am (n= 58) † MF 200mcg q pm (n=54) † MF 400mcg q am (n=58) MF 200mcg bid (n=58) † Placebo (n=58)	-0.22 ± 0.06 0.03 ± 0.06* -0.01 ± 0.06* -0.03 ± 0.06* -0.30 ± 0.06
D'Urzo[8]	12-weeks	78-79% predicted	Yes	MF 200mcg q pm (n=78) MF 200mcg bid (n=80) MF 400mcg q pm (n=78) Placebo (n=83)	0.41* 0.51* 0.49* 0.16
Wardlaw[9]	8-weeks	75-76% predicted	Yes	MF 400mcg q pm (n=82) † FP 250mcg bid (n=85)	0.11 0.16
O'Connor[10]	12-weeks	75-76% predicted	Yes	MF 100mcg bid (n=182) † MF 200mcg bid (n=182) MF 400mcg bid (n=184) FP 250mcg bid (184)	0.07 ± 0.04 0.16 ± 0.04 0.19 ± 0.04+ 0.16 ± 0.04
Corren[11]	8-weeks	71-75% predicted	Yes	MF 400mcg q am (n=104) BUD 400mcg q am (n=106) Placebo (n=51)	0.19 ± 0.04*^ 0.03 ±0.04 -0.10 ± 0.06
Bousquet[12]	12-weeks	76-78% predicted	Yes	MF 100mcg bid (n=185) † MF 200mcg bid (n=176) MF 400mcg bid (n=188) BUD 400mcg bid (n=181)	0.1 ± 0.03 0.16 ± 0.03^ 0.16 ± 0.03^ 0.06 ± 0.03
Nathan[13]	12-weeks	75-78% predicted	Yes	MF 100mcg bid (n=56) † MF 200mcg bid (n=56) BDP 168mcg bid (n=57) Placebo (n=57)	0.12 ± 0.05* 0.25 ± 0.06* 0.11 ± 0.05* -0.21 ± 0.05
Bernstein[14]	12-weeks	74-78% predicted	Yes	MF 100mcg bid (n= 76) † MF 200mcg bid (n=70) MF 400mcg bid (n=74) †	4.8%* 7.1%* 6.2%*

	BDP 168mcg bid (N=71)	3.0%*
	Placebo (n=74)	-6.6%

¶ Bernsterin et al. present results as % change in FEV1
† Used unapproved delivery device
[+]Significant vs. MF 100mcg bid
*Significant vs. placebo
^Significant vs. budesonide

Extension trials in asthma (data on file-Schering)
In the study by Nayak, patients completing the 3-month trial (n=166) were eligible to enter a 9-month extension trial. Patients were randomized to mometasone 200mcg or 400mcg once daily in the morning or 200mcg or 400mcg once daily in the evening. Baseline was considered to be the start of the 9-month study. Patients who were originally randomized to placebo in the parent study had an increase in FEV1, FVC, and $FEF_{25-75\%}$ from baseline. For those initially randomized to active treatment, pulmonary functions were maintained from baseline to endpoint (data not shown).

Mometasone was compared to beclomethasone MDI in a 52-week randomized, evaluator-blinded study (n=239). Patients aged 12-80 years with FEV1 between 60-90% predicted were randomized to mometasone 200mcg or 400mcg bid, mometasone 800mcg once daily or beclomethasone MDI 168mcg bid. All treatments resulted in improvement from baseline for FEV1, FVC, and $FEF_{25-75\%}$ (results not shown).

Patients receiving oral prednisone
A 2-phase trial evaluated mometasone in oral steroid-dependent patients with asthma.[15] The first phase was 12-week double-blind, randomized controlled trial comparing mometasone 400mcg and 800mcg bid to placebo. The second phase was a 9-month open label trial using mometasone 800mcg bid (the dose could be tapered to 400mcg bid if the oral steroid was completely discontinued for $\geq$ 4 weeks). The patient's usual non steroid asthma medications were continued. At each visit, the dosage of oral steroids was reduced if the patient fulfilled the predefined criteria. The mean prednisone dose at baseline was approximately 12mg/day.

During the randomized phase, the daily dose of prednisone was reduced by a mean of 6.33mg and 3.19mg in the mometasone 400mcg and 800mcg groups respectively compared to a mean increase of 11.81mg in the placebo group. Oral steroids were discontinued in approximately 40% of the mometasone groups and in none of the placebo patients. The dose of oral steroids was reduced by at least half in 60% of the mometasone patients compared to 7% of the placebo patients. There was significantly greater improvement in FEV1, symptoms scores, and as needed albuterol with both mometasone groups versus placebo.

During the open-label phase (n=127), percent reduction in prednisone dose at endpoint was 58.1% / 42.5%/ 61.6% and complete discontinuation of prednisone at endpoint was 71%/ 62%/ 58% for those previously randomized to MF400/ MF800/ placebo respectively. Among the 95 patients completing the entire 12-months, 76% completely discontinued use of prednisone and 31% were able to reduce the dose of mometasone from 800mcg bid to 400mcg bid.

Studies in COPD
None of the ICS, including mometasone are approved for use in COPD; however, the combination product containing fluticasone 250mcg and salmeterol 50mcg is approved for use in COPD.

There are 2 randomized double-blind 52-week trials (unpublished) comparing mometasone to placebo in patients with COPD.[16]

To be included patients had to be > 40 years old with COPD, non-smoker for $\geq$1 year prior to baseline, FEV1/FVC $\leq$ 70%, and FEV1 reversibility of < 10% predicted after albuterol 400mcg. Exclusion criteria included: ventilatory support for COPD in the last year; history of lobectomy, pneumonectomy, or lung volume reduction; required CPAP or Bi-PAP therapy; started pulmonary rehab within the past 3 months;

oxygen use > 2L/min for > 2hrs/day; chronic or prophylactic antibiotic treatment; abnormal CXR other than that which is consistent with COPD; oropharyngeal candidiasis.

The primary outcome was change in baseline post-bronchodilator FEV1, total COPD symptom score, and percentage of patients with ≥ 1 COPD exacerbation. For FEV1 and total symptoms score, only the p values were provided (actual numerical changes were not shown).

Table 3: Results of primary outcomes in COPD trials

Study	Duration	Required prior use of ICS	Dosing	Change in post-BD FEV1	Total symptom score	% ≥ 1 COPD exacerbation
Study P00345[16]	52-weeks	Yes	MF 800mcg q pm (n=318) Placebo (n=313)	MF > Placebo (p=0.017)	MF > Placebo (p< 0.001)	43% vs. 50% (p = 0.055) MF prolonged the median time to 1st exacerbation (p< 0.0001)
Study P00340[16]	52-weeks	No	MF 800mcg q pm (n=308) MF 400mcg bid (n=308) Placebo (n=295)	Both MF doses > placebo (p < 0.001)	MF400bid > placebo (p< 0.001)	MF sig vs placebo Data not shown

† Used unapproved delivery device

Secondary outcomes included: pre-bronchodilator FEV1, pre- and post-bronchodilator FEF $_{25\% -75\%,}$ FVC, AM/PM symptoms scores, as needed albuterol use, health-related quality of life, 6-minute walk distance and Borg score, and physician evaluated response to therapy (only p-values were provided).

In study P00345, pre-bronchodilator FEV1, AM/PM symptom scores, physician assessment of response, prn albuterol use, and total SGRQ scores were significantly better with mometasone 800mcg q pm than placebo. Results for FEF $_{25\% -75\%,}$ FVC, and 6-minute walk distance and Borg score were not discussed.

In study P00340, both mometasone groups had significant improvement in pre- and post-bronchodilator FEF $_{25\% -75\%}$ and FVC and physician assessed response to treatment compared to placebo. However, only mometasone 400mcg bid was significantly better than placebo for AM/PM symptoms scores, prn albuterol use, and total SGRQ scores. Results for pre-bronchodilator FEV1 and 6-minute walk distance and Borg score were not discussed.

ADVERSE EVENTS

Adverse events, compiled by the manufacturer, from 10 double-blind placebo controlled trials of up to 12 weeks duration are reported in table 4. Data are from 2809 patients (males n=1140, females n=1669) aged 12-83 years. Mometasone was well tolerated and adverse events were generally mild-moderate in severity. The most commonly reported adverse events were headache, allergic rhinitis, pharyngitis and upper respiratory tract infection. There was a slight dose-related increase in adverse events when looking at the individual trials; however, this was not evident with the compiled data. The overall incidence of treatment related adverse events was similar to placebo. Discontinuations due to adverse events were less frequent or similar to placebo. Oral candidiasis occurred more frequently in the groups receiving ICS compared to placebo.

In general, the incidence of adverse events was similar for mometasone compared to fluticasone or budesonide. Compared to beclomethasone 168mcg, the incidence of oral candidiasis, pharyngitis, and dysphonia were higher with mometasone 200mcg bid and 400mcg bid; however, the beclomethasone doses were probably not equipotent to the mometasone doses. (Table 5)

In the prednisone withdrawal study, 46%, 33%, and 16% of patients in the mometasone 400mcg, 800mcg bid, and placebo groups respectively experienced symptoms of steroid withdrawal (musculoskeletal pain, fatigue, depression).[15]

There was a greater incidence of adverse events in the extension trials than in the 8-12 week trials. A placebo arm was not included in the extension trials so it is unknown if the incidence would have increased in that group as well (table 6).

Table 4: Adverse events with ≥ 3% incidence from placebo-controlled trials

	MF 220mcg bid	MF 440 mcg QD	MF 220mcg q pm	Placebo
n	443	497	232	720
Headache	22	17	20	20
Allergic rhinitis	15	11	14	13
Pharyngitis	11	8	13	7
URI	10	8	15	7
Sinusitis	6	6	5	5
Oral candidiasis	6	4	4	2
Musculoskeletal pain	8	4	4	5
Back pain	6	3	3	4
Dyspepsia	5	3	3	3
Myalgia	3	2	3	2
Abdominal pain	3	1	3	2
Nausea	3	1	3	2

From product package insert

Table 5: Treatment-related adverse events from published clinical trials

	Any tx-related AE	Discontinue due to AE	Headache	Oral candidiasis	Pharyngitis	Dysphonia
Kemp MF200qam/ MF400qam/MF200bid/ placebo	23/ 23/ 23/ 19%	n=5/ 2/ 3/ 7	9/ 11/ 5/ 11%	1/ 5/ 3/ 0%	5/ 4/ 3/ 1%	NR
Nayak MF200qam/ MF400qam/ placebo	19/ 25/ 22%	8/ 12/ 10%	8/ 6/ 6%	3/ 4/ 1%	3/ 5/ 6%	1/ 3/ 2%
Noonan MF200qam/ MF200qpm MF400qam/MF200bid/ placebo	NR	n=5 (not broken down by group)	NR	NR	NR	NR
D'Urzo MF200qpm/ MR200bid/ MF400qpm[1]/ MF400qpm[2]/ placebo	12/ 16/ 18/ 17/ 6%	NR	8/ 11/ 9/ 8/ 7%	6/ 7/ 6/ 6/ 2%	4/ 1/ 0/ 1/ 1%	NR
Wardlaw MF400qpm/FP250bid	13.4/ 8.2%	NR	3.7/ 2.4%	2.4/ 2.4%	0/ 1.2%	2.4/ 0%
O'Connor MF100bid/ MF200bid/ MF400bid/ FP250bid	20/ 26/ 30/ 29%	5/ 3/ 5/ 4%	NR	1/ 7/ 19/ 10%	12-16% similar between groups	2-7% similar between groups
Corren MF400qam/ BUD400qam/ Placebo	8/ 9/ 8%	NR	<4% in each group	n=1 MF	<4% in each group	NR
Bousquet MF100bid/ MF200bid/ MF400bid/ BUD400bid	17-20% similar between groups	3/ <1/ 2/ 4%	4-8% similar between groups	n=4/ 6/ 4/ 3	4-5% similar between groups	n=8/ 5/ 9/ 4
Nathan MF100bid/ MF200bid/ BDP168bid/ placebo	NR	n=1/ 2/ 1/ 5	5/ 2/ 4/ 2%	4/ 11/ 5/ 0%	7/ 2/ 0/ 2%	4/ 4/ 2/ 0%
Bernstein MF100bid/ MF200bid/ MF400bid/ BDP168bid/ placebo	18/ 26/ 28/ 21/ 22/ 18%	5/ 3/ 4/ 8/ 11%	3/ 4/ 4/ 4/ 5%	4/ 6/ 15/ 3/ 1%	1/ 10/ 8/ 4/ 4%	1/ 1/ 3/ 1/ 1%
Fish MF 400mcg bid +prednisone MF 800mcg bid + prednisone placebo + prednisone	NR	n=3 (double –blind) n=2 (open-label)	NR	20/ 23/ 9%	NR	7/ 12/ 0%

NR=Not reported

Table 6: Adverse events reported in 52-week asthma trials

	Sinusitis	Viral infection	Headache	Oral candidiasis	Pharyngitis	Aggravated allergy
52-week trial (unpublished) MF200bid/ MF400bid/ MF800QD/ BDP168bid	32/ 21/ 25/ 21%	N28/ 34/ 31/ 22%	43/ 45/ 44/ 55%	23/ 18/ 17/ 16%	25/ 19/ 17/ 24%	35/ 34/ 27/ 26%
52-week trial (unpublished) MF200qam/ MF200qpm/ MF400qam/ MF400qpm	24/ 23/ 9/ 20%	24/ 20/ 20/ 29%	34/ 33/ 27/ 49%	NR*	NR	49/ 50/ 36/ 39%

NR=Not reported
*Incidence in the 9-month phase was 0-10% relative to the 3-month phase

Bone mineral density (BMD)
Changes in BMD with mometasone were determined in male and female patients (ages 18-50) with asthma in two 2-year studies. Compared to placebo, there was a small but statistically significant decrease in lumbar spine BMD with mometasone 200mcg bid. Changes between mometasone 400mcg bid and placebo were not significant. There were no significant changes in total femoral BMD with either dose of mometasone and placebo. (Data on file Schering-Plough)

There were no significant differences in serum osteocalcin or urinary N-telopeptide between mometasone 200mcg and placebo. For mometasone 400mcg bid, there was a trend towards decrease in serum osteocalcin compared to placebo.

Table 7: Changes in BMD in patients with asthma

		Lumbar spine		Total femoral	
	n	Mometasone	Placebo	Mometasone	Placebo
Mometasone 200mcg bid	103	-1.693%*	-0.165%	-0.026%	-0.512%
Mometasone 400mcg bid	87	-1.245%	-0.082%	-1.333%	0.237

*significant vs. placebo

Changes in BMD with mometasone versus placebo were determined in patients in the 1-year COPD trial (P00340). At endpoint, changes in lumbar spine BMD were not significant between groups. There was a trend towards greater loss in total femoral BMD with mometasone 400mcg bid compared to placebo. (Data on file Schering-Plough)

Table 8: Changes in BMD in patients with COPD

	n	Lumbar spine	Total femoral
Mometasone 800mcg q PM		0.857%	0.347%
Mometasone 400mcg bid		-0.944	-2.002%
Placebo		-0.068%	-0.677%

Hypothalamic-pituitary-adrenal axis (HPA)
Three studies have evaluated the effect of mometasone on the HPA function in patients with asthma. Two of these studies included beclomethasone or fluticasone as a comparator.

In Affrime et al, study 1 showed no significant differences in 18-h cortisol AUC, 24h urinary free cortisol, 8am cortisol and 250mcg cosyntropin stim test for mometasone 400mcg qam, 200mcg bid, 800mcg qam, and 1200mcg qam compared to placebo after 28-days of treatment. In study 2, mometasone 400mcg bid and 800mcg bid for 28- days resulted in a significant dose-dependent decrease in 24-h cortisol AUC compared to placebo. Study 3 compared mometasone-HFA (not marketed) to fluticasone (unclear which propellant was used). Both mometasone 800mcg bid and fluticasone 880mcg bid significantly lowered 24-h cortisol AUC compared to placebo. There was no significant difference between mometasone 400mcg bid and placebo.[17]

After 14-days of treatment, mometasone DPI 400mcg once daily suppressed 24-hour cortisol AUC and 24-h urinary free cortisol to a significantly lesser extent than beclomethasone-HFA 200mcg bid and beclomethasone-CFC 400mcg bid.[18] In a randomized cross-over study, equivalent doses of mometasone and fluticasone were compared.[19] Mometasone was dosed in the following fashion 200mcg bid x 2 weeks,

then 400mcg bid x 2weeks, then 800mcg bid x 2 weeks. Similarly, fluticasone was given 250mcg bid x 2weeks, then 500mcg bid x 2 weeks, then 1000mcg bid x 2 weeks. Compared to baseline, the 10-hour overnight urinary cortisol decreased to a similar extent with both agents at the 2 highest doses tested.

Three of the large 12-week clinical trials [7, 12, 14] and a 52-week study comparing 3 doses of mometasone and beclomethasone (data on file-Schering) evaluated HPA-axis function as part of the safety assessment. Three used the standard 250mcg cosyntropin stimulation test to assess HPA axis responsiveness. Some have criticized using the 250mcg dose because it is supraphysiologic and may not be able to detect mild adrenal gland suppression. Alternatively, 1mcg of cosyntropin has been suggested. Bousquet evaluated basal cortisol secretion by measuring the 8am cortisol level. This measure is poorly predictive for adrenal suppression. More sensitive measures include 24-hour area under the curve for plasma cortisol or urinary free cortisol secretion. Results are shown in appendix 3. Evaluation of HPA-axis using more sensitive measures is needed with long-term use of mometasone.

CONTRAINDICATIONS/PRECAUTIONS
Contraindications and precautions are the same as with other orally inhaled corticosteroids. There are no specific contraindications or precautions unique to mometasone.

LOOK-ALIKE/SOUND-ALIKE
LA/SA for trade name Asmanex: Azmacort

Both agents are orally inhaled corticosteroids

DRUG INTERACTIONS
Ketoconazole, a CYP3A4 inhibitor, may increase mometasone plasma concentrations

COST
A BPA for mometasone has been proposed and will be discussed with the MAP and VISN formulary leaders.

Table 9: Cost of orally inhaled steroids

Drug	Dosage form	Commonly used doses*	VA cost per unit
Mometasone 220mcg	DPI	220-440mcg daily	30, 60, 120 inhalation units
Flunisolide 250mcg	MDI	500mcg BID	$18.09 (100puffs)
Fluticasone HFA	MDI		
44mcg		88-220mcg BID	$32.66 (120 puffs)
110mcg			$46.46
220mcg			$71.78
Beclomethasone HFA	MDI	40-160mcg BID	
40mcg			$25.73 (100 puffs)
80mcg			$32.56
Budesonide 200mcg	DPI	200-400mcg BID	$85.79 (200 puffs)
Triamcinolone 100mcg	MDI	200mcg TID-QID or 400mcg BID	$39.70 (240 puffs)

MDI=metered dose inhaler; DPI=dry powder inhaler
*These represent commonly used doses and do not represent highest doses that can be used

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Appendix 1: Clinical trials comparing mometasone to placebo in patients with asthma

<table>
<tr><th>Study</th><th>Inclusion/exclusion</th><th>Dosage</th><th>Patient characteristics</th><th>Results</th></tr>
<tr>
<td>Kemp 2000
R, DB PC, PR
12-weeks
n=306

ITT

Study site(s)
USA</td>
<td>Asthma ≥ 6 months
Age 12-70 years
Using SABA ≥ 3x/week for sx relief for ≥ 2 weeks prior to screening
No ICS use within previous 3 months
FEV1 55-85% predicted
FEV1 reversibility 12% or 200mL
Non-smoker or stopped smoking ≥ 6months prior to screening

See exclusion criteria listed in footnote plus the following:

ER tx for asthma ≥2 in previous 6 months
Respiratory disease other than asthma
Daily use of nebulized albuterol ≥ 12 inhalations of albuterol/ day on any 2 consecutive days</td>
<td>1:1:1:1 randomization
Mometasone 200mcg q am
Mometasone 400mcg q am
Mometasone 200mcg bid
Placebo

Prn albuterol allowed. No other asthma medications allowed</td>
<td>Values for MF 200/ MF400/ MF200bid/ Placebo
Age (years): 30 ± 11 / 29 ± 11/ 32 ± 14/ 32 ± 15
% Male: 43/ 54/ 44/ 58
Duration of asthma (years): 16 ± 11/ 17 ± 11/ 17 ± 12/ 16 ± 11
FEV1 % predicted: 73 ± 8/ 72 ± 10/ 72 ± 8/ 71 ± 9
FEV1 (L): 2.58 ± 0.07/ 2.64 ± 0.07/ 2.56 ± 0.07/ 2.55 ± 0.007

Mean ± SD except for FEV1 (L)= mean ± SEM</td>
<td>
<table>
<tr><th></th><th>MF200</th><th>MF400</th><th>MF200 bid</th><th>Placebo</th></tr>
<tr><td>All d/c</td><td>15.2%</td><td>8.1%</td><td>8.9%</td><td>24.3%</td></tr>
<tr><td>d/c due to LOE</td><td>1.3%</td><td>1.4%</td><td>3.8%</td><td>9.5%</td></tr>
<tr><td>FEV1 (L)</td><td>0.27 ± 0.06</td><td>0.41± 0.06*</td><td>0.4 ± 0.05*</td><td>0.14 ± 0.06</td></tr>
<tr><td>PEFRam (L/min)</td><td>26 ± 7</td><td>52 ± 7*</td><td>64 ± 7*</td><td>23 ± 7</td></tr>
<tr><td>Am sx score</td><td colspan="4">Significant improvement in all 3 domains with MF400 and MF200bid</td></tr>
<tr><td>Nocturnal awakening req. albuterol</td><td>-0.22</td><td>-0.25</td><td>-0.20</td><td>-0.12</td></tr>
<tr><td>Prn albuterol (puffs/day)</td><td>-1.84*</td><td>-2.22*</td><td>-1.99*</td><td>-1.08</td></tr>
<tr><td>Physician evaluation</td><td colspan="4">Improvement with all active treatments significantly better than placebo</td></tr>
</table>
*Significant vs. placebo
Mean ± SEM
</td>
</tr>
<tr>
<td>Nayak 2000
R, DB, PC, PR
12-weeks
n=236

ITT

Study site(s)
USA</td>
<td>Asthma ≥ 6 months
Age ≥ 12 years
Using SABA ≥ 3x/week for sx relief for ≥ 2 weeks prior to screening
FEV1 55-85% predicted
FEV1 reversibility 12% or 200mL
No ICS use within previous 3 months
Non-smoker or stopped smoking ≥ 6months prior to screening

See exclusion criteria listed in footnote plus the following:

ICS in previous 3 months
Daily nebulized albuterol ≥ 12 inhalations of albuterol/ day on 2 consecutive days between screening and prebaseline visit</td>
<td>1:1:1 randomization

MF 200mcg q am
MF 400mcg q am
Placebo

Prn albuterol was allowed. Other asthma medications were prohibited

immunotherapy allowed if on stable dose</td>
<td>Age (years): 33/ 31/ 35
% Male: 47/ 45/ 47
Duration of asthma (years): 17/ 15/ 15
FEV1 % predicted: 72/ 72/ 73
FEV1 (L): 2.60 ± 0.08/ 2.57 ± 0.07/ 2.61 ± 0.06

Mean ± SEM</td>
<td>
<table>
<tr><th></th><th>MF200</th><th>MF400</th><th>Placebo</th></tr>
<tr><td>All d/c</td><td>10%</td><td>19%</td><td>25%</td></tr>
<tr><td>d/c due to LOE</td><td>N=1</td><td>N=1</td><td>N=7</td></tr>
<tr><td>FEV1 (L)</td><td>0.35 ± 0.05*</td><td>0.35 ± 0.04*</td><td>0.06 ± 0.05</td></tr>
<tr><td>FEF 25-75% (L/sec)</td><td>0.65 ± 0.09*</td><td>0.37 ± 0.07^</td><td>0.08 ± 0.08</td></tr>
<tr><td>FVC (L)</td><td>0.23 ± 0.08*</td><td>0.37 ± 0.07*</td><td>0.02 ± 0.08</td></tr>
<tr><td>PEFRam (L/min)</td><td>15</td><td>41*^</td><td>7</td></tr>
<tr><td>Am sx score</td><td colspan="3">Both active treatments significantly improved vs. placebo for the wheezing and difficulty breathing domains (NS for the cough domain)</td></tr>
<tr><td>Prn albuterol (puffs/day)</td><td>-1.58 ± 7*</td><td>-2.23 ± 7*</td><td>-0.47 ± 7</td></tr>
<tr><td>Physician evaluation</td><td colspan="3">Improvement with both active treatments significantly better than placebo</td></tr>
</table>
*Significant vs. placebo
^Significant vs. MF200
</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>Respiratory tract infection 2 weeks prior to screening
Oropharyngeal candidiasis
Use of methotrexate, cyclosporin, gold w/i 3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noonan 2001
R, DB, PC, PR
12-weeks
n=286

ITT

Study site(s)
USA</td>
<td>Asthma ≥ 6 months
Age ≥ 12 years
Daily ICS use for at least the previous 30 days
FEV1 60-90% predicted
FEV1 reversibility 12% or 200mL
Non-smoker or stopped smoking ≥ 6months prior to screening

See exclusion criteria listed in footnote plus the following:

ER tx for asthma ≥2 in previous 6 months
Systemic steroids 1 month prior to screening
Daily use of LABAs
≥ 12 inhalations of albuterol/ day on 2 consecutive days between screening and prebaseline visit
Respiratory tract infection 2 weeks prior to screening
Other clinically significant dx
Oropharyngeal candidiasis</td>
<td>1:1:1:1:1 randomization
Mometasone 200mcg q am
Mometasone 200mcg q pm
Mometasone 400mcg q am
Mometasone 200mcg bid
Placebo

Prn albuterol allowed</td>
<td>Values for MF 200am/ MF200pm/ MF400am/MF200bid/ Placebo
Age (years): 40/ 38/ 36/ 42/ 41
% Male: 55/ 37/ 48/ 45/ 31
Duration of asthma (years): 18/ 20/ 17/ 21/ 20
FEV1 % predicted: 78/ 76/ 79/ 79/ 81
FEV1 (L): 2.57/ 2.49/ 2.64/ 2.75/ 2.68

ICS use mean dose (n)
Beclomethasone 338mcg (n=100)
Flunisolide 1179mcg (n=35)
Fluticasone 377mcg (n=78)
Triamcinolone 791mcg (n=93)</td>
<td>
<table>
<tr><th></th><th>MF200am</th><th>MF200pm</th><th>MF400am</th><th>MF200bid</th><th>Placebo</th></tr>
<tr><td>All d/c d/c due to LOE</td><td>17%</td><td>4%</td><td>17%</td><td>0</td><td>33%</td></tr>
<tr><td>FEV1 (L)</td><td>-0.22 ± 0.06</td><td>0.03 ± 0.06*</td><td>-0.01 ± 0.06*</td><td>-0.03 ± 0.06*</td><td>-0.30 ± 0.06</td></tr>
<tr><td>FEF $_{25-75\%}$ (L/sec)</td><td>-0.29 ± 0.10</td><td>-0.03 ± 0.11*</td><td>-0.04 ± 0.10*</td><td>-0.15 ± 0.10*</td><td>-0.47 ± 0.10</td></tr>
<tr><td>FVC (L)</td><td>-0.16 ± 0.07</td><td>0.06 ± 0.07*</td><td>0.01 ± 0.07*</td><td>-0.02 ± 0.07*</td><td>-0.32 ± 0.07</td></tr>
<tr><td>PEFRam (L/min)</td><td>-8.9 ± 6.8*</td><td>4.3 ± 7.1*</td><td>-6.0 ± 6.8*</td><td>6.9 ± 6.8*</td><td>-36.9 ± 6.8</td></tr>
<tr><td>Am sx score</td><td colspan="5">All active treatments significantly improved vs. placebo for wheezing and difficulty breathing domains. For cough domain, significant improvement vs. placebo seen for all active treatments except MF200pm</td></tr>
<tr><td>Nocturnal awakening req. albuterol</td><td>0.07*</td><td>0.15</td><td>0.07*</td><td>-0.07*</td><td>0.30</td></tr>
<tr><td>Prn albuterol (puffs/day)</td><td>0.54*</td><td>0.73</td><td>0.21*</td><td>-0.15*</td><td>1.53</td></tr>
<tr><td>Physician evaluation</td><td colspan="5">Improvement with all active treatments significantly better than placebo</td></tr>
</table>
Mean ± SEM
*Significant vs. placebo
</td>
</tr>
</table>

<table>
<tr>
<td>D'Urzo 2005
R, DB, PC, PR
12-weeks
n=</td>
<td>Age ≥ 12 years
Persistent asthma for ≥ 12-months
ICS dependent for ≥ 12 weeks prior to screening w/i predefined dosage ranges*
Using ICS on a bid basis
FEV1 ≥ 60% predicted
FEV1 reversibility 12% or 200mL
*BDP(CFC) 168-840mcg, BDP (HFA) 40-320mcg, BUD 200-1600mcg, FP 88-660mcg, TCA 400-2000mcg, FLU 500-2000mcg

ER tx for asthma ≥2 in previous 6 months
hospitalized for asthma in past 3 months
Cytotoxic agents in past 3 mos.
Receiving immunotherapy
Daily use of nebulized beta-agonists
Daily use of LABAs
Respiratory tract infection 2 weeks prior to screening
Required ventilator support for asthma in past 10 years
Smoked in past 6 months
Cumulative smoking history of > 10 pack years
Other clinically significant dx</td>
<td>1:1:1:1 randomization
4-week period prior to randomization to determine if patient is ICS dependent

Mometasone 200mcg q pm
Mometasone 200mcg bid
Mometasone 400mcg q pm
Placebo

Evening dose to be taken late afternoon or early evening

Prn albuterol allowed</td>
<td>Age (years): 39.9/ 36.6/ 40.3/ 35.9
% Male: 40/ 34/ 42/ 45
Duration of asthma (years): 21/ 19/ 18/ 17
FEV1 % predicted: 78.6 ± 11, 79.2 ± 10.6, 77.8 ± 11
FEV1 (L): 2.56, 2.66, 2.65, 2.61

ICS use mean dose (n)
Beclomethasone (n=30)
Budesonide n=40
Flunisolide n=13
Fluticasone n=220
Triamcinolone n=21</td>
<td>
<table>
<tr><th></th><th>MF200 q pm</th><th>MF 200 bid</th><th>MF400 q pm</th><th>Placebo</th></tr>
<tr><td>dropouts</td><td colspan="4">not shown</td></tr>
<tr><td>FEV1 (L)</td><td>0.41*</td><td>0.51*</td><td>0.49*</td><td>0.16</td></tr>
<tr><td>FVC (L)</td><td>0.37*</td><td>0.45*</td><td>0.48*</td><td>0.17</td></tr>
<tr><td>FEF 25-75% (L/sec)</td><td>0.46*</td><td>0.69*</td><td>0.59*</td><td>0.17</td></tr>
<tr><td>PEFRam (L/min)</td><td>23.6*</td><td>40.2*^</td><td>41.5*^</td><td>-2.9</td></tr>
<tr><td>PEFRpm (L/min)</td><td>15.7*</td><td>36.7*^</td><td>39.3*^</td><td>1.4</td></tr>
<tr><td>AM sx score</td><td colspan="4">All active treatments significantly improved vs. placebo for total score and all domains</td></tr>
<tr><td>PM sx score</td><td colspan="4">All active treatments significantly improved vs. placebo for total score and all domains (except for wheezing domain with MF 200 q pm)</td></tr>
<tr><td>Nocturnal awakening/d</td><td>-0.17*</td><td>-0.28*</td><td>-0.34*</td><td>0.09</td></tr>
<tr><td>Prn albuterol (puffs/day)</td><td>-1.36*</td><td>-1.7*</td><td>-1.84*</td><td>0.52</td></tr>
</table>
*Significant vs. placebo
^Significant vs. MF 200 qpm
</td>
</tr>
<tr>
<td>Fish 2000
R, DB, PC, PR
12-weeks followed by 9-months open-label of MF 800mcg bid
n=132

ITT</td>
<td>Age ≥ 12 years
Severe persistent asthma for ≥ 12-months
OCS-dependent (5-30mg daily or 10-60mg qod) asthma for at least 5 or more of the 6 months before enrollment
FEV1 40-85% predicted
FEV1 reversibility 12% or 200mL</td>
<td>1:1:1 randomization

Mometasone 400mcg bid
Mometasone 800mcg bid
Placebo

Open-label MF 800mcg bid. Dose could be tapered to 400mcg bid if OCS was completely d/c'd for ≥ 4 weeks

Patients usual asthma meds were continued</td>
<td>Age (years): 49/ 53/ 55
% Male: 48/ 37/ 56
Duration of asthma (years): 21/19/ 23
FEV1 % predicted: 59/ 61/ 57
FEV1 (L): 1.87/ 1.79/ 1.78
Prednisone dose (mg/day): 11.93/ 12.02/ 11.56

ICS use mean dose (n)
Beclomethasone 436mcg (n=16)
Budesonide 1067mcg (n=3)
Flunisolide 1375mcg (n=20)
Fluticasone 563mcg (n=36)</td>
<td>
<table>
<tr><th></th><th>MF400</th><th>MF800</th><th>Placebo</th></tr>
<tr><td>All d/c</td><td></td><td></td><td></td></tr>
<tr><td>d/c due to LOE</td><td>7%</td><td>12%</td><td>55%</td></tr>
<tr><td>Prednisone dose (mg/day)</td><td>-6.33*</td><td>-3.19*</td><td>11.81</td></tr>
<tr><td>d/c OCS (% pts.)</td><td>40%</td><td>37%</td><td>0%</td></tr>
<tr><td>↓OCS dose by ≥ 50% (% pts.)</td><td>62%</td><td>60%</td><td>7%</td></tr>
<tr><td>Increase in OCS dose (% pts.)</td><td>13%</td><td>16%</td><td>60%</td></tr>
<tr><td>FEV1 (L)</td><td>0.25 ± 0.07*</td><td>0.17 ± 0.07*</td><td>-0.19 ± 0.05</td></tr>
<tr><td>PEFRam (L/min)</td><td>40.97 ± 9.56*</td><td>42.21 ± 13.21*</td><td>-37.51 ± 7.19</td></tr>
</table>
</td>
</tr>
</table>

			Triamcinolone 1123mcg (n=40)	Am sx score — Both active treatments significantly improved vs. placebo for all 3 domains Nocturnal awakening (n): -0.30* / -0.29* / 0.18 Prn albuterol puffs/day: -1.83* / -0.88 / 0.29 Mean ± SEM *Significant vs. placebo **Open label phase (n=127, completed entire 12-months n=95)** Those previously randomized to MF400/ MF800/ Placebo • % Reduction in prednisone dose at endpoint: 58.1% / 42.5%/ 61.6% • Complete d/c prednisone at endpoint among the 127 patients: 64% (by prior randomization in double-blind phase: 71%/ 62%/ 58%) • Among the 95 patients completing the entire 12-months, 76% completely d/c'd use of prednisone and mometasone was decreased from 800mcg bid to 400mcg bid in 31% of patients

≥ 14 days of systemic steroids in the previous 6 months; hospitalized for asthma in previous 3 months; ventilatory support for asthma in past 5 years;

Appendix 2: Comparative trials in asthma

<table>
<tr><th>Study</th><th>Inclusion/exclusion criteria</th><th>Dosage</th><th>Baseline patient characteristics</th><th>Results</th></tr>
<tr>
<td>Wardlaw 2004
R, OL, PR
mometasone vs. fluticasone
8-weeks
n=167

ITT

Study site(s)
Canada, Europe, U.K.</td>
<td>Moderate persistent asthma ≥ 6 months
Daily tx with fluticasone ≥ 30 days before screening
≥ 12 y/o
FEV1 60-90% predicted
FEV1 reversibility > 12% or 200ml post SABA

See exclusion criteria listed in footnote plus the following:

Hospitalized for asthma ≥ 1 in past 6months</td>
<td>1:1 randomization

MF 400mcg qd evening
FP 250mcg bid

rescue inhaler allowed</td>
<td>Values for MF / FP
Age (years): 42.8 ± 17.4 / 43.3 ± 16
% male: 37% / 37%
Duration of asthma (years): 15.5 ± 14.2 / 14.7 ± 11.7
FEV1 % pred: 75.5 ± 11.2 / 76.2 ± 8.7
% using ≤ FP 250mcg: 20.7 / 22.4
% using FP 500mcg: 68.3/ 69.4
% using FP 1000 or 1125mcg: 4.9 / 4.7</td>
<td>
<table>
<tr><th></th><th>MF</th><th>FP</th><th>LS mean diff [95%CI]</th></tr>
<tr><td>FEV1 (L)</td><td>+0.11</td><td>+0.16</td><td>-0.05 [-0.15, 0.05]</td></tr>
<tr><td>FEV1 (% change)</td><td>4.56%</td><td>6.98%</td><td>-2.40 [-6.64, 1.84]</td></tr>
<tr><td>FVC (% incease)</td><td>2.78</td><td>4.65</td><td>-1.87 [-5.36, 1.63]</td></tr>
<tr><td>PEFRam</td><td>10.9 L/min</td><td>18.4 L/min</td><td>-</td></tr>
<tr><td>PEFRpm</td><td>8.3 L/min</td><td>12.5 L/min</td><td>-</td></tr>
<tr><td>total am sx score</td><td>-0.1</td><td>-0.2</td><td>-</td></tr>
<tr><td>total pm sx score</td><td>0.1</td><td>-0.1</td><td>-</td></tr>
<tr><td>prn albuterol</td><td>0.2</td><td>-0.8</td><td>-</td></tr>
<tr><td>% much imp. and imp.</td><td>62%*</td><td>47%</td><td>-</td></tr>
</table>
*Significant vs. fluticasone
</td>
</tr>
<tr>
<td>O'Connor 2001
R, evaluator-blinded, PR
mometasone vs. fluticasone
n=733
12-weeks

ITT

Study site(s)
S. America, S. Africa, Australia, Europe, U.K., Mexico</td>
<td>Asthma ≥ 6 months
Daily tx with ICS ≥ 30 days days w/i predefined dosage ranges*
≥ 12 y/o
FEV1 60-90% predicted
FEV1 reversibility > 12% or 200ml
nonsmoker or stopped smoking for ≥ 6months

*BDP 400-1000mcg, BUD 400-800mcg, FP 200-500mcg, TCA 600-800mcg, FLU 500-1000mcg

See exclusion criteria listed in footnote plus the following:

Respiratory tract infection 2 weeks prior to screening
> 12 puffs of albuterol on any 2 consecutive days between screening and baseline</td>
<td>1:1:1:1 randomization

MF 100mcg bid
MF 200mcg bid
MF 400mcg bid
FP 250mcg bid (via Diskhaler)
rescue inhaler and prior theophylline allowed

allergen specific immunotherapy allowed if on stable dose</td>
<td>Values for MF 100 / MF 200/ MF 400/ FP
Age (years): 42 / 42 / 42 / 40
% male: 45 /40 / 38 / 39
Duration of asthma (years): 16 / 16 / 15 / 13
FEV1 (L): 2.53 / 2.43/ 2.38/ 2.46
FEV1 % pred: 75/ 75/ 75/ 76

ICS dose (range of means):
BDP 567-635mcg(n=362)
BUD 608-640mcg (n=230)
FLU 727- 833mcg (n=34)
FP 443-481mcg (n=103)
TCA 600mcg (n=1)</td>
<td>
<table>
<tr><th></th><th>MF100</th><th>MF200</th><th>MF400</th><th>FP</th></tr>
<tr><td>all d/c</td><td>19%</td><td>12%</td><td>12%</td><td>12%</td></tr>
<tr><td>d/c due to LOE</td><td>7%</td><td>4%</td><td>3%</td><td>4%</td></tr>
<tr><td>FEV (L)</td><td>0.07 ± 0.04</td><td>0.16 ± 0.04</td><td>0.19 ± 0.04*</td><td>0.16 ± 0.04</td></tr>
<tr><td>FEF 25-75% (L/sec)</td><td>0.04 ± 0.07</td><td>0.21± 0.07</td><td>0.28 ± 0.07*</td><td>0.25 ± 0.07*</td></tr>
<tr><td>FVC (L)</td><td>0.03 ± 0.05</td><td>0.08 ± 0.06</td><td>0.11 ± 0.05</td><td>0.08 ± 0.05</td></tr>
<tr><td>PEFRam (L/min)</td><td>15 ± 5</td><td>29 ± 6*</td><td>30± 5*</td><td>32 ± 5*</td></tr>
<tr><td>am sx score</td><td colspan="4">all treatments reduced symptoms (NS between treatments except FP better than MF100, MF200 for difficulty breathing domain)</td></tr>
<tr><td>nocturnal awakening (number)</td><td>0.07</td><td>0.01</td><td>-0.06</td><td>-0.14*</td></tr>
<tr><td>prn albuterol (mcg/day)</td><td>-13.23</td><td>-94.84*</td><td>-38.10</td><td>-52.06</td></tr>
<tr><td>physician evaluation</td><td colspan="4">MF200, MF400, and FP significantly more improvement than MF100</td></tr>
</table>
Mean ± SEM
</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td>*significant vs. MF100</td></tr>
<tr><td>Corren 2003
R, DB, DD, PC, PR
mometasone vs. budesonide vs. placebo
8-weeks
n=262

ITT

Study site(s)
USA</td><td>Moderate persistent asthma ≥ 6 months
Daily tx with ICS ≥ 30 days days w/i predefined dosage ranges*
≥ 12 y/o
FEV1 50-85% predicted
FEV1 reversibility > 12% or 200ml
Nonsmoker for at least the past 6 months prior to study

*BDP 252-840mcg, BUD 400-800mcg, FP 200-500mcg, TCA 600-1600mcg, FLU 1000-2000mcg
See exclusion criteria listed in footnote plus the following:

Use of leukotriene modifiers 2 weeks prior to screening</td><td>2:2:1 randomization

MF 400mcg q am
BUD 400mcg q am
Placebo

rescue inhaler and prior theophylline allowed</td><td>Values for MF/BUD/placebo
Age (years): 37 ± 14 / 39 ± 17 / 37± 13
% male: 29 / 43 / 39
Duration of asthma (years): 19 ± 15 / 20 ± 15 / 20 ± 13
FEV1 (L): 2.33 ± 0.06 / 2.48 ± 0.06/ 2.50 ± 0.08
FEV1 % pred: 71.6 ± 0.9 / 73.4 ± 0.9 / 75.1 ± 1.3

Mean ICS dose:
BDP 328mcg(n=69)
BUD 664mcg (n=22)
FLU 1136mcg (n=22)
FP 338mcg (n=97)
TCA 696mcg (n=52)

mean ± SD for age/duration asthma
mean ± SEM for FEV1</td><td>
<table>
<tr><th></th><th>MF</th><th>BUD</th><th>Placebo</th></tr>
<tr><td>d/c due to LOE</td><td>6%</td><td>10%</td><td>35%</td></tr>
<tr><td>FEV1 (L)</td><td>0.19 ± 0.04*^</td><td>0.03 ±0.04</td><td>-0.10 ± 0.06</td></tr>
<tr><td>FEV1 (% change)</td><td>8.9 ± 1.8*^</td><td>2.1 ± 1.18</td><td>-3.9 ± 2.6</td></tr>
<tr><td>FEF 25%-75% (L/sec)</td><td>0.24 ± 0.06*^</td><td>-0.03 ± 0.06</td><td>-0.15 ± 0.09</td></tr>
<tr><td>FVC (L)</td><td>0.19 ± 0.05*</td><td>0.09 ± 0.05</td><td>-0.06 ± 0.07</td></tr>
<tr><td>PEFRam (% change)</td><td>19.96 ± 4.15*^</td><td>0.54 ± 4.08</td><td>-11.0 ± 5.97</td></tr>
<tr><td>PEFRpm (% change)</td><td>19.04 ± 4.19*^</td><td>4.93 ± 4.13*</td><td>-9.46 ± 6.03</td></tr>
<tr><td>am sx score</td><td>-0.42 ± 0.12*^</td><td>-0.12 ± 0.11</td><td>0.16 ± 0.17</td></tr>
<tr><td>pm sx score</td><td>-0.46 ± 0.12*^</td><td>-0.11 ± 0.12</td><td>0.24 ± 0.17</td></tr>
<tr><td>prn albuterol (inhal/day)</td><td>-0.91 ± 0.23*^</td><td>-0.21 ± 0.23*</td><td>1.09 ± 0.34</td></tr>
<tr><td>% sx-free days (8wks)</td><td>39.7 ± 3.4*^</td><td>26.8 ± 3.3</td><td>26.5 ± 0.17</td></tr>
<tr><td>nocturnal awakenings</td><td colspan="3">both active txs decreased more than placebo, but differences were not significant</td></tr>
<tr><td>physician evaluation</td><td colspan="3">both active treatments significantly better than placebo</td></tr>
</table>
Mean ± SEM
*significant vs. placebo
^significant vs. BUD</td></tr>
<tr><td>Bousquet 2000
R, evaluator-blind, PR
mometasone vs. budesonide
12-weeks
n=730

ITT

Study site(s)
S. America, S. Africa, Australia, Europe, U.K., Mexico</td><td>Asthma ≥ 6 months
Daily tx with ICS ≥ 30 days
≥ 12 y/o
FEV1 60-90% predicted
FEV1 reversibility > 12% or 200ml
nonsmoker or stopped smoking for ≥ 6months
See exclusion criteria listed in footnote plus the following:

Respiratory tract infection 2 weeks prior to screening
> 12 puffs of albuterol on any 2 consecutive days between screening and baseline</td><td>1:1:1:1 randomization

MF 100mcg bid
MF 200mcg bid
MF 400mcg bid
BUD 400mcg bid

rescue inhaler and prior theophylline allowed

allergen specific immunotherapy allowed if on stable dose</td><td>Values for MF 100 / MF 200/ MF 400/ BUD
Age (years): 39 / 42 / 41 / 42
% male: 43 /46 / 40 / 43
Duration of asthma (years): 16 / 17 / 15 / 15
FEV1 % pred: 76.2 ± 0.7 / 77.1 ± 0.8 / 77.9 ± 0.7 / 76 ± 0.7
FEV1 (L): 2.48 / 2.52 / 2.54 / 2.47
% never smoked: 66 / 73 / 70 / 70
% no smoking in last 6mos: 33/ 26/ 30/ 29

ICS dose (range of means):
BDP 679-736mcg (n=373)
BUD 645-688mcg (n=262)</td><td>
<table>
<tr><th></th><th>MF100</th><th>MF200</th><th>MF400</th><th>BUD</th></tr>
<tr><td>all d/c</td><td>15%</td><td>10%</td><td>18%</td><td>14%</td></tr>
<tr><td>d/c due to tx failure</td><td>5%</td><td>3%</td><td>6%</td><td>3%</td></tr>
<tr><td>FEV1 (L)</td><td>0.1 ± 0.03</td><td>0.16 ± 0.03*</td><td>0.16 ± 0.03*</td><td>0.06 ± 0.03</td></tr>
<tr><td>FVC (L)</td><td>0.07 ± 0.04</td><td>0.16 ± 0.04</td><td>0.15 ± 0.04</td><td>0.06 ± 0.04</td></tr>
<tr><td>PEFRam (L/min)</td><td>18.2 ± 5.3</td><td>37.8 ± 5.4^</td><td>37.3 ± 5.2^</td><td>24.7 ± 5.3</td></tr>
<tr><td>am sx</td><td colspan="4">symptoms improved in all groups, but significance was seen only with MF400 for wheezing*^ and difficulty breathing^ domains</td></tr>
<tr><td>nocturnal</td><td>-0.06</td><td>-0.09</td><td>-0.16</td><td>-0.07</td></tr>
</table>
</td></tr>
</table>

	Hospitalized for asthma ≥ 1 in past 6months Use of a LABA 2 weeks prior to screening		FLU 625- 760mcg (n=14) FP 422-452mcg (n=83) TCA 200-550mcg (n=7)	awakening (number) prn albuterol (mcg/day): -45.86 / -99.66* / -72.13 / -33.90 Physician evaluation: MF200, and MF400 significantly more improvement than BUD Mean ± SEM *significant vs. budesonide ^significant vs. MF 100
Nathan 2001 R, DB, DD, PC, PR mometasone vs. beclomethasone vs. placebo 12-weeks n=225 ITT Study site(s) USA	Asthma ≥ 6 months Daily tx with ICS ≥ 30 days ≥ 12 y/o FEV1 60-90% predicted FEV1 reversibility > 12% or 200ml Nonsmoker for at least the past 6 months prior to study See Exclusion criteria listed in footnote	1:1:1:1 randomization MF 100mcg bid MF 200mcg bid BDP 168mcg bid Placebo	Values for MF 100 / MF 200/ BDP/ Placebo Age (years): 40/ 40/ 40/ 42 % male: 42 /34 / 30 / 32 Duration of asthma (years): 16 / 17 / 15 / 15 FEV1 % pred: 76 / 78/ 76/ 75 **ICS dose (range of means):** BDP 300-323mcg (n=67) FLU 1000-1260mcg (n=32) FP 333-393mcg (n=52) TCA 617-800mcg (n=76)	**MF100 / MF200 / BDP / Placebo** d/c due to LOE: 9% / 4% / 11% / 44% FEV1 (L): 0.12 ± 0.05* / 0.25 ± 0.06* / 0.11 ± 0.05* / -0.21 ± 0.05 PEFRam: 26.7 ± 7.5* / 37.4 ± 7.7* / 19.3 ± 7.5* / -21.4 ± 7.4 FEF 25-75% (L/sec): 0.15 ± 0.08* / 0.28 ± 0.09* / 0.08 ± 0.08* / -0.22 ± 0.08 FVC (L): 0.16 ± 0.06* / 0.27 ± 0.06* / 0.17 ± 0.06* / -0.22 ± 0.06 am sx score: All active treatments significantly better than placebo for wheezing and difficulty breathing domain. Both MF groups significantly better than placebo for the cough domain prn albuterol (puffs/d): -1.18 ± 0.39* / -0.94 ± 0.39* / -1.05 ± 0.39* / 1.31 ± 0.38 nocturnal awakening (per night): -0.09 ± 0.13 / -0.18 ± 0.13 / 0.06 ± 0.13 / 0.09 ± 0.13 physician evaluation: All active treatments significantly better than placebo Mean ± SEM *Significant vs. placebo
Bernstein 1999 R, DB, DD, PC, PR 12-weeks n=365 ITT? Study site(s) USA	Asthma ≥ 6 months Age ≥ 12 years Daily ICS use for at least the previous 30 days FEV1 60-90% predicted FEV1 reversibility 12% or 200mL Non-smoker or stopped smoking ≥ 6months prior to screening	1:1:1:1:1:1 randomization Mometasone 100mcg bid Mometasone 200mcg bid Mometasone 400mcg bid Beclomethasone 168mcg bid Placebo PRN albuterol allowed. Not mentioned if other asthma meds	Values for MF100/ MF200/MF400/ BDP/ Placebo **Age (years):** 38/ 36/ 37/ 37/ 37 **% Male:** 54/ 66/ 64/ 66/ 61 **Duration of asthma (years):** 21/18/ 16/ 18/ 18 **FEV1 % predicted:** 74/ 76/ 77/ 78/ 74 **FEV1 (L):** 2.61/ 2.67/ 2.49/ 2.62/ 2.48	**MF100 / MF200 / MF400 / BDP / Placebo** All d/c d/c due to LOE: 7-8% / 38% FEV1 (% change): 4.8* / 7.1* / 6.2* / 3.0* / -6.6 FEF 25-75% (% change): 6.2* / 18.8* / 15.2* / 7.5* / -9.5 FVC (% change): 4.7* / 3.3* / 3.5* / 2.0* / -4.7

	See exclusion criteria listed in footnote plus the following: Respiratory tract infection 2 weeks prior to screening > 12 puffs of albuterol on any 2 consecutive days between screening and baseline	were allowed allergen specific immunotherapy allowed if on stable dose	<u>ICS use mean dose (n)</u> Beclomethasone 335.2mcg (n=133) Flunisolide 1123.4mcg (n=39) Fluticasone 435.2mcg (n=39) Triamcinolone 761.4mcg (n=154	PEFRam (% change)	4.6*	9.9*	9.3*	5.7*	-7.0
				PEFRpm (% change)	3.8*	9.3*	6.4*	3.1*	-3.9
				Am sx score	All active treatments significantly improved vs. placebo for all 3 domains				
				Nocturnal awakening (n)	-0.02*	-0.08*	-0.12*	0.00*	0.31
				% Prn albuterol/day	22	-21.4*	-2.3*	-21.4*	25.3
				physician evaluation	All active treatments significantly better than placebo				
				*Significant vs. placebo					

Hospitalization for asthma in the past 3 months; requirement of ventilatory support for asthma in the last 5 years; oral corticosteroids for > 14 days in the past 6 months prior to screening (not listed as an exclusion in Nathan et al.); respiratory disease other than asthma; clinically significant oropharyngeal candidiasis (not listed as an exclusion in Corren et al.); free of any other clinically significant diseases; use of methotrexate, cyclosporin, gold, or other immunotherapy in the past 3 months (not listed as exclusions in Wardlaw et al and Nathan et al.); ER treatment for asthma twice in the previous 6 months (not listed as an exclusion in Wardlaw et al. and Bernstein et al.); regularly uses nebulized beta-2-agonists (not listed as an exclusion in Wardlaw et a.); required systemic corticosteroid one month prior to screening (not listed as an exclusion in Nathan et al.)

Appendix 3: Results of HPA-axis testing in subjects with asthma

Study	Dur	Dose	Cortisol AUC	Urinary free cortisol	8am cortisol	Cosyntropin stim-test
Affrime Study 1 12 pts. per arm DPI	28-days	MF 400mcg q AM MF 200mcg bid MF 800mcg q AM MF 1200mcg q AM Placebo	There was no significant difference in $AUC_{0\text{-}18h}$ between mometasone and placebo except for MF 400 q AM group where AUC was 18% lower than placebo on day 28	No significant difference in urinary free cortisol compared to placebo. Baseline values ranged from 17-30mcg/24h and values during tx from 10-34mcg/24h	No significant treatment effects. All patients had values within the normal range (data not shown)	• Baseline cortisol value > 10mcg/dL in all but 1 patient (in placebo group with value of 9mcg/dL) • All patients had 30-minute post-stimulation serum cortisol > 18mcg/dL • All had pre- to post-stimulation > 7mg/dL
Study 2 16 pts. per arm DPI	28-days	MF 400mcg bid MF 800mcg bid Prednisone 10mg daily Placebo	Compared to placebo, the 24-h AUC was 10-25%, 21-40%, and 64-72% lower for the 400mcg, 800mcg and prednisone groups respectively (sig vs. placebo)	Not done	Not shown	Mean post-cosyntropin serum cortisol values were 23, 21, 14.5 and 25mcg/dL for MF 400, 800, prednisone, and placebo respectively. 14, 11, 1, 15 pts. in MF 400, MF 800, prednisone, and placebo groups respectively had a post-cosyntropin cortisol value > 18mcg/dL
Study 3 16 pts. arm MDI	28-days	MF 400mcg bid MF 800mcg bid FP 880mcg bid Placebo	Compared to placebo, the 24-h AUC was 20-30% and 43-56% lower for the MF800 and FP880 groups respectively (sig. vs. placebo). There was no sig difference between MF 400 and placebo.	Not done	Not shown	All patients had a normal response to cosyntropin stimulation following the last treatment dose (results not shown)
Chrousos n=55	14-days	MF-DPI 400mcg qam BDP-HFA 200mcg bid BDP-CFC 400mcg bid	24-h AUC (median % change and range) MF: -9% (-34 to 25%) BDP-HFA: -23% (-204 to 17%) BDP-CFC: -24% (-87 to 29%) Change in 24-h AUC (nmol/L/24h) mean ± SD MF: -210 ± 484 BDP-HFA : -767 ± 627 BDP-CFC : -875 ± 948	24-h UFC (nmol/L/24h) mean and % change MF: -8.2 (9.6%) BDP-HFA: -27.9 (34.3%) BDP-CFC: -18 (33.4%)	Not done	Not done
Fardon n=24 crossover study	6-weeks per arm (1-week washout period)	MF 200mcg bid x 2 weeks then 400mcg bid x2 weeks then 800mcg bid x 2 weeks FP-DPI 250mcg bid x 2 weeks then 500mcg bid		10-h overnight urinary cortisol Geometric mean fold difference from baseline FP 500/ 1000/ 2000 : 1.18/ 1.54*/ 1.98*	8am urinary cortisol/creatinine Geometric mean fold difference from baseline FP 500/ 1000/ 2000 : 0.95/	Not done

<table>
<tr><td></td><td></td><td>x 2 weeks then
1000mcg bid x 2 weeks</td><td></td><td>MF 400/ 800/ 1600: 1.22/ 1.48*/ 2.09*

* significant vs. baseline</td><td>1.23/ 1.85*

MF 400/ 800/ 1600: 1.26/ 1.16/ 1.8*

* significant vs. baseline</td><td></td></tr>
<tr><td>Noonan (n=113; 20-24 patients per group)</td><td>12-weeks</td><td>MF 200mcg q am
MF 200mcg q pm
MF 400mcg q am
MF 200mcg bid
Placebo</td><td>Not done</td><td>Not done</td><td>Not done</td><td>No significant difference in mean pre- and post-stimulation cortisol levels between baseline and week 12
<u>Cosyntropin stim test at week 12</u>
• mean pre-stimulation serum cortisol > 5mcg/dL in all patients
• 30-minute post-stimulation serum cortisol > 18mcg/dL in all but 1 patient in the mometasone 200mcg q PM group
• Pre- to post-stimulation > 7mg/dL in all but 8 patients: 1(mometasone 200mcg q PM, 4 mometasone 400mcg q AM, 2 mometasone 200mcg BID, 1 placebo)</td></tr>
<tr><td>Bernstein (n=98; 18-20 patients per group)</td><td>12-weeks</td><td>MF 100mcg bid
MF 200mcg bid
MF 400mcg bid
BDP 168mcg bid
Placebo</td><td>Not done</td><td>Not done</td><td>Not done</td><td>No significant difference in mean pre- and post-stimulation cortisol levels between baseline and week 12
<u>Cosyntropin stim test at week 12 (individual patient values not shown)</u>
• Mean pre-stimulation serum cortisol > 5mcg/dL
• Mean 30-minute post-stimulation serum cortisol > 18mcg/dL
• Mean pre- to post-stimulation > 7mg/dL</td></tr>
<tr><td>Bousquet (all patients)</td><td>12-weeks</td><td>MF100mcg bid
MF 200mcg bid
MF 400mcg bid
BUD 400mcg bid</td><td></td><td></td><td>At week 12, there was a 3%, 5%, 2, % and 9% increase in the mean 8am cortisol for MF 100, 200, 400, and BUD groups respectively, compared to baseline. There were no significant differences among treatment groups when compared at screening or week 12.</td><td>Not done</td></tr>
<tr><td>Data on file (Schering) n=239</td><td>52-weeks</td><td>MF 200mcg bid
MF 400mcg bid
MF 800mcg once daily
BDP-MDI 168mcg bid</td><td>Not done</td><td>Not done</td><td></td><td>Mean Plasma cortisol (mcg/dL)
<table>
<tr><th>Cosyntropin</th><th>MF 200 bid</th><th>MF 400 bid</th><th>MF 800 qd</th><th>BDP 168 bid</th></tr>
<tr><td colspan="5">Screening</td></tr>
<tr><td>pre</td><td>13.04</td><td>13.55</td><td>16.11</td><td>15.31</td></tr>
<tr><td>post</td><td>28.01</td><td>28.25</td><td>27.94</td><td>28.97</td></tr>
<tr><td colspan="5">Week- 52</td></tr>
<tr><td>pre</td><td>12.81</td><td>12.97</td><td>14.37</td><td>15.27</td></tr>
<tr><td>post</td><td>26.35</td><td>25.15</td><td>25.93</td><td>30.77</td></tr>
</table>
changes not significant</td></tr>
</table>