

## National PBM Drug Monograph Ciclesonide (Alvesco®)

### VHA Pharmacy Benefits Management Services and Medical Advisory Panel

*The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

#### EXECUTIVE SUMMARY

- Ciclesonide (CIC) is an orally inhaled corticosteroid (ICS) delivered via hydrofluoroalkane pressurized metered dose inhaler (HFA pMDI). Ciclesonide is a pro-drug that is converted to its active form desisobutyryl-ciclesonide (des-CIC) via esterases in the lung. It is approved for prophylactic maintenance therapy of asthma in patients  $\geq 12$  years of age.
- Like mometasone and fluticasone, the oral bioavailability of CIC is  $<1\%$ . The relative clinical potency of CIC is probably similar to fluticasone, mometasone, and beclomethasone HFA.
- Ciclesonide is available in 2 strengths (80mcg/actuation and 160mcg/actuation) and is administered twice daily.
- There are 5 trials in adults comparing CIC twice daily to either beclomethasone (BDP) or fluticasone (FTC) that range from 8-52 weeks duration. At equipotent doses, CIC was generally comparable to BDP and FTC for improvement in pulmonary function, asthma symptoms, and rescue beta-agonist use. The need for oral steroids for asthma exacerbation was similar between CIC and FTC. There are no comparative studies evaluating hospitalizations/ER visits or other healthcare utilization due to asthma exacerbations.
- The most commonly reported adverse effects were headache, nasopharyngitis, sinusitis, pharyngolaryngeal pain, and upper respiratory tract infection.
- Because ciclesonide is activated in the lung, it is theorized that local adverse events that occur in the mouth and throat (e.g., oral candidiasis, hoarseness) may be reduced. Routine safety monitoring in clinical trials show a lower incidence of local adverse events with twice daily CIC compared to twice daily FTC or BDP. Studies that systematically evaluate local adverse effects need to be conducted to see if CIC offers an advantage over other ICSs.

#### INTRODUCTION

Ciclesonide is the 7<sup>th</sup> orally inhaled corticosteroid (ICS) to join beclomethasone, budesonide, flunisolide, fluticasone, mometasone, and triamcinolone. Ciclesonide is available as a hydrofluoroalkane pressurized metered dose inhaler (HFA pMDI). Ciclesonide is a pro-drug that is converted to its active form desisobutyryl-ciclesonide (des-CIC) via esterases in the lung. Beclomethasone is another ICS that is a pro-drug requiring conversion into its active form. The relative clinical potency of ciclesonide is probably similar to fluticasone, mometasone, and beclomethasone HFA. Ciclesonide, like beclomethasone, is a solution that is delivered via metered dose inhaler (MDI) as an extra fine aerosol containing a smaller particle size ( $<2\mu\text{m}$ ) than drugs in suspension or dry powder. Drugs with smaller particle size are more likely to be deposited in the lung and less likely to be deposited in the oropharyngeal cavity.

This review is limited to trials conducted in adults and adolescents.

#### FDA INDICATIONS

Ciclesonide is indicated for prophylactic maintenance therapy of asthma in patients  $\geq 12$  years of age. There are no trials at this time evaluating ciclesonide in patients with COPD (personal communication Sepracor).

## VA FORMULARY ALTERNATIVES

Mometasone dry powder inhaler and flunisolide metered dose inhaler.

## DOSAGE FORM AND STRENGTHS

Ciclesonide is available in a HFA metered dose inhaler in 2 strengths (80mcg/actuation and 160mcg/actuation). Each canister provided 60 actuations.

A dose indicator window displays the number of doses remaining. Ciclesonide should be primed by actuating the inhaler 3 times prior to using for the first time or when the inhaler has not been used for more than 10 days.

## DOSAGE AND ADMINISTRATION

- For patients who received bronchodilators alone, the recommended starting dose is 80mcg twice daily (maximum dose 160mcg twice daily).
- For patients who received an ICS, the recommended starting dose is 80mcg twice daily (maximum 320mcg twice daily).
- For patients who received oral steroids, the recommended starting dose (also the maximum dose) is 320mcg twice daily. Prednisone may be tapered by no faster than 2.5mg/day on a weekly basis, beginning after at least 1 week of ciclesonide therapy. Monitor patient's asthma control, which should include objective measurements of airflow. Patients should also be monitored for signs of adrenal insufficiency.
- Shaking canister prior to use is not necessary

## PHARMACOKINETICS

Ciclesonide is a pro-drug and is converted to des-CIC via esterases in the lung. Des-CIC is a substrate of CYP3A4. Ketoconazole, a strong inhibitor of CYP3A4 can increase des-CIC by approximately four-fold. Des-CIC does not induce or inhibit CYP enzymes.<sup>1,2</sup>

**Table 1: Pharmacokinetic Properties**

<b>t<sub>1/2</sub> (h)</b>	<b>Lung Deposition</b>	<b>Oral Bioavailability</b>	<b>Protein Binding</b>	<b>Active Metabolite</b>	<b>Metabolism</b>	<b>Excretion</b>
3.4	52%	<1%	99%	Des-CIC	Liver primarily via CYP3A4	66% feces

## EFFICACY IN ASTHMA

A 2008 Cochrane review showed that ciclesonide improved lung function, asthma symptoms and rescue inhaler use compared to placebo in patients with mild-moderate asthma.<sup>3</sup>

Ciclesonide has been compared to budesonide, fluticasone, and beclomethasone in head-to-head clinical trials (appendix 1 and 2). In many of these trials, ciclesonide was administered once daily.<sup>11-17</sup> However, trials submitted to the FDA showed that once daily dosing is less optimal than twice daily dosing. The approved frequency of administration for ciclesonide is twice daily; therefore, the focus of this review will be on twice daily administration.<sup>4-6</sup> Results of the once daily administration comparative studies are shown in appendix 2 for reference purposes only.

There are 5 trials comparing ciclesonide twice daily to either beclomethasone or fluticasone. Two of these were 1-year trials whose primary outcome was safety; however, pulmonary function was also assessed. Current use of ICS was a requirement for study eligibility. Baseline FEV1 was variable with means ranging from 54-93% predicted.

An 8-week open label study conducted in Japanese patients (n=319) compared CIC 320mcg once daily, CIC320mcg twice daily and BDP-CFC 400mcg twice daily.<sup>4</sup> Use of a spacer was required for the group receiving BDP and not for the CIC groups. Change in peak flow, need for rescue meds, and symptoms were significantly better with CIC 320mcg twice daily than BDP. It is not clear if equipotent doses of CIC and BDP were used. For example, the GINA asthma guidelines list BDP-CFC 500-1000mcg (equiv. to 240-480mcg BDP-HFA) to be

equipotent to 160-320mcg of CIC. Another comparison shows BDP-HFA 240-480mcg to be comparable to CIC 320-640mcg.

In a 6-month randomized, open-label study conducted in the US (n=528), Bateman found no significant difference between CIC 320mcg twice daily and FTC 330mcg twice daily for pulmonary function, exacerbations requiring oral steroids, peak flow, asthma symptoms, use of rescue meds, discontinuation rates, and asthma quality of life.<sup>5</sup>

In a 12-week unpublished, double-blind study conducted in the US, CIC 160mcg, CIC 320mcg and FTC 440mcg (all given twice daily) were compared (n=531).<sup>6</sup> The analysis compared the active agents versus placebo; comparisons between active agents were not described in the report. Improvement in pulmonary function, rescue medication use, asthma symptoms, and quality of life were numerically greater with FTC.

Two unpublished 1-year trials found no difference in pulmonary function between CIC 320mcg and BDP 320mcg both given twice daily via HFA pMDI (secondary outcome).<sup>6</sup>

***Exacerbations***

Only 1 head-to-head trial evaluated exacerbations. In the 6-month trial by Bateman, asthma exacerbation was defined as worsening asthma symptoms or a reduction in lung function requiring treatment with oral steroids. Six patients in the CIC group and 7 in the FTC group required oral steroids for treatment of exacerbation.<sup>5</sup>

There are no comparative studies evaluating hospitalizations/ER visits or other healthcare utilization due to asthma exacerbations.

**SAFETY**

Table 2 shows adverse event rates compiled from 6 placebo controlled trials. Patients were previously using either controller therapy (mainly ICS) or bronchodilator therapy alone. The mean age of patients was 39.1 years. Table 3 shows adverse events reported in the head-to-head trials.<sup>1</sup>

**Table 2: Adverse Events in Adults and Adolescents with ≥ 3% Incidence**

	CIC 80mcg BID	CIC 160mcg BID	CIC 320mcg BID	Placebo
n	325	127	172	507
≥ 1 adverse event (%)	52.3	59.8	54.1	58
Headache (%)	4.9	11	8.7	7.3
Nasopharyngitis (%)	10.5	8.7	7.0	7.5
Sinusitis (%)	3.1	5.5	5.2	3.0
Pharyngolaryngeal pain (%)	4.3	2.4	4.7	4.3
Upper respiratory tract infection (%)	7.1	8.7	4.1	6.5
Arthralgia (%)	0.9	2.4	3.5	1.0
Nasal Congestion (%)	1.8	5.5	2.9	1.6
Pain in extremity (%)	0.3	3.1	2.3	1.0
Back pain (%)	0.6	3.1	1.2	2.0

Data obtained from product package insert

**Table 3: Adverse Events from Head-to-Head Trials Using Twice Daily Dosing of Ciclesonide<sup>4-6</sup>**

	Adachi		Bateman		Study 323/324				Study 323/324LT		Study 3027	
	CIC 320	BDP 400*	CIC 320	FTC 330	CIC 160	CIC 320	FTC 440*	PBO	CIC 320	BDP 320	CIC 320	BDP 320
Duration of study	8 weeks		6 months		12 weeks				1 year		1 year	
TEAE (%)	67.3	56.6	61.2	63	61.4	54.6	60.1	61.8	74.1	79.2	83.5	85.6
Nasopharyngitis (%)	37.4	35.9	11.8	8.8	10.2	6.9	10.9	7.4	14.2	19.8	20.9	17.5
Upper respiratory tract infection (%)	7.5	6.6	8.2	7.3	NR	NR	NR	NR	11.2	17.7	19.5	19.1
Pharyngitis (%)	3.7	3.8	4.3	4.4	4.7	3.1	5.1	2.9	0.5	0	NR	NR
Headache (%)	5.6	1.9	2.4	4.4	NR	NR	NR	NR	9.6	15.6	>10%	>10%
Dysphonia (%)	2.8	< 1.0	3.1	9.2	0	1.5	3.6	0.7	2.5	1.0	NR	NR
Oral candidiasis (%)	0	0	2.0	4.8	1.6	0	11.6	2.2	4.1	10.4	NR	NR

All drugs administered twice daily

Delivery device for all agents was HFA pMDI except where asterisked (\*), the CFC pMDI was used

BDP=beclomethasone; CIC=ciclesonide; FTC=fluticasone; NR=not reported; PBO=placebo; TEAE=treatment emergent adverse event

### Adrenal Suppression

Several studies published either as abstracts or using once daily dosing of CIC showed negligible HPA-axis suppression.<sup>2</sup> Data from published studies using twice daily dosing are discussed. Although data from the 1-year extension study is not published, it is included because it is a longer term evaluation.

The effect of CIC, FTC, and placebo on hypothalamic-pituitary-adrenal-axis (HPA-axis) function was determined in a 4-week randomized, double-blind study in patients with moderate-severe asthma (n=59).<sup>8</sup> Doses of CIC (HFA) 320 and 640mcg were compared to FTC (CFC) 440 and 880mcg all given twice daily. Cortisol AUC<sub>0-24h</sub> was significantly reduced only with FTC 880mcg bid compared to placebo and the other treatments. There was no difference between treatments for the cosyntropin test. None of the drugs significantly decreased 24-h urinary cortisol levels from baseline compared to placebo. There was a significant increase in urinary cortisol with CIC 640mcg group.

In a 12-week study, HPA-axis function was also evaluated for CIC 320mcg once daily, CIC 320mcg twice daily, and FTC (CFC) 440mcg twice daily (n=164).<sup>9</sup> There was no significant difference in the low-dose and high-dose cosyntropin stimulation between placebo and either dose of CIC whereas the decrease in cortisol levels was significantly lower with FTC than placebo. These changes were seen by week 6 and persisted through the remainder of the study. For 24-h urinary free cortisol, only the FTC had a significant change versus placebo (mean decrease 60.8% vs. 19.8%).

In a 1-year extension study (n=297) comparing twice daily dosing of CIC160 or 320mcg and BDP 160 or 320mcg, there was no clinically meaningful adverse effect on HPA-axis as measured by serum and urinary free cortisol. (Study 323/324LT)<sup>6</sup>

### Glaucoma and cataracts

An ophthalmology exam was performed in a 1-year study (Study 3027) in patients with asthma receiving CIC 320mcg twice daily (n=743) and BDP-HFA 320mcg twice daily (n=742).<sup>6</sup> The exam included tests for visual acuity, intraocular pressure and slit lamp examination. The Lens Opacification System III was used to grade lens opacities. Minimally detected changes (class 1) were noted in 36.1% and 38.4% of CIC and BDP patients respectively. Class III effects were noted in 8.1% of CIC patients and 9.2% of BDP patients. Among those with Class III effects, the incidence of sub-capsular opacities was 0.5% and 0.9% for CIC and BDP respectively.

In the 1-year extension study (Study 323/324LT) 3% of CIC patients and 2.1% of BDP patients, and 1 patient receiving both drugs who had normal lenses at baseline developed lenticular opacities. Glaucoma was reported in 2 CIC patients and none in the BDP group. Both groups received 320mcg twice daily with the option to titrate down to 160mcg twice daily if appropriate.<sup>6</sup>

### Oral Candidiasis

Because ciclesonide is activated in the lung, it is theorized that local adverse events that occur in the mouth and throat (e.g., oral candidiasis, hoarseness) may be reduced. A recent Cochrane review found that oral candidiasis

was reduced by 75% (relative risk 0.24, 95% CI 0.1 to 0.58) when ciclesonide and fluticasone were compared at a dose ratio of 1:1; however, the authors state that the methods used to obtain results may overestimate the effect of ciclesonide. They recommend that oral candidiasis be assessed in a systematic way using fungal throat cultures.<sup>7</sup>

In Bateman et al., culture confirmation was required for a diagnosis of oral candidiasis. Oral candidiasis occurred in 2.0% and 4.8% of CIC 320mcg and FTC (HFA) 330mcg twice daily groups respectively. The remaining head-to-head twice daily trials did not describe the method used to diagnosis oral candidiasis (table 3).<sup>5</sup>

Bone Density

There are no studies evaluating bone density or fracture at this time (personal communication Sepracor).

**LOOK-ALIKE/SOUND-ALIKE (LA/SA) ERROR RISK POTENTIAL**

For the generic name ciclesonide and the brand name Alvesco, Lexi-Drugs Online identified no other drugs as having a LA/SA error risk potential.<sup>10</sup>

**COMPARATIVE COST OF ORALLY INHALED STEROIDS**

**Table 4: Cost of Orally Inhaled Steroids**

	Strength (mcg/puff)	Delivery	Usual Dose*	Number of Doses	Cost
Ciclesonide	80, 160	pMDI (HFA)	1 inhalation BID	60 puffs/canister 30 doses/inhaler (110mcg strength)	\$97.31 (both strengths)
Mometasone	110, 220	DPI	1-2 inhalations QD or 1 inhalation BID	30, 60, 120 doses/inhaler (220mcg strength)	\$18.64 (for 30's and 60's) \$28.88 (for 120's)
Flunisolide	250	pMDI (CFC)	2 inhalations BID	100 puffs/canister	\$15.08
Fluticasone	50, 100, 250	DPI	1 inhalation BID	60 doses/inhaler	\$56.70 (for 50mcg) \$62.17 (for 100mcg) \$83.24 (for 250mcg)
	44, 110, 220	pMDI (HFA)	2 inhalations BID	120 puffs/canister	\$58.50 (for 44mcg) \$78.84 (for 110mcg) \$121.79 (for 220mcg)
Beclomethasone	40, 80	pMDI (HFA)	1-2 inhalations BID	100 puffs/canister 60 doses/inhaler (90mcg strength only)	\$42.05 (for 40mcg) \$53.08 (for 80mcg) \$57.32
Budesonide	90, 180	DPI	2 inhalations BID	120 doses/inhaler (180mcg strength only)	\$77.27
Triamcinolone	100	pMDI (CFC)	2 inhalations TID-QID or 4 inhalations BID	240 puffs/canister	\$44.77

BID=twice daily, CFC=DPI=dry powder inhaler, HFA=hydrofluoroalkane, pMDI=pressurized metered dose inhaler, TID=three times daily

\*Doses shown do not necessarily reflect highest dose that can be given

Prices current as of 4/28/09

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VHA PBM Services Contact Person: Deb Khachikian, PharmD

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### Once Daily Studies

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### Appendix 1: Head-to-Head Trials of Ciclesonide Administered Twice Daily

Study	Inclusion/Exclusion Criteria	Dosage/Administration	Demographics/Baseline Values	Results																																				
				CIC 320 QD	CIC 320 BID	BDP 400 BID																																		
<p>Adachi 2007 R, OL</p> <p>Conducted in Japan</p> <p>Non-inferiority ITT analysis</p> <p>8 weeks</p> <p>N=319</p>	<p><b>Inclusions</b> Moderate-severe asthma 16-75 years old ICS use with ≥ 800mcg/d BDP-CFC or ≥ 400mcg/d FTC for ≥ 4 weeks PEFam during last week of baseline period of ≤ 80% predicted FEV1 reversibility ≥ 15%</p> <p><b>Exclusions</b> Hospitalization or ER visit for asthma or treatment with systemic steroids within 4 weeks of baseline</p>	<p>CIC 320mcg QDpm (n=106) CIC 320mcg BID (n=107) BDP 400mcg BID (n=106) this is ex-valve, find out ex-actuator</p> <p>CIC was administered via HFA pMDI And BDP as CFC pMDI</p> <p>Use of a spacer was required for the BDP group only</p> <p>As needed albuterol allowed; unclear if other baseline non-ICS meds were allowed</p>	<p>Values for CIC QD; CIC BID; BDP respectively</p> <p><b>% male:</b> 52.8; 45.8; 59.4 <b>Age (years):</b> 52.2±15.3; 52.4±14.4; 51.6±15.9 <b>Predicted PEF (L/min):</b> 492.7±116.5; 478.1±106.7; 510.2±118 <b>PEFam (% of predicted):</b> 60.6±12.2; 60.4±12.2; 60.5±13 <b>PEFam (L/min):</b> 299.7±100.1; 285.5±77; 306.1±90 <b>Moderate asthma (%):</b> 93.4; 93.5; 94.3 <b>Rescue SABA use (times/d):</b> 0.96±1.53; 1.31±2.91; 1.13±2.76 <b>FEV1 % predicted:</b> 70.5 ±14.6; 67.3±14.5; 69±14.4</p>	<table border="1"> <thead> <tr> <th></th> <th>CIC 320 QD</th> <th>CIC 320 BID</th> <th>BDP 400 BID</th> </tr> </thead> <tbody> <tr> <td>D/C treatment</td> <td>NR</td> <td>NR</td> <td>NR</td> </tr> <tr> <td>Change PEFam (L/min)*</td> <td>16.02± 3.78</td> <td>23.98± 3.74</td> <td>5.91 ± 3.75</td> </tr> <tr> <td>Change in PEFpm (L/min)</td> <td>9.17±3.68</td> <td>18.69±3.67¶</td> <td>5.37±3.68</td> </tr> <tr> <td>Rescue meds (times/day)</td> <td>-0.01</td> <td>-0.44¶^</td> <td>+0.07</td> </tr> <tr> <td>Asthma sx score‡</td> <td colspan="3">Improvement in score CIC320 BID &gt; BDP¶</td> </tr> <tr> <td>FEV1 (L)</td> <td>-0.01±0.24</td> <td>0.09±0.32</td> <td>0.02±0.26</td> </tr> </tbody> </table> <p>*Primary outcome: Non-inferiority CIC320QD vs. BDP and superiority for CIC 320 BID vs. BDP ¶Significant vs. BDP ^Significant vs. CIC320 QD ‡Used rating standard of the Japanese Society of Allergology</p>		CIC 320 QD	CIC 320 BID	BDP 400 BID	D/C treatment	NR	NR	NR	Change PEFam (L/min)*	16.02± 3.78	23.98± 3.74	5.91 ± 3.75	Change in PEFpm (L/min)	9.17±3.68	18.69±3.67¶	5.37±3.68	Rescue meds (times/day)	-0.01	-0.44¶^	+0.07	Asthma sx score‡	Improvement in score CIC320 BID > BDP¶			FEV1 (L)	-0.01±0.24	0.09±0.32	0.02±0.26								
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<p>Bateman 2008 R, OL</p> <p>Conducted in Europe, UK, S. Africa, Canada</p> <p>Non-inferiority</p> <p>Modified ITT analysis</p> <p>6 months</p> <p>N=528</p>	<p><b>Inclusions</b> 12-75 years old ≥ 6 month history of moderate-severe asthma FTC 500-1000mcg/day (or equivalent) at stable dose for ≥ 4 weeks FEV1 ≥ 80% predicted FEV1 reversibility ≥ 12% and ≥ 200mL Diurnal PEF fluctuation ≥ 15% during ≥ 3 days ≥ 1 day of no asthma symptoms during the last 7 days prior to baseline</p> <p><b>Exclusions</b> Use of systemic steroids within 4 weeks (6 weeks for depot inj.) prior to entry or &gt; 3 times during last 6 months Concomitant severe disease COPD or other relevant non-asthma pulmonary disease Clinically relevant I abnormal. History ≥ 10 pack-years smoking</p>	<p>2-week run-in period where patient continued usual ICS</p> <p>CIC 320mcg BID (n=255) FTC 330 mcg BID (n=273)</p> <p>Both drugs administered via HFA pMDI</p> <p>LABAs, oral beta-agonists, leukotriene modifiers could continue use provided dosage kept constant throughout trial</p>	<p>Values for CIC; FTC respectively</p> <p><b>% male:</b> 38; 40 <b>Age (years):</b> 43 (13-74); 44 (12-75) <b>Non-smokers (%):</b> 68; 66 <b>ICS dose (BDP-CFC equivalent mcg/d):</b> 1125±378; 1146±408 <b>Use of other asthma controllers (%):</b> 59; 60 <b>FEV1 (L):</b> 2.94±0.76; 2.88±0.75 <b>FEV1 %predicted:</b> 93.5±11.6; 93±10.7 <b>FEV1 reversibility (%):</b> 16.6±8.0; 17.6±8.3 <b>Use of combination ICS/LABA (%):</b> 39.6; 37 <b>Use of LABA (%):</b> 24.3; 22</p>	<table border="1"> <thead> <tr> <th></th> <th>CIC 320 BID</th> <th>FTC 330 BID</th> </tr> </thead> <tbody> <tr> <td>D/C treatment (n)</td> <td>43</td> <td>38</td> </tr> <tr> <td>Change in FEV1 (mL)*</td> <td>11±22</td> <td>24±21</td> </tr> <tr> <td>Exacerbation requiring OCS (n)</td> <td>6</td> <td>7</td> </tr> <tr> <td>Change in PEF (L/min)</td> <td>8.6±4.4^</td> <td>8.4±4.1^</td> </tr> <tr> <td>Change in diary PEFam (L/min)</td> <td>26.2±4.9^</td> <td>21±4.6^</td> </tr> <tr> <td>Asthma sx scores</td> <td>-0.14^</td> <td>-0.14^</td> </tr> <tr> <td>Rescue meds</td> <td>-0.07^</td> <td>-0.14^</td> </tr> <tr> <td>% symptom-free days</td> <td>82</td> <td>81</td> </tr> <tr> <td>% rescue-med free days</td> <td>89</td> <td>84</td> </tr> <tr> <td>% days no symptoms AND no rescue med</td> <td>74</td> <td>73</td> </tr> <tr> <td>AQLQ</td> <td>0.18±0.05^</td> <td>0.15±0.05^</td> </tr> </tbody> </table> <p>*Primary outcome Tx difference -13 ± 29 [95%CI -70, 44] in ITT group and -27 ± 34 [95%CI -93, 40] in per-protocol group. ^Significant vs. baseline Non-inferiority was demonstrated for FEV1, PEF, and exacerbations; there was no significant difference between agents for all other outcomes Similar results were seen with both ITT and per-protocol analyses</p>		CIC 320 BID	FTC 330 BID	D/C treatment (n)	43	38	Change in FEV1 (mL)*	11±22	24±21	Exacerbation requiring OCS (n)	6	7	Change in PEF (L/min)	8.6±4.4^	8.4±4.1^	Change in diary PEFam (L/min)	26.2±4.9^	21±4.6^	Asthma sx scores	-0.14^	-0.14^	Rescue meds	-0.07^	-0.14^	% symptom-free days	82	81	% rescue-med free days	89	84	% days no symptoms AND no rescue med	74	73	AQLQ	0.18±0.05^	0.15±0.05^
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Study 323/324 R, DB  Conducted in US  ITT analysis  12 weeks  N=531	Inclusions Moderate-severe persistent asthma ≥ 12 years old ≥ 1 year history of persistent asthma FEV1 ≤ 80% predicted following a 6-h beta-agonist tx withholding period at screening FEV1 40-64% predicted following a 6-h beta-agonist treatment withholding ICS use (≥ 500mcg/d of FTC or MM or ≥ 800mcg/d of BUD, FLU, or TCA) Use of beta-agonist ≥ 2x weekly for month prior to screening	CIC 160mcg BID (n=127) CIC 320mcg BID (n=130) FTC 440mcg BID (n=138) Placebo (n=136)  CIC administered via HFA pMDI and FTC via CFC pMDI	12-88 years old (mean range 42-44) FEV1 % predicted 53.7%	<table border="1"> <thead> <tr> <th></th> <th>CIC 160 BID</th> <th>CIC 320 BID</th> <th>FTC 440 BID</th> </tr> </thead> <tbody> <tr> <td>D/C treatment<sup>^</sup></td> <td>6.3%</td> <td>7.7%</td> <td>4.3%</td> </tr> <tr> <td>Pre-dose FEV1 (L) v. PL*</td> <td>0.11 [0.01, 0.21]</td> <td>0.18 [0.07, 0.28]</td> <td>0.24 [0.14, 0.35]</td> </tr> <tr> <td>PEFam (L/min) v. PL</td> <td>27.8<sup>^</sup> [16.8, 38.8]</td> <td>30.4 [19.5, 41.3]</td> <td>41.4 [30.6, 52.2]</td> </tr> <tr> <td>Albuterol use (puffs/day)</td> <td>-1.69 [-2.35, -1.04]</td> <td>-1.57 [-2.22, -0.92]</td> <td>-2.19 [-2.84, -1.54]</td> </tr> <tr> <td>Total asthma sx score</td> <td>-0.71 [-1.05, -0.37]</td> <td>-0.80 [-1.14, -0.46]</td> <td>-0.91 [-1.24, -0.58]</td> </tr> <tr> <td>% achieving MID in improvement for AQLQ overall score<sup>§</sup></td> <td>42.5</td> <td>43.1</td> <td>58.8</td> </tr> </tbody> </table>		CIC 160 BID	CIC 320 BID	FTC 440 BID	D/C treatment <sup>^</sup>	6.3%	7.7%	4.3%	Pre-dose FEV1 (L) v. PL*	0.11 [0.01, 0.21]	0.18 [0.07, 0.28]	0.24 [0.14, 0.35]	PEFam (L/min) v. PL	27.8 <sup>^</sup> [16.8, 38.8]	30.4 [19.5, 41.3]	41.4 [30.6, 52.2]	Albuterol use (puffs/day)	-1.69 [-2.35, -1.04]	-1.57 [-2.22, -0.92]	-2.19 [-2.84, -1.54]	Total asthma sx score	-0.71 [-1.05, -0.37]	-0.80 [-1.14, -0.46]	-0.91 [-1.24, -0.58]	% achieving MID in improvement for AQLQ overall score <sup>§</sup>	42.5	43.1	58.8
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Study 323/324LT (extension of study 323/324) R, DB  N=297  1 year	See above  Patients completing original study or at least 2 weeks of the double-blind tx were eligible	Randomized 2:1 CIC:BDP CIC 320mcg BID (n=198) BDP 320mcg BID (n=99) After 2 weeks, may titrate down to 160mcg BID  All inhalers were administered via HFA pMDI	12-76 years old (mean range 44.7-45.2) FEV1% predicted at baseline 64.8%	The primary endpoint was long-term safety (see safety section in text)  LS mean change in FEV1 from baseline to end of study was 0.11L for both groups																												
Study 3027 R, DB  Non-inferiority Modified ITT analysis  N=1568 1 year	≥ 18 years old Moderate-severe persistent asthma for ≥ 2 months FEV1 ≥40% and ≤80% predicted ICS use ≥ 1 month Non-smoker for at least past year and ≤10-pack year history if previous smoker	CIC 320mcg BID (n=785) BDP 320mcg BID (n=783)  All inhalers were administered via HFA pMDI	Mean age 43.1 years No relevant differences in any demographic variables (data not shown)	Primary analysis was occurrence of a Class I lens event for nuclear opalescence, cortical, or posterior subcapsular lens opacification within 12 months (see safety section in text under Glaucoma and cataracts)  Change in FEV1 from baseline to end of study was 1.14% predicted (CIC) and 1.76% predicted (BDP). 95%CI for difference [1.497, 0.249]																												

AQLQ= asthma quality of life questionnaire BDP=beclomethasone dipropionate; BID=twice daily; BUD=budesonide; CIC=ciclesonide; CFC=chlorofluorocarbon; DB=double-blind; FEV1=forced expiratory volume in 1 second; FLU=flunisolide; FTC=fluticasone; HFA=hydrofluoroalkane; ICS=inhaled corticosteroid; ITT=intent-to-treat; LABA=long-acting beta-agonist; MID= minimally important difference ;MM=mometasone; OCS=oral corticosteroid; OL=open-label; PEFam=morning peak expiratory flow; PL=placebo; pMDI=pressurized metered dose inhaler; QD=once daily; R=randomized; SABA=short-acting beta-agonist; TCA=triamcinolone

## Appendix 2: Head-to-Head Trials of Ciclesonide Administered Once Daily

	Study Design	Dose	Inhaler Device	Treatment Period	Mean Age (range)	Baseline FEV1	Primary Outcome	Other secondary outcomes
Niphadkar 2005	R, DD, OL (BUD arm only)  Non-inferiority	CIC 160mcg QDam (n=139) CIC 160mcg QDpm (n=131) BUD 200mcg BID (n=133)  As needed albuterol allowed; use of 1 other concomitant asthma med was allowed	pMDI (all)	12-weeks	31 (18-69)	2200mL 93% predicted	<u>Change in FEV1 difference vs. BUD</u> 10mL (CICam) 36mL (CICpm)  Difference NS	No significant difference in FVC, PEF am and pm (diary), PEF (clinic measured), PEF fluctuation, % sx-free days, % rescue med-free days, rescue med use
Hansel 2006	R, DD, OL (BUD arm only)  Non-inferiority of CIC320 vs. BUD	CIC 80mcg QDam (n=182) CIC 320mcg QDam (n=195) BUD 160mcg BID (n=177)  As needed albuterol allowed; no other asthma meds allowed	HFA pMDI (CIC) DPI (BUD)	12-weeks	41 (12-74)	2452mL 72% predicted	<u>Change in FEV1 (mL)</u> 267 ± 35 (CIC80) 256 ± 33 (CIC320) 355 ± 34 (BUD)  Difference NS	No significant difference in PEFam, symptom scores, use of rescue meds between CIC320 and BUD
Boulet 2006	R, DB, DD Non-inferiority	CIC 320mcg QDam (n=179) BUD 320mcg QDam (n=180)  As needed albuterol allowed; no other asthma meds allowed	HFA pMDI (CIC) Turbohaler (BUD)	12-weeks	40.5 (12-72)	2805mL 90% predicted	<u>Change in FEV1 (mL)</u> 180 (CIC) 230 (BUD)  Difference NS	CIC was significantly better than BUD for FVC, % sx-free days, use of rescue meds  No significant difference in am and pm PEF, % rescue med-free days
Ukena 2007	R, DB, DD Non-inferiority	CIC 320mcg QD (n=198) BUD 400mcg QD (n=201)  As needed albuterol allowed; no other asthma meds allowed	HFA pMDI (CIC) Turbohaler (BUD)	12-weeks	45 (12-75)	2330mL 72% predicted	<u>Change in FEV1 (mL)</u> 416 (CIC) 321 (BUD)  Difference exceeded non-inferiority margin and superiority demonstrated	CIC was significantly better than BUD for FVC and PEF (clinic measured)  No significant differences in symptom scores, use of rescue meds, patient diary obtained PEF
Buhl 2006	R, DB, DD Non-inferiority	CIC 160mcg QDpm (n=266) FTC 88mcg BID (n=263)  As needed albuterol allowed; no other asthma meds allowed	HFA pMDI (both)	12-weeks	39.5 (12-74)	2411mL 75% predicted	<u>Change in FEV1 (mL)</u> 489 ± 29 (CIC) 499 ± 29 (FTC)  Difference NS	No significant difference in FVC, PEFam, PEFpm, FEF25-75%, symptom scores, use of rescue meds, % sx-free days, % rescue med-free days, % nocturnal awakening free nights
Boulet 2007	R, OL Non-inferiority	CIC 320mcg QDpm (n=233) FTC 200mcg BID (n=239)  As needed albuterol allowed; no other asthma meds allowed	HFA pMDI (CIC) Diskus (FTC)	12-weeks	39 (12-74)	2804mL 89% predicted	<u>Change in FEV1(mL)</u> 171 ± 29 (CIC) 186 ± 29 (FTC)	No significant difference in FEV1% predicted, FVC, PEF, am and pm symptom scores, use of rescue meds, % of sx-free days, % of rescue med-free days  Overall AQLQ score higher with CIC than FTC, but no difference with the individual domain scores

Magnussen	R, DD, DB	CIC 80mcg QDpm (n=278)	HFA pMDI (all)	12-weeks	31 (12-75)	2658mL	<u>Change in FEV1(mL)</u>	No significant difference in daytime and
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2007	Non-inferiority	CIC 160mcg QDpm (n=270) FTC 88mcg BID (n=259)  As needed albuterol allowed; unclear if other baseline non-ICS meds were allowed				79% predicted	412 ± 29 (CIC80) 378 ± 29 (CIC160) 437 ± 30 (FTC)	nighttime symptom scores, use of rescue meds, % sx-free days, % rescue med free days, PEFam, FVC
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AQLQ=asthma quality of life questionnaire; BID=twice daily; BUD=budesonide; CIC=ciclesonide; DB=double-blind; DD=double dummy; FEF25-75%= forced expiratory flow from 25% to 75% of vital capacity; FEV1=forced expiratory volume in 1 second; FTC=fluticasone; FVC= forced vital capacity; HFA=hydrofluoroalkane; OL=open-label; PEFam=morning peak expiratory flow; pMDI=pressurized metered dose inhaler; QD=once daily; R=randomized;

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