

Ciclesonide: a safe and effective inhaled corticosteroid for the treatment of asthma

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Abstract: Ciclesonide is a novel inhaled corticosteroid used in the continuous treatment of mild-to-severe asthma. Its formulation and mechanism of action yield a low oral and systemic bioavailability, and high pulmonary deposition. In multiple clinical trials, ciclesonide is at least as effective as either fluticasone propionate or budesonide at symptom control, while in many cases having improved safety outcomes and tolerability. The improved safety and comparable efficacy profiles of ciclesonide demonstrated in current studies could potentially yield a treatment option that may lead to improved adherence and outcome.

Keywords: ciclesonide, asthma, inhaled corticosteroid

Introduction

Asthma poses a significant burden to society in terms of morbidity, mortality, quality of life, and healthcare costs.¹⁻³ Among children, asthma rates in the United States are currently at record highs, with a nationwide prevalence of approximately 9% of children aged 1 to 17 years.³ Its burden on the economy is estimated at between US\$4 to 6 billion annually, considering healthcare costs and lost work days for caregivers and patients alike.⁴ Inhaled corticosteroids (ICS) are recommended as first-line therapy for the treatment of asthma,^{5,6} and can improve both asthma symptomatology and the markers of airway inflammation.⁷⁻⁹ However, despite being demonstrated as an efficacious controller therapy, concerns remain regarding the potential for adverse side effects associated with chronic ICS treatment. Specifically, some ICS molecules have been demonstrated to cause reductions in growth velocity⁹⁻¹¹ and bone mineral density,^{12,13} HPA-axis suppression,^{14,15} and oral candidiasis.^{16,17}

Ciclesonide (Alvesco[®]; Sepracor, Inc., Nycomed, Inc.) is a novel, new corticosteroid developed for the treatment of mild to severe persistent asthma. It is delivered by metered-dose inhaler (MDI) once daily or twice daily (dosing depends on country). This review will focus on the safety and efficacy profile of ciclesonide, as well as to establish its mechanism of action.

Mechanism of action

Ciclesonide ([R]-11 β , 16 α , 17, 21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with cyclohexanecarboxaldehyde 21-isobutyrate; CIC) is inhaled into the lungs via hydrofluoroalkane-MDI (HFA-MDI), where it is converted by local esterases to its active metabolite, desisobutyryl-ciclesonide (des-CIC, Figure 1). Relative to dexamethasone (100), CIC has a low glucocorticoid receptor binding affinity of 12, while des-CIC has a significantly higher binding affinity of 1212.^{18,19} Studies demonstrate no conversion of R-CIC or des-CIC to the S-epimer in vivo, which has different physicochemical properties, and a markedly lower receptor affinity.²⁰ Pharmacokinetic profiles of des-CIC were similar in comparative healthy and asthma patients, likely indicating that bronchial narrowing and airway inflammation do not affect the distribution of CIC and its subsequent activation to des-CIC in the

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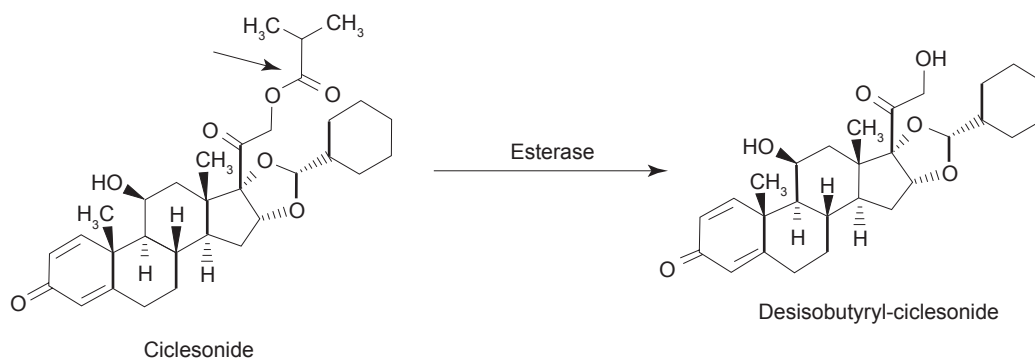


Figure 1 Molecular structure of ciclesonide and its activated metabolite, desisobutyryl-ciclesonide (des-CIC). Christie P. Ciclesonide: A novel inhaled corticosteroid for asthma. *Drugs Today (Barc)*. 2004; 40(7):569–576.¹⁹ Copyright © 2004 Prous Science, S.A.U. All rights reserved.

lungs.²¹ An additional study also demonstrated equivalent PK/PD profiles of CIC-HFA when administered with and without a spacer.²²

In vitro data indicate metabolism of des-CIC was different in precision-cut human lung and liver tissue slices.²³ After 24 hours incubation with [¹⁴C]-CIC, 7.2 times more radioactivity was present in the lung tissue, as compared with the liver. Furthermore, in the lung tissue [¹⁴C]-CIC was converted to des-CIC and subsequently conjugated with fatty acid metabolites, a reversible process which increases lipophilicity of des-CIC and may result in prolonged drug retention and anti-inflammatory activity in the lung (Figure 2).^{23,24} Alternatively, [¹⁴C]-CIC was catabolically inactivated in liver tissue into at least 5 different polar compounds, with dihydroxylated des-CIC being the major metabolite.²³ Additionally, other findings demonstrated that orally and intravenous-administered [¹⁴C]-CIC resulted in a negligible serum concentration of des-CIC and no accumulation in red blood cells, indicating a low absorption and almost complete first-pass metabolism (systemic bioavailability of des-CIC < 1%).²⁵

The demonstrated mean lung deposition of CIC is 52%.²⁶ The internal diameter of the smallest airways in adults are typically ~2 μm, thus, it can be inferred that smaller ICS particles lead to greater pulmonary deposition and more even distribution throughout the lungs (Table 1). Accordingly, the HFA-MDI formulation of CIC contains a majority of ICS particles which range between 1.1 and 2.1 μm.^{27,28} This particle size is likely related to the high observed pulmonary deposition of CIC.²⁸ Furthermore, uptake of CIC, budesonide (BUD), and fluticasone propionate (FP) in human alveolar type II epithelial cells (A549) was measured, and at all incubation timepoints, intracellular concentration of CIC was higher than that of BUD and FP.²⁹ This indicates a more rapid uptake of CIC

molecules into target tissue, and at a higher concentration. Additionally, separate *in vitro* data indicate intracellular concentration of des-CIC in A549 cells to be maintained for >20 hours.²⁹

Efficacy Placebo-controlled

The therapeutic action of ciclesonide is achieved after the inhaled parent compound (CIC) is cleaved by esterases in the lungs to its active metabolite (des-CIC), a corticosteroid with high receptor affinity and anti-inflammatory activity.^{18,19,30} In a randomized, double-blind trial, early (EAR) and late (LAR) phase allergen-induced asthmatic reactions were significantly inhibited ($p < 0.05$) by treatment with CIC, versus placebo (as evaluated by decrease in FEV₁ following allergen challenge).³¹ These anti-inflammatory properties were also exhibited *in vitro*, as CIC attenuated EAR/LAR, infiltration of inflammatory cells into bronchoalveolar lumen, and airway hyperresponsiveness in sensitized Brown Norway rats.³² These effects were observed in a dose-dependent manner.

These anti-inflammatory properties have been noted in patients with mild, persistent asthma, treated with CIC 160 μg (all doses noted in this review are ex-actuator) once-daily over a period of 4 weeks.³³ Measurements were made before and after treatment in this double-blind study for adenosine monophosphate (AMP) bronchial challenge, and exhaled nitric oxide (eNO). Mean AMP challenge PC₂₀ following ciclesonide treatment was significantly increased ($p < 0.001$) compared to placebo, and decreases in eNO (ppb) and induced sputum eosinophil cell counts were also noted.³³ Additionally, Bateman et al³⁴ demonstrated the effectiveness of CIC 320 μg and 640 μg in reducing oral corticosteroid use in adults with severe, persistent asthma, versus placebo.

Table 1 Characteristics of ciclesonide

Method of delivery	HFA-MDI
Particle size ²⁷	1.1–2.1 μm
Pulmonary Deposition ²⁶	52%
Oral deposition ²⁶	38%
Systemic bioavailability ³⁰	CIC = 18% Des-CIC = 50%
Serum protein binding (des-CIC) ⁶²	~99%, <1% unbound fraction
Target tissue retention (des-CIC) ²⁵	>24 hours
Mean terminal half-life ($t_{1/2}$; des-CIC) ²⁷	3.5 hours
Elimination half-life ($t_{1/2}$; CIC) ²⁷	0.71 hours

Abbreviations: CIC, ciclesonide; des-CIC, desisobutryl-ciclesonide; HFA-MDI, hydrofluoroalkane metered dose inhaler.

Three double-blind studies demonstrated that treatment with CIC improves symptom control in patients who were previously treated with another ICS. O'Connor, et al³⁵ demonstrated significant improvement in FEV₁ in moderate-to-severe asthmatics treated with either CIC 800 μg or 1600 μg daily, compared to placebo (12-week treatment, pretreatment with 800–2000 $\mu\text{g}/\text{day}$ BDP). A similarly designed study by Langdon et al³⁶ noted improvements in baseline FEV₁ and morning PEF in subjects treated with CIC over a period of 12 weeks, but at more clinically-relevant doses (CIC 80 μg , 320 μg daily, versus placebo). Subjects were also previously treated with lower, constant doses of BDP or its equivalent (400–800 μg daily) for at least 4 weeks prior to randomization. Asthma control in previously treated subjects was maintained by CIC 160 μg or 640 μg once daily in another study by Chapman.³⁷

In a large, double-blind, 12-week study ($n = 1031$), Gelfand³⁸ studied the effect of multiple strength doses of CIC (40 μg , 80 μg , or 160 μg) on children aged 4 to 11 with mild to severe persistent asthma. Following run-in, subjects were randomized to one of three once-daily CIC treatments, or placebo. All CIC doses were associated with significant increases in FEV₁ compared to placebo at study endpoint (CIC 40 μg , 11.91; CIC 80 μg , 13.58; CIC 160 μg , 14.17). Reductions in rescue medication use within study treatment cohorts were also reported.

Comparative studies

Once-daily dosing of CIC (which is approved in some, but not all countries) is a significant distinction between it and other common ICS for treatment of asthma, such as BUD and FP. Currently, there have not been any comparative efficacy trials between CIC and mometasone furoate, another commonly used ICS which is approved for once-daily dosing;

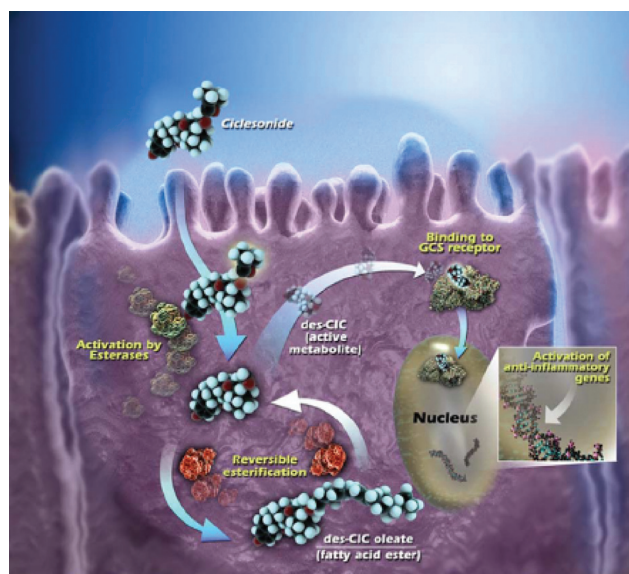


Figure 2 Intracellular activation of ciclesonide and reversible esterification of desisobutryl-ciclesonide (des-CIC). Ciclesonide is activated by intracellular esterases to active metabolite, des-CIC, which has high affinity to the glucocorticosteroid (GCS) receptor. Desisobutryl-ciclesonide can undergo reversible esterification to des-CIC oleate (fatty acid ester). Reprinted with permission from Nave R, Meyer W, Fuhst R, Zech K. Formation of fatty acid conjugates of ciclesonide active metabolite in the rat lung after 4-week inhalation of ciclesonide. *Pulm Pharmacol Ther.* 2005;18:390–396.⁶² Copyright © 2005 Elsevier.

future studies should directly compare efficacy of these two agents. CIC has demonstrated efficacy with a single daily dose,^{33–42} as well as when administered either in the morning or evening.³⁹ The effectiveness of a single daily dose could lead to improved compliance and symptom control in patients using CIC as asthma control therapy.

CIC comparative efficacy trials are summarized in Table 2. Ukena⁴³ demonstrated CIC 320 μg once daily to be superior to BUD 200 μg twice-daily in increasing FEV₁ from baseline (416 mL in CIC versus 321 mL in BUD; $p = 0.019$, 95% CI). While improvements were seen in FVC for both cohorts, a significantly larger difference was seen in CIC-treated subjects. Additionally, significant improvement versus baseline in morning PEF was seen after Day 2 in the CIC cohort ($p = 0.039$ versus baseline) and Day 7 in the BUD cohort ($p = 0.047$ versus baseline), indicating a more rapid onset of action for CIC.

However, these findings appear to be an outlier, as the majority of trials have found CIC at least as effective as BUD (Turbohaler®/DPI) in controlling asthma, in varying subject populations and disease severities.^{44–48} FEV₁ improvement was noted in these studies with both BUD and CIC, and no significant between-group differences were noted. Pediatric Asthma Quality of Life Questionnaire (PAQLQ) and Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) scores were similarly improved

Table 2 Ciclesonide comparative efficacy trials

Author/citation	Dosing	Subject characteristics	Treatment duration	Outcome
Knox ⁴⁰ , 2007	CIC 160 µg qd; FP 250 µg bid	17–75 y; controlled asthma w/pretreatment ^a	2-week baseline w/ current ICS, 12 week treatment	CIC and FP had similar FEV ₁ maintenance and symptom-free days
Lee ⁴¹ , 2004	CIC 160 µg qd; FP 110 µg bid; placebo	mild to moderate asthmatics	separate 4 week treatment arms, separated by 2-week washout w/ salmeterol + montelukast	No difference between groups in methacholine PC ₂₀ hyperresponsiveness
Buhl ⁴² , 2006	CIC 160 µg qd; FP 88 µg bid	12–74 y; mild to moderate asthma (GINA)	1- to 2-week baseline w/ rescue med only; 12-week treatment	CIC and FP similarly improved lung function, symptom scores, and rescue med use. During last 4 weeks, CIC had higher percentage of symptom-free days
Niphadkar ⁴⁴ , 2005	CIC 160 µg qd; BUD 200 µg bid	adults w/ FEV ₁ ≤ 70%, pretreated	12 weeks, 2-week run-in w/BUD 200 µg bid	CIC as effective as BUD at symptom control
Boulet ⁴⁵ , 2006	CIC 320 µg qd; BUD 200 µg bid	pretreated, FEV ₁ inc. ≥ 7% and 65%–90% pred. after run-in	2-week baseline w/ BUD 1600 µg qd, 12-week treatment	CIC qd as effective as BUD bid
Hansel ⁴⁶ , 2006	CIC 80 µg qd; CIC 320 µg qd; BUD 200 µg bid	FEV ₁ 50%–90% pred.	12 weeks	CIC and BUD improved FEV ₁ , FVC, and PEF similarly
von Berg ⁴⁷ , 2007	CIC 160 µg qd; BUD 400 µg qd	children w/moderate to severe asthma (GINA 1995)	2- to 4-week run-in w/rescue med only, 12 week treatment	CIC and BUD similarly improved FEV ₁ , morning PEF, rescue med use, and QoL scores
Vermeulen ⁴⁸ , 2007	CIC 320 µg qd; BUD 800 µg qd	Children 12–17 y w/severe asthma (GINA 1995)	2-week baseline w/BUD 400 µg qd, 12-week treatment	CIC and BUD comparably improved FEV ₁ , FVC, PEF, symptom-free days, and rescue med use
Boulet ⁴⁹ , 2007	CIC 320 µg qd; FP 200 µg bid	12–75 y; FEV ₁ ≥ 80% w/pretreatment, or FEV ₁ 60–80 and pred	1- to 4-week run-in, 12-week treatment	CIC and FP similarly increased FEV ₁ and resulted in comparable numbers of symptom-free days
Bateman ⁵⁰ , 2008	CIC 320 µg bid; FP 330 µg bid	12–75 y; moderate to severe controlled asthma w/pretreatment	2-week baseline w/ current ICS, 24-week treatment	CIC and FP maintained FEV ₁ , and improved morning/evening PEF, rescue med use, and QoL scores
Pedersen ⁵¹ , 2006	CIC 80 µg bid; FP 88 µg bid	symptomatic children 6–15 y; FEV ₁ 50%–90% pred	2- to 4-week baseline w/ rescue med only; 12-week treatment	CIC and FP similarly improved FEV ₁ , morning/evening PEF, rescue med usage, and reported symptoms

^aPretreatment defined as subjects having daily ICS treatment prior to randomization. All doses noted are ex-actuator.

Abbreviations: BUD, budesonide; CIC, ciclesonide; FP, fluticasone propionate; ICS, inhaled corticosteroids.

over a 12-week study comparing CIC 160 µg once daily to BUD 400 µg once daily.⁴⁷ Some modest benefit was seen for CIC, with Boulet⁴⁵ finding a greater percentage of symptom-free days for CIC (43%) than BUD (34%; $p = 0.0288$), but overall, both ICS seem to be comparably efficacious. Similarly, comparative studies between CIC and FP show clear non-inferiority of CIC.^{40–42,49–51} No difference in comparative efficacy was observed when comparing CIC to both FP-DPI⁴⁹ and FP-MDI.^{40–42,50,51} FP and CIC were equally effective at maintaining asthma control

in subjects who were on continuous ICS therapy prior to randomization.^{40,50}

Safety and tolerability

Oral candidiasis

Considering CIC is relatively inactive, and is converted to active des-CIC in the lungs versus some conversion in the oral cavity, this profile would suggest a lower oropharyngeal deposition and frequency of side effects (ie, candidiasis). Indeed, comparative studies indicate low deposition and

activated des-CIC within the oropharynx. Two similarly designed studies compared CIC to FP⁵² and BUD⁵³, using mouthwash solutions containing 50% ethanol at 5 time points (immediate, 15, 30, 45, and 60 minutes after inhalation) to compare deposition. The sum of CIC and des-CIC molar AUCs_{0-60 min} was 53% (95% CI: 40%–69%) of FP deposition⁵² and 47% of the BUD deposition.⁵³ Furthermore, oral deposition of des-CIC was less than 10% that of FP and BUD.

Incidence of candidiasis from continuous ICS treatment is a concern, and a common reason for poor adherence, and in some cases, not beginning an asthma patient on an ICS treatment regimen.¹⁶ For example, in one of the aforementioned efficacy studies, 9 cases of candidiasis were noted (over a 12-week treatment period) among subjects receiving FP 200 µg twice-daily, compared to no reported cases in subjects treated with CIC 320 once-daily.⁴⁹ Likewise, Gelfand³⁸ found the incidence of oral candidiasis and pharyngitis over a 12-week treatment period with CIC 40 µg, 80 µg, and 160 µg to be not significantly different from placebo. This finding is consistent with that of Pearlman,⁵⁴ who found incidences of oropharyngeal side effects similar to placebo in patients treated with CIC 80 µg, 160 µg, or 320 µg over the same duration.

HPA-axis function

Concerns of ICS acting as endogenous glucocorticoids, thereby suppressing the HPA-axis, have resulted in reluctance of some physicians to prescribe such a treatment continuously. CIC has high protein binding and high systemic clearance, a profile that would seem to minimize interference with normal HPA-axis function. In one double-blind, randomized, crossover trial, Agertoft⁵⁵ studied children aged 6 to 12 years who were given placebo, CIC 40 µg, 80 µg, or 160 µg once daily during four 2-week treatment periods, followed by 2-week washouts. Analysis of 12 hours urinary cortisol at the end of each treatment period yielded no significant between-group differences or dose-response effects. This is of interest because these subjects were given clinically relevant doses of CIC for their age and disease severity.

Vermeulen et al⁴⁸ found that over 12 weeks of treatment in children, CIC 320 µg once-daily was not associated with a significant decrease in 24 urinary free cortisol ($\Delta = +1.05$; nmol/mmol), while BUD 800 µg once daily was ($\Delta = -2.63$). This between-group difference was significant ($p = 0.003$). Adult patients ($n = 60$, ≥ 18 years) in a separate study were randomized to receive CIC 320 µg or 640 µg twice daily, FP 440 µg or 880 µg twice daily (CFC-MDI), or placebo. Neither

CIC nor FP treatment was associated with a significant change in mean serum cortisol AUC_{0-24 h} at these clinically relevant doses.⁵⁶ Alternatively, a study by Lipworth et al using the same comparative doses of FP and CIC, found evidence of adrenal suppression by FP, using cosyntropin-stimulated peak serum cortisol levels to analyze HPA-axis function.⁵⁷

Noteworthy is that this pattern of adrenal safety continued even when CIC was administered in doses higher than would normally be used in clinical practice. Derom et al⁵⁸ concluded that doses as high as CIC 640 µg twice daily had no significant effect on mean urinary cortisol levels (AUC_{0-24 h}), while FP 440 µg and 880 µg twice daily suppressed them by 29% (95% CI, 15–41), compared with placebo. Decreases in PC₂₀ hyperresponsiveness were similar in all cohorts.⁵⁸ In the previously mentioned study by Szeffler,⁵⁶ serum and urinary cortisol suppression was associated with high-dose FP 2000 µg daily, but not with CIC 1600 µg daily.⁵⁶ Again, airway outcomes (PC₂₀ hyperresponsiveness, exhaled nitric oxide) were improved with both treatments.

Growth effects

The effects of continuous CIC treatment on childhood growth velocity have been studied. Knemometry, though not a predictor of long-term growth velocity or final adult height, is an extremely sensitive measure of short-term changes in lower-leg growth. This method was utilized by Agertoft⁵⁵ to determine if 2-week treatment with CIC 40 µg, 80 µg, and 160 µg once daily resulted in any short-term changes in growth velocity. Lower leg growth rates for CIC were not significantly different from placebo, and no dose-response effects were noted (placebo: 0.412 mm/week; CIC 40: 0.425 mm/week; CIC 80: 0.397 mm/week; CIC 160: 0.370 mm/week).

To date, the only long-term assessment of growth velocity in children treated with CIC was completed by Skoner et al⁵⁹ where height was assessed by stadiometry. Children ($n = 661$) aged 5 to 8½ years were randomized to receive placebo, CIC 40 µg, or CIC 160 µg once daily, for a treatment period of 1 year. Mean differences in yearly height from placebo (5.75 cm/year) were nonsignificant (-0.02 cm/year for CIC 40 and -0.15 cm/year for CIC 160), illustrating the noninferiority of CIC for growth velocity, when compared to placebo (Figure 3).⁵⁹ Ideally, a study similar to that of Agertoft and Pedersen,⁶⁰ which determined children treated with BUD eventually reached normal adult height despite some initial reduction in growth velocity, should be performed with CIC.

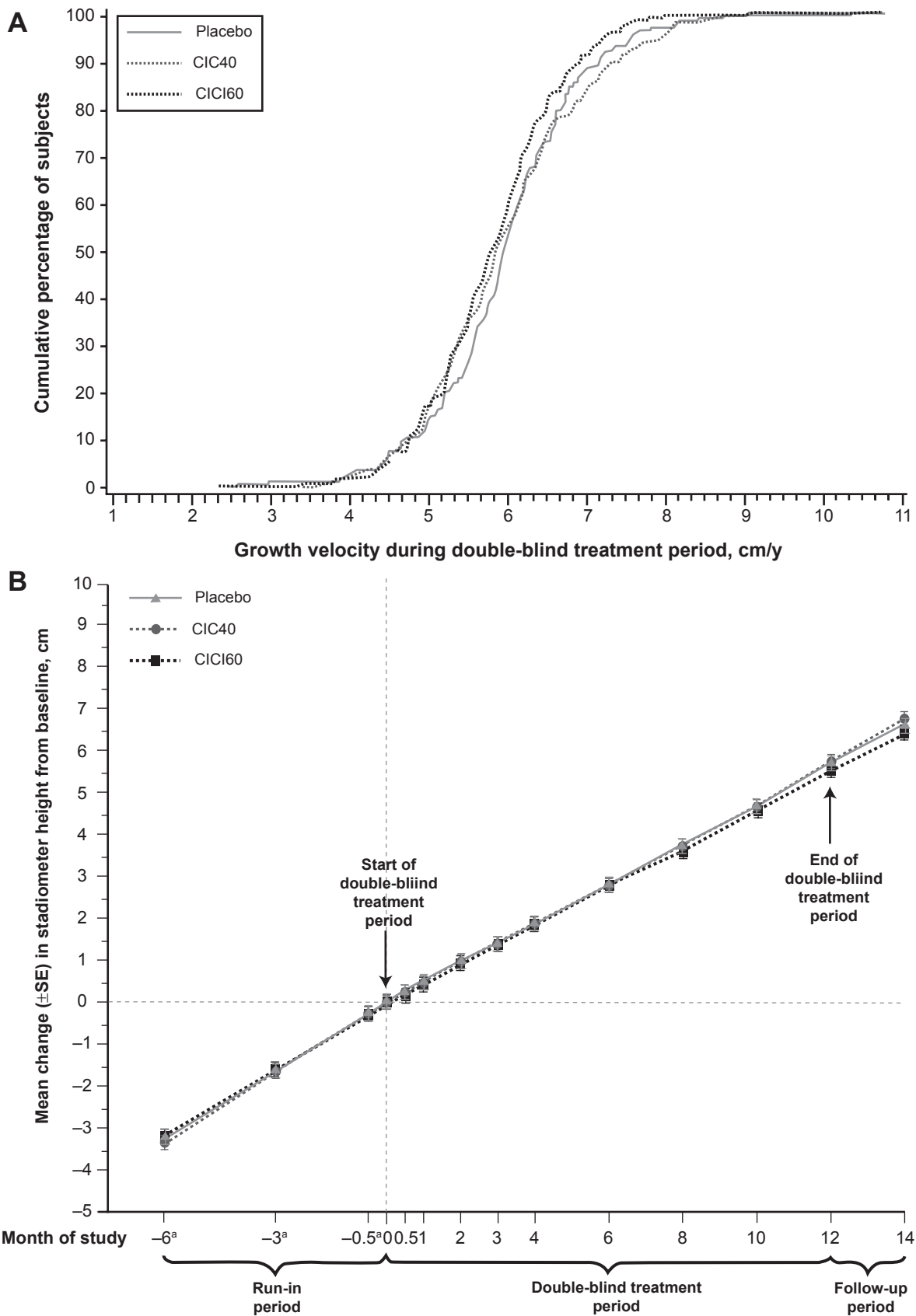


Figure 3 Subjects in all cohorts (CIC40, CIC160, placebo) achieved virtually the same growth velocity during one year of continuous CIC treatment. Reprinted with permission from Skoner DP, Maspero J, Banerji D, and the Ciclesonide Pediatric Growth Study Group. Assessment of the Long-term Safety of Inhaled Ciclesonide on Growth in Children with Asthma. *Pediatrics*. 2008 Jan;121(1):e1-14.⁵⁹ Copyright © 2008 American Academy of Pediatrics.

Conclusion

From the evidence currently available, CIC appears to be a novel, safe, and efficacious ICS for use in the continuous treatment of asthma. The low oral bioavailability can likely be attributed to the low affinity of CIC to glucocorticoid receptors, as compared to its active metabolite, des-CIC, which is activated in the lungs. des-CIC is highly lipid conjugated in the lungs, allowing for greater retention in target tissues, and clinically, once-daily dosing (in at least some patients). While these pharmacokinetic properties result in an efficacious ICS, they directly contribute to the noticeably enhanced safety profile of CIC, especially in comparison with other ICS molecules, such as BUD and FP. High protein binding and the aforementioned receptor affinity of CIC result in low systemic bioavailability, and potentially explain the low occurrence of adverse events such as candidiasis, adrenal suppression, and growth velocity disturbance. Comparative studies indicate the effectiveness of CIC to be similar to that of FP and BUD, but with an improved safety profile, indicating the potential of this alternative treatment option in patients concerned about the risks of continuous ICS treatment. Minimizing risk of treatment while maintaining efficacy is a top clinical priority to improve treatment adherence and gain optimal outcome of therapy.

Disclosures

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