



Cost-effectiveness analysis of early intervention with budesonide in mild persistent asthma

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Background: The Inhaled Steroid as Regular Therapy in Early Asthma (START) study reported that early intervention with budesonide in mild persistent asthma reduces severe asthmatic events and improves symptom outcomes and lung function in adults and children.

Objective: We sought to estimate the incremental cost-effectiveness of early intervention with budesonide, as observed within the START study.

Methods: START was a randomized, 3-year controlled trial of budesonide in early onset mild asthma among 7165 subjects ages 5 to 66 years. Three age groups (5-10, 11-17, and ≥ 18 years) were studied separately and overall. Differences in the probability of emergency treatments, symptom-free days (SFDs), and costs of health care were determined. Incremental cost-effectiveness ratios were estimated from the health care payer and societal perspectives.

Results: Compared with usual therapy, patients receiving budesonide experienced an average of 14.1 (SE, 1.3) more SFDs per year ($P < .001$), fewer hospital days (69%, $P < .001$), and fewer emergency department visits (67%, $P < .05$). From the health care payer perspective, the net cost of early use of budesonide was an additional US\$0.42 (SE, \$0.04) per day, and the resultant cost-effectiveness ratio was \$11.30 (95% CI, \$8.60-\$14.90) per SFD gained. From the societal perspective, the cost offsets of lower absence from school or work reduced the net cost of early budesonide to \$0.14 (SE, \$0.07) per day and decreased the cost-effectiveness ratio to \$3.70 (95% CI,

\$0.10-\$8.00). Early intervention was more effective and cost saving in the youngest age group.

Conclusion: Long-term treatment with budesonide appears to be cost-effective in patients with mild persistent asthma of recent onset. (*J Allergy Clin Immunol* 2003;112:1229-36.)

Key words: Asthma, START, cost-effectiveness, budesonide, inhaled corticosteroids, symptom-free days

The burden and cost of asthma is substantial, particularly among patients with moderate and severe disease.^{1,2} Patients with mild asthma comprise the largest group of patients, yet have the lowest per capita costs, in part because most do not use scheduled controller medications and have infrequent hospitalizations.³⁻⁵ Mild asthma is often undertreated, particularly in the primary care setting.⁶⁻⁸ Undertreatment of asthma is associated with unresolved morbidity, higher symptom burden, and increased health care costs.⁹

Adding regular inhaled corticosteroid (ICS) treatment to as-needed β -agonist therapy is advocated by US and international guidelines.^{2,10} However, no well-controlled economic evaluation has been undertaken to evaluate the financial implications of early secondary prevention in mild, persistent recent-onset asthma. To investigate this question, we conducted an economic evaluation alongside the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study.

The START study was a 3-year, multinational, randomized, double-blind, controlled clinical trial of early intervention with budesonide (Pulmicort Turbuhaler; AstraZeneca, London, United Kingdom) once daily among patients with recent-onset mild asthma. The primary objective was to evaluate whether early intervention with budesonide affects the evolution of recent-onset asthma. The results showed that long-term treatment with low-dose budesonide once daily delayed the time to the first severe asthma event, decreased the risk of severe exacerbations, and improved asthma symptom control and lung function in patients with mild persistent asthma compared with the usual asthma therapy.¹¹ In this article we report the results of a cost-effectiveness analysis using patient-reported outcomes and resource use data collected as part of the study.³

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Abbreviations used

GNP: Gross national product
 ICER: Incremental cost-effectiveness ratio
 ICS: Inhaled corticosteroid
 SFD: Symptom-free day
 START: Inhaled Steroid as Regular Therapy in Early Asthma

METHODS

START was a pragmatic study conducted in 32 countries in which 7241 patients were randomized to budesonide once daily (200 µg for children <11 years at baseline and 400 µg for other patients) or usual asthma therapy. If judged appropriate by the investigators, all patients were allowed to receive other asthma treatments, including other inhaled or oral corticosteroids, according to local practice.

We have previously reported the design and analysis plan of the cost-effectiveness evaluation for the START study in compliance with the US Public Health Service Panel on Cost-Effectiveness recommendations for complete reporting and transparency of methods.^{12,13}

In brief, the cost-effectiveness evaluation of the START study was conducted primarily from the health care payer perspective and secondarily from the societal perspective. Clinical outcomes and resource use were determined by using pooled data from the 3-year study period. Costs are reported by using unit cost estimates from the United States.

The difference between treatment arms in costs and in effectiveness and the incremental cost-effectiveness ratio (ICER) was computed. The main patient-reported outcome measure for effectiveness was the number of symptom-free days (SFDs).¹⁴

Study population and clinical trial protocol

Patients who were given a diagnosis of asthma 2 years or less before randomization qualified for the study. Eligible patients were required to exhibit mild persistent asthma according to symptom scores (at least 1 symptom, such as wheeze, cough, and chest tightness per week but not as often as every day during the 3 months preceding visit 1) and airway reversibility. Patients with significant comorbidity were not included.³

During the study period, all patients continued their usual asthma therapy according to local practice. At randomization, continued use of concurrent asthma medications was permitted, with the exception of inhaled or systemic corticosteroids. Patients experiencing deterioration of asthma status were eligible to receive inhaled corticosteroids, systemic corticosteroids, or both. During the study, there were no restrictions regarding the type or dose of concurrent asthma therapy, no requirements to reduce therapy to the lowest effective dose, and no enforced discontinuations of other medications. At some point during the 3-year study period, 45% of control patients compared with 31% of budesonide-treated patients received inhaled, oral, or systemic glucocorticoids ($P < .0001$) in addition to study medication. After randomization, patients returned to the clinic at weeks 6 and 12 and then every 3 months thereafter (a total of 14 visits).

The sample size of the study was determined such that a 35% reduction in the risk of emergency treatment or hospitalization could be detected with 95% statistical power at a significance level of 5% (2 sided).³

The study was conducted in accordance with the principles of the Declaration of Helsinki. Patients (or caregivers) provided written informed consent, and the local ethics committees of all participating centers approved the study.

Effectiveness measure

We prespecified the patient-reported outcome of SFDs as the denominator for the cost-effectiveness analysis. SFDs have been recognized as a clinical outcome with relevance to patients, providers, and other decision makers.¹⁴ An SFD was defined as a complete 24-hour period with no asthma symptoms. Symptoms were measured on the basis of 2-week recall at every clinic visit. Patients recorded details of asthma-related events and asthma control in a notebook between scheduled visits. These data represented the proportion of the aggregate annual number of SFDs during the study period.

Resource use

Medical resource use data for asthma care were collected prospectively and pooled for the analysis.¹³ These data included hospital days, emergency department visits, physician or nurse visits, and telephone calls (to health care providers). Concomitant medication use was recorded and classified by the investigator as asthma or nonasthma related. Asthma-related drugs were grouped into 8 therapeutic classes: short-acting β -agonists, long-acting β -agonists, methylxanthines, cromoglycate and cromoglycate derivatives, ICSs (including combinations), leukotriene antagonists, systemic corticosteroids, and other asthma medications (eg, ipratropium bromide and over-the-counter drugs). Nonasthma-related prescription drugs were ignored.

The number of days a patient missed work or school and the number of days a caregiver missed work as a result of a child's asthma were recorded at each scheduled visit.

Unit cost estimation

The unit cost (in 1999 US dollars) values on the basis of reimbursed amounts for each of the health care resource items was derived from a large medical and pharmacy claims database (PharMetrics Integrated Outcomes Database, 1999). The database contained patient-level reimbursement histories of greater than 16 million managed-care lives throughout the United States. This represented greater than 400 million patient observations of medical and pharmacy-related claims over a rolling 4-year period. This source ensures that the unit costs are typical for the United States.

The unit cost of physician visits was calculated as a weighted average of the cost of a first visit and the cost of a follow-up visit. In some countries nurses or other physician extenders provide asthma-related care. The unit cost for a nurse visit relative to a physician visit was assumed to be proportional to the average annual salary for ambulatory-care nurses compared with family-practice physicians in the United States.

Costs of the 25 most frequently used asthma-related medications (including the active study drug) represented 88% of all concomitant drug days in the study. Unit cost estimates were based on US average wholesale prices (or unit costs) and were reduced by 15% to approximate actual acquisition costs.¹⁵ Because exact dosing information was not available from the study database, cost calculations were based on a standard dose per day (recommended daily dose per product formulation weighted by relative frequency of use in the study database estimated separately for adults and children). Cost estimates for less frequently used drugs or drugs unavailable in the United States were calculated by using average prices within the defined therapeutic class.

The costs for a day absent from work were estimated by using the human capital approach. For children, absences from school were valued by using an estimate of the daily wage rate of the caregiver. Mean daily wage rates were estimated by using the method of Rice and Max for the US workforce.¹⁶

Estimates of costs and outcomes were discounted at a standard annual rate of 3% and presented in 1999 values. In sensitivity analyses other discount rates were used.

Sensitivity analysis

One-way sensitivity analyses were conducted on choice of discount rate and variability in unit cost values applied to trial-derived medical-care resources. Regression analysis was used to adjust the estimates on costs, SFDs, and the ICER for the overall mean values of the gross national product (GNP) per capita and a number of pre-specified baseline socioeconomic and clinical variables.¹³ Evaluation was also conducted on the raw data scale to study the influence from extreme data outliers. The published analysis plan proposed the use of the societal perspective as a sensitivity analysis. Because of its methodologic and quantitative importance, the societal perspective is presented in more detail as a secondary analysis.

Statistical analysis

For each patient, the total discounted 3-year cost and the total discounted number of SFDs were estimated as described in the analysis plan.¹³ Intent-to-treat analysis was performed. Estimates of the arithmetic mean and variance of SFDs and costs and of the covariance between SFDs and costs were computed separately within each age group (5-10, 11-17, and ≥ 18 years) by treatment stratum, assuming that SFDs and the logarithm of cost were bivariate normally distributed. (Mean values from the log-scale are back-transformed into arithmetic and not geometric means on the raw data scale.) The decision to base the analysis on log-transformed cost was made on the observation at blinded review that cost, disregarding treatment group, was extremely positively skewed and heteroscedastic. This decision is in line with recommendations by others and did not change the overall ICERs.¹⁷ Details of the estimation algorithms are provided in a Technical Appendix in the Online Repository (at www.mosby.com/jaci).

For presentation of cost components, costs were computed on the raw data scale to maintain additivity. Results based on the log-transformed scale are more suitable for statistical inference, whereas results on the raw data scale describe the actual costs (including those from extreme outliers).

Linear regression analyses, run separately within each age group by treatment stratum, of SFDs and of log-transformed costs were made by using the following: (1) GNP per capita; (2) sex; (3) smoking status; (4) prebronchodilator FEV₁ as a percentage of predicted normal values; and (5) percentage SFDs at baseline as covariates. Adjusted (to the mean value of each covariate by age group) and back-transformed estimates were included in the sensitivity analysis. Statistical analysis was performed with SAS software (version 8; SAS Institute Inc, Cary, NC).

Role of the funding source

The study was funded through a contract from AstraZeneca Research and Development. The sponsors of the study had no role in the cost-effectiveness study design, data analysis, and interpretation of the results, with the exception of the company coauthors who participated in all aspects of the study. All investigators had unlimited access to the raw data and statistical reports.

RESULTS

Background data

Seven thousand two hundred forty-one patients entered the study. Data from 4 centers (56 patients) were discarded for administrative reasons. Twenty patients did not receive the study drug, leaving 7165 patients (budesonide, 3597; usual asthma therapy, 3568) for analysis. Drop-out rates and reasons for discontinuation were equally distributed between the 2 groups.¹¹ A total of 5155 patients completed the 3-year follow-up.

TABLE I. Demographics, clinical characteristics, and drug use at baseline

Variable	Usual asthma therapy (n = 3568)	Budesonide (n = 3597)
Age, y (mean [SD])	24.3 (14.8)	23.7 (14.6)
Distribution, y (%)		
5-10	27.3	27.8
11-17	16.3	17.8
≥ 18	56.4	54.4
Sex (% female)	54.0	54.2
SFDs in past 14 d, mean (SD)	9.05 (3.76)	9.03 (3.79)
Distribution, d (%)		
0	8.8	8.6
1-3	34.6	36.3
4-7	35.8	33.5
>7	20.8	21.6
Smoking status (%)*		
Active	20.3	20.5
Passive	30.1	28.0
Never	49.6	51.5
Duration of asthma, mo (%)		
<3	35.7	36.8
3-6	13.3	14.4
6-12	16.9	15.5
>12	34.1	33.3
Prebronchodilator FEV ₁ (% predicted), mean (SD)	86.6 (13.9)	86.3 (13.9)
Drug use at start of study (%)†		
Inhaled glucocorticosteroids	5.1	4.9
Oral-systemic glucocorticosteroids	4.5	4.0
Short-acting β_2 -agonist	64.6	63.5
Long-acting β_2 -agonist	3.1	2.6
Xanthine	11.4	11.4
Cromone	7.5	7.9
Leukotriene modifier	0.1	0.1
Other	11.9	12.6
None	24.3	24.6

*Active denotes current or previous smoker. Passive denotes passive but not active smoker. Never denotes neither active nor passive smoker.

†Percentage of patients receiving additional antiasthma therapy during the 6 weeks preceding the entry visit.

Cost data were available for all 7165 patients of the analysis set, but efficacy data were available for only 6829 patients because 336 (4.7%) patients dropped out before the first efficacy assessment. Hence the outcome measure of the cost-effectiveness ratio is based on a 95.3% subset of the patients contributing to the cost variable. For patients who dropped out of the trial, costs were linearly extrapolated to the full 3-year study period.

Table I presents baseline characteristics of the enrollees. At baseline, recently experienced rates of SFDs were equally balanced between the 2 treatment groups.

Effectiveness

Patients receiving both budesonide and usual asthma therapy had improvement in SFDs in the first 6 weeks, and these effects were sustained over the trial period. The

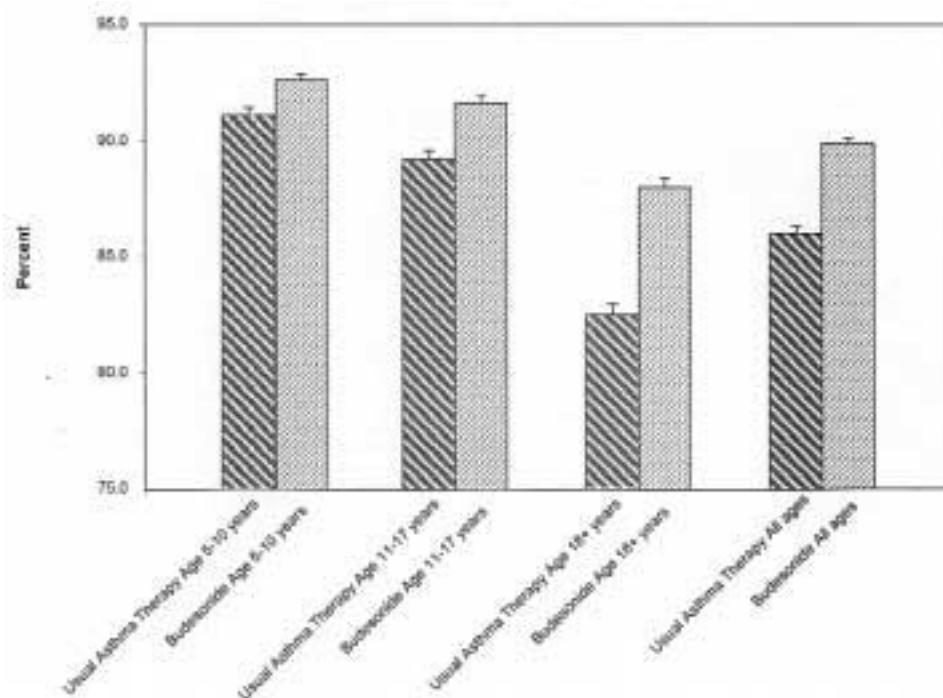


FIG 1. Percentage of SFDs (nondiscounted) over the 3-year study period.

difference in SFDs between the 2 groups was statistically significant ($P < .001$) and favored budesonide at every time point. Budesonide-treated patients experienced an average of 14.1 (SE, 1.3) fewer days with asthma symptoms per year than the usual asthma therapy group. The mean number of SFDs gained per year in each of the 3 age groups was 5.6 for children, 8.9 for adolescents, and 20.0 for adults ($P < .001$ for all age groups), as can be determined from Fig 1. Discounted values were approximately 5% lower.

Unit costs and resource use

Unit costs and resource data are presented by age group and overall in Table II. At the end of 3 years, patients in the budesonide group experienced a reduction of 69% in the number of hospital days ($P < .001$), a 67% reduction in the number of emergency treatments ($P < .05$), and a 36% reduction in the number of physician visits ($P < .001$). Schooldays and workdays lost were reduced by 37% ($P < .001$). In addition, there were 25% fewer workdays lost by caregivers on behalf of asthmatic patients ($P = .07$).

Table III shows the use of asthma-related concomitant medication by drug class presented separately within each stratum and overall within each treatment group. In the budesonide group the reductions compared with usual therapy in daily doses of additional inhaled and oral-systemic corticosteroids were 49% and 58%, respectively ($P < .001$). Consumption of drugs in other classes also was reduced in the budesonide group.

Taken together, the major cost components were concomitant medications (42% of total costs in the usual asthma therapy group and 34% in the budesonide group), absences from work or school (34% and 21%), hospitalizations (15% and 5%), and budesonide (35%).

Cost-effectiveness

Table IV presents the denominator and numerator for the assessment of cost-effectiveness and the ICER. In the primary analysis, from the health care payer perspective, the net difference in discounted costs was \$458, which translated into an additional cost in the budesonide treatment group of \$0.42 (SE, \$0.036) per day. When, in the secondary analysis from a societal perspective, the costs of absences from work or school are included, the net difference in costs over 3 years is \$152, which is equivalent to a daily additional cost of \$0.14 (SE, \$0.07). By using the entire study sample, the ICER was \$11.30 per SFD gained (95% CI, \$8.60-\$14.90) from the health care payer perspective and \$3.70 per SFD gained (95% CI, \$0.10-\$8.00) from the societal perspective.

The results varied between age groups, particularly when the costs for being absent from school or work were included. In the youngest age group, budesonide treatment improved SFDs by 16.7 (SE, 4.8) and reduced costs compared with usual therapy by an average of \$192 (SE, \$184) during the 3-year period. The cost reduction in the youngest age group was due to a lower dose of budesonide and lower rates of health care services and schooldays lost.

TABLE II. Unit cost values and 3-year health care resource use rates by age and treatment group

		Units, mean (SE)								
		Usual asthma therapy (n = 3568)				Budesonide (n = 3597)				
Item	Unit cost (US\$)	5-10 y	11-17y	≥ 18 y	Overall (all ages)	5-10 y	11-17 y	≥ 18 y	Overall (all ages)	Overall difference* [% difference]
Direct medical care										
Hospital days	694.00	0.39	0.44	0.66	0.55 (0.12)	0.20	0.12	0.17	0.17 (0.03)	−0.38§ (0.12) [−69%]
Emergency visits	89.00	0.05	0.06	0.11	0.09 (0.02)	0.03	0.01	0.03	0.03 (0.01)	−0.06† (0.03) [−67%]
Physician visits	47.00	2.53	1.33	1.99	2.03 (0.07)	1.73	1.02	1.17	1.30 (0.05)	−0.73§ (0.09) [−36%]
Nurse visits	36.00	0.17	0.11	0.12	0.13 (0.02)	0.06	0.09	0.08	0.08 (0.01)	−0.05‡ (0.02) [−38%]
Telephone contacts	8.00	0.89	0.47	0.57	0.64 (0.04)	0.57	0.47	0.34	0.42 (0.03)	−0.22§ (0.05) [−34%]
Indirect nonmedical care										
Workdays and schooldays lost	162.50	5.67	3.97	5.27	5.16 (0.35)	4.30	3.41	2.63	3.22 (0.22)	−1.94§ (0.42) [−37%]
Caregiver workdays lost	162.50	2.19	0.46	0.05	0.71 (0.10)	1.45	0.45	0.09	0.53 (0.08)	−0.18 (0.13) [−25%]

*Difference = Budesonide – Usual asthma therapy; % Difference = $100 \times (\text{Budesonide} - \text{Usual asthma therapy}) / \text{Usual asthma therapy}$. Statistical test of difference: Stratified Wilcoxon test for hospital days and stratified z test for other items. Tests are 2 tailed.

†Significant at $P < .05$; ‡significant at $P < .01$; §significant at $P < .001$.

TABLE III. Drug cost per daily dose and 3-year anti-asthma drug consumption by age and treatment group

Item	Drug cost† (US\$) child/adult	Daily doses, mean (SE)								Overall difference* [% difference]
		Usual asthma therapy (n = 3568)				Budesonide (n = 3597)				
		5-10 y	11-17 y	≥ 18 y	Overall (all ages)	5-10 y	11-17 y	≥ 18 y	Overall (all ages)	
Drug class										
Additional inhaled ICS	1.09/1.64	170.0	131.6	163.9	160.1 (5.2)	87.1	79.8	79.0	81.0 (3.7)	−79.0§ (6.4) [−49%]
Oral/systemic steroid	0.45/0.57	4.4	5.3	11.5	8.5 (1.0)	2.7	1.1	4.8	3.6 (0.4)	−4.9§ (1.0) [−58%]
Short-acting β ₂ -agonist	1.10/1.03	415.9	447.7	427.4	427.7 (5.3)	388.9	418.8	399.3	398.2 (5.1)	−29.5§ (7.3) [−7%]
Long-acting β ₂ -agonist	1.77/1.86	25.9	44.3	69.8	53.4 (3.3)	18.9	21.8	52.1	37.7 (2.8)	−15.6§ (4.3) [−29%]
Xanthine	0.50/0.91	34.9	21.7	72.8	53.6 (3.2)	25.6	20.5	56.8	41.9 (2.8)	−11.7‡ (4.2) [−22%]
Cromone	2.34/2.34	95.8	67.1	32.3	55.7 (3.6)	93.5	65.5	30.7	53.6 (3.5)	−2.1 (5.0) [−4%]
Leukotriene modifier	1.77/1.77	6.7	2.3	6.7	6.0 (1.0)	8.2	4.9	4.2	5.4 (0.9)	−0.6 (1.3) [−10%]
Other	0.47/1.22	86.7	63.1	64.8	70.5 (3.9)	87.1	37.3	64.1	65.5 (3.9)	−5.0 (5.6) [−7%]
Study drug	0.46/0.92									

*Difference = Budesonide – Usual asthma therapy; % Difference = $100 \times (\text{Budesonide} - \text{Usual asthma therapy}) / \text{Usual asthma therapy}$. Statistical test of difference: stratified z test for all items. Tests are 2 tailed.

†Drug cost per daily dose is given as follows: cost at age 5 to 10 years/cost at age 11 years or more.

‡Significant at $P < .01$.

§Significant at $P < .001$.

Sensitivity analysis

The sensitivity analyses were conducted on the health care payer perspective findings. Varying the discount rate

for both costs and health outcomes to 0% and then to 5% changes left the cost-effectiveness ratio (and 95% CI) basically unchanged. Setting the discount rate for costs to 5% and SFDs to 0% produced a cost-effectiveness ratio

TABLE IV. Three-year SFDs, costs, and cost-effectiveness by age

Age group	SFDs,* mean (SE)		Direct costs,* mean (SE)		Total costs,* mean (SE)		Direct cost ICER* (95% CI)	Total cost ICER* (95% CI)
	Usual asthma therapy	Budesonide	Usual asthma therapy	Budesonide	Usual asthma therapy	Budesonide		
5-10 y	948 (3.4)	964 (3.2)	1347 (60)	1516 (45)	2581 (149)	2389 (108)	10.5 (1.2-33.3)	Dominant (-38.1 to 13.7)
11-17 y	928 (5.6)	953 (5.0)	1245 (70)	1907 (48)	1855 (126)	2428 (91)	25.9 (14.2- 66.4)	22.4 (8.4-64.3)
≥18 y	858 (4.4)	916 (3.7)	1402 (45)	1940 (31)	2056 (79)	2249 (47)	9.4 (6.8-12.9)	3.4 (0.2-7.1)
Overall	895 (2.8)	935 (2.4)	1360 (32)	1818 (23)	2166 (64)	2318 (43)	11.3 (8.6-14.9)	3.7 (0.1-8.0)

Dominant, More effective and cost-saving.

*Discounted at 3% per year: mean and SE of SFDs are computed on the raw data scale. Mean and SE of direct costs and total costs are computed by using transformation to log-scale and back-transformation (including smearing). Measurement units for costs and for ICER are US dollars and US dollars per SFD, respectively.

of \$10.5 (95% CI, \$8.0-\$13.9). When all drug costs (concomitant medication and study medication) were decreased by 20% to investigate the effect of discounts and other adjustments to drug-acquisition costs, the result was reduced to \$8.60 (95% CI, \$6.50-\$11.40). Increasing nondrug unit costs by 100% (ICER \$8.70; 95% CI, \$6.00-\$12.30) and decreasing them by 50% (ICER \$12.70; 95% CI, \$10.00-\$16.50) illustrated the effect of extreme variation in resource pricing. In the regression analyses of SFDs and cost, dependence on GNP per capita and baseline SFDs were statistically significant ($P < .001$) within each of the age groups by treatment strata. The ICER, computed by using regression-adjusted estimates, was only marginally lower at \$10.70 (95% CI, \$8.20-\$14.00). Furthermore, the ratio based on direct calculations on the raw data scale was \$8.30 compared with \$11.30 when based on log-transformed costs.

DISCUSSION

The START study investigators have reported that once-daily treatment with low-dose budesonide reduced the risk of a severe asthma-related event by nearly 50%, improved symptom-free time, reduced the need for additional courses of systemic glucocorticoids, and improved FEV₁.¹¹ These data support earlier studies that have shown that regular treatment with ICSs initiated in the year after recognition and diagnosis of asthma can reduce the risk of asthma exacerbations and hospitalizations for asthma and asthma symptoms and can slow the loss of lung function.¹⁸⁻²²

However, clinical data alone, although important, do not address the potential financial effect of this strategy on health care systems nor the question of "value for money." The START study was designed from the outset as a pragmatic, long-term trial to address cost-effectiveness. Enrolled patients were allowed to seek health care, as they would in real life, including the addition of controller medications. Evaluating the results of this trial for

cost-effectiveness, we show that use of budesonide is associated with positive clinical benefits at low additional health care costs.

To put these economic results from mild early onset asthma into context, Ädelroth and Thompson²³ showed that adding budesonide to the treatment of patients with severe (oral-steroid dependent) asthma leads to an overall reduction in health care costs. Rutten-van Mölken et al²⁴ calculated an ICER of \$5.35 per SFD gained (1989 value) when reporting the addition of ICS in adult patients with moderate-to-severe asthma, chronic obstructive pulmonary disease, or both. A recent study based on a computer simulation model of the long-term cost-effectiveness of ICS in mild-to-moderate asthma over a 10-year period arrived at a cost per SFD of \$7.50, which is comparable with the estimate reported above.²⁵ This was translated into an incremental cost of \$13,500 per quality-adjusted life-year, a value generally considered to be cost-effective.

The results from our analyses appear generally comparable with those of previous studies involving patients with more severe asthma. Additionally, the findings from the simulation model provide indirect evidence on a cost per quality-adjusted life-year basis that the START study findings are in the range of what would be considered a cost-effective intervention. However, it is important to note that the methodology might differ substantially between different studies in the asthma area.²⁶

The sensitivity analyses in this study suggested that plausible variation in the discount rate had little effect on the results, even when the rate applied to costs and benefits were different. In addition, setting the cost of school or work absence equal to zero (the health care payer perspective) produced cost-effectiveness ratios that were in line with other studies of ICSs in populations of patients with more severe disease. However, the main findings were sensitive to the range of different cost components included and also somewhat sensitive to relative changes in the unit cost estimates for health care resources and the daily wage

rate. The most notable effect on the result was the relative changes on the unit costs for drugs. In light of these findings, it is important to reemphasize that this health economic analysis used the full international study results but applied US-specific unit costs. Additional analyses with other country unit cost estimates are underway.

We followed prescribed guidelines for reporting the results of cost-effectiveness analyses by publishing our analysis plan and analytic considerations ahead of the completion of the trial. Even with careful consideration of all methodologic aspects, there are a number of potential limitations of this analysis. The patient-reported outcome of SFDs is based on a 3-month extrapolation of a repeated recall period of 2 weeks. Although this approach might affect the estimate of benefit, it is unlikely that it would be different between the 2 treatment groups. A potential problem in this analysis is the existence of a small fraction (<1%) of patients with extreme costs, which heavily skew the cost distribution. Such outliers could occur when a high-cost patient drops out early in the study, and his or her costs are then extrapolated to the full study period. In the present analysis log-transformation/back-transformation of costs reduced the influence of extreme outliers on the final results. In addition, the observed statistical efficiency increases dramatically (by a factor of 5 for the incremental cost and by a factor of 2 for the cost-effectiveness ratio). It should be noted that in this study the log-transformation/back-transformation procedure favors usual care because most of the extreme cost outliers were in the usual asthma therapy group. Finally, although the sample is large, it contains patients from 32 countries. There is no consensus on how best to estimate cost-effectiveness in a multicountry trial such as this, in which the trial is not powered to produce statistically significant differences in the outcomes that drive costs at a country level, therefore preventing meaningful cost-effectiveness analysis at a country level.^{27,28} We chose to use US unit costs, but the data on health care use and the number of SFDs were based on the complete (pooled) trial data for all participating countries. Both the supply of health care and the behavior of individuals and physicians differ between and within countries. However, our sensitivity analysis of the regression-adjusted results supported our main results.

On the basis of data from the START study, long-term treatment with budesonide appears to be cost-effective in patients with mild persistent asthma of recent onset and might be cost saving in the youngest age group.

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