RESEARCH PAPER

Early Improvement in Asthma Control with Budesonide–Formoterol Compared with Budesonide Monotherapy in Newly Diagnosed Asthma: A Three-Month Prospective Real-World Cohort Study

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Received: 24th April, 2026; Revised: 20th May 2026; Accepted: 30th June, 2026; Available Online: 10th July, 2026

ABSTRACT
Asthma remains a major chronic respiratory burden, and inhaled corticosteroid (ICS) therapy is the cornerstone of long-term control. Whether initiating newly diagnosed patients on a budesonide–formoterol (ICS–long-acting β2-agonist) combination delivered through a single inhaler accelerates control compared with budesonide monotherapy has been poorly documented in Indonesian real-world settings. This prospective two-arm cohort study enrolled 44 ICS-naïve adults (18–55 years) with newly diagnosed bronchial asthma in Makassar, allocated by treating-physician decision to budesonide monotherapy (n = 22) or budesonide–formoterol (n = 22). The Asthma Control Test (ACT) score and forced expiratory volume in one second (FEV1) were measured at baseline and at months 1, 2 and 3. Numerical variables are reported as median (interquartile range) and compared using the Mann–Whitney U test; within-group change was assessed by the Friedman test with Wilcoxon post-hoc analysis. The groups were comparable at baseline (ACT 14.0 vs 13.5; p = 0.322). Both regimens improved ACT progressively (Friedman p < 0.001 for each). The combination produced significantly higher ACT scores from month 1 (19.0 vs 16.0; p = 0.001; r = 0.587), widening by month 3 (23.0 vs 19.5; p < 0.001; r = 0.707; Hodges–Lehmann median difference 3.0 points, 95% CI 2.0–4.0) and reaching the 3-point minimal clinically important difference. The greatest separation occurred during the first month (ΔACT 5 vs 3; p < 0.0001; r = 0.926). By month 3, no combination-group patient remained uncontrolled, versus 31.8% on monotherapy (p = 0.009); FEV1 was also consistently higher with the combination. Early budesonide–formoterol delivered meaningfully faster asthma control, and a first-month ACT assessment may identify patients requiring early treatment escalation.

Keywords: asthma; budesonide; formoterol; inhaled corticosteroid; Asthma Control Test; inhalation drug delivery

How to cite this article: Permatasari DI, Tabri NA, Pango FH, Bakri S, Alimuddin S, Zainuddin AA, Early Improvement in Asthma Control with Budesonide–Formoterol Compared with Budesonide Monotherapy in Newly Diagnosed Asthma: A Three-Month Prospective Real-World Cohort Study Int J Drug Deliv Technol2026;16(6): 662-668. DOI: 10.25258/ijddt.16.6.104
Source of support: Nil.
Conflict of interest: None

INTRODUCTION

Bronchial asthma is a chronic inflammatory airway disease that imposes a substantial global health burden. Analysis of the Global Burden of Disease Study 2021 ranked asthma as the second leading cause of death among chronic respiratory diseases, with a global prevalence of about 3,340 cases per 100,000 population and a projected rise in incidence through 2050, particularly in low- and middle-income countries.[1] In Indonesia, the 2023 Indonesian Health Survey reported 877,531 physician-diagnosed asthma patients, corresponding to a national prevalence of 1.6%, a figure likely to underestimate the true burden because of undiagnosed cases in areas with limited access to care.[2] Across low- and middle-income settings, including Southeast Asia, asthma management and control remain frequently inadequate, driven by treatment adherence, inhaler technique and limited access to modern inhaled therapy.[3,4]

Inhaled corticosteroids are the most effective maintenance therapy across all severities of asthma and form the basis of every treatment strategy.[5] The Global Initiative for Asthma (GINA) 2025 defines two treatment tracks for adults and adolescents. Track 1 (preferred) uses low-dose ICS–formoterol as both maintenance and reliever therapy (MART) within a single inhaler across steps 1–4, simplifying treatment and reducing device-handling errors, whereas Track 2 (alternative) uses separate daily maintenance ICS with a short-acting β_2-agonist (SABA) reliever and is recommended only when Track 1 is unavailable or unaffordable.[6,7] Budesonide is among the most widely used ICS and suppresses airway inflammation by binding cytoplasmic glucocorticoid receptors and inhibiting pro-inflammatory transcription factors, with favourable pulmonary deposition and minimal systemic effect.[8]

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Because effectiveness depends on what is delivered to the airway, the inhaled combination of budesonide with the rapid-onset long-acting β_2-agonist formoterol is mechanistically attractive: formoterol produces prompt bronchodilatation and enhances glucocorticoid-receptor sensitivity, complementing the anti-inflammatory action of budesonide.[9] Reliance on SABA reliever monotherapy, by contrast, is associated with increased exacerbation and mortality risk, reinforcing the rationale for ICS–formoterol strategies.[10] Landmark randomised trials, including the SYGMA programme and subsequent studies, have shown that budesonide–formoterol reduces severe exacerbations relative to ICS-based comparators and supports the MART approach.[11,12,13] Nonetheless, comparative real-world evidence on clinical control and lung function during routine use in Indonesian patients remains scarce.

Clinical asthma control is commonly assessed with the Asthma Control Test (ACT), a validated five-item questionnaire scored from 5 to 25 and recommended by GINA for routine monitoring; a change of ≥3 points represents the minimal clinically important difference perceptible to patients.[14,15] Local comparative data on budesonide monotherapy versus budesonide–formoterol with respect to ACT and FEV_1 in Makassar are very limited. This study therefore aimed to compare the effect of the two inhaled regimens on ACT score and FEV_1 in newly diagnosed, ICS-naïve patients over three months of treatment, providing evidence relevant to implementation of GINA 2025 in Indonesian practice.

MATERIALS AND METHODS

Study design and setting. This was an analytic observational study with a prospective, two parallel-group cohort design and a repeated-measures approach, with assessments at baseline (month 0) and at months 1, 2 and 3. The study was conducted at hospitals in Makassar, Indonesia, from January 2026 until the required sample was reached, with each participant observed for three months.

Participants. Eligible participants were adults aged 18–55 years with newly diagnosed bronchial asthma confirmed clinically and by spirometry (post-bronchodilator FEV_1 reversibility ≥12% and ≥200 mL) according to GINA criteria, who were ICS-naïve and had no other pulmonary disease (chronic obstructive pulmonary disease, bronchiectasis or lung malignancy).[6] Patients were excluded if pregnant or breastfeeding, using concomitant systemic corticosteroids or other ICS, experiencing a severe exacerbation or requiring hospitalisation during observation, or having inhaler adherence below 80%. All participants gave written informed consent.

Sample size and groups. The sample size was calculated using the formula for comparison of two independent means ($\alpha = 0.05$ two-sided, power 80%, assumed SD of ACT = 2.1, minimal important difference d = 1.8 ACT points as a conservative bound), yielding a minimum of 22 participants per group. No drop-out occurred, giving 44 analysable participants: 22 receiving budesonide monotherapy (Group A) and 22 receiving budesonide–formoterol (Group B), with treatment allocated by the treating physician's clinical judgment.

Interventions. Group A received budesonide 200 mcg per inhalation via metered-dose or dry-powder inhaler, two inhalations twice daily. Group B received budesonide–formoterol 160/4.5 mcg via Turbuhaler, two inhalations twice daily plus additional as-needed inhalations as reliever (MART).

Outcomes. The primary outcome was the ACT score (five items, each 1–5; total 5–25; ≤19 uncontrolled, 20–24 partly controlled, 25 fully controlled). The secondary outcome was FEV_1 (litres and % predicted) by spirometry. Both were measured at baseline and at months 1, 2 and 3.

Statistical analysis. Data were analysed in SPSS version 22. Normality was tested with the Shapiro–Wilk test given the per-group sample of 22. Within-group change across time was assessed by the Friedman test, with Wilcoxon signed-rank post-hoc tests where significant. Between-group comparisons at each time point used the Mann–Whitney U test, and all numerical variables are reported uniformly as median (interquartile range, IQR) to ensure consistent reporting at small sample size. The distribution of asthma control categories was compared with the chi-square test, or Fisher's exact test when an expected cell frequency was below 5. A two-sided $p < 0.05$ was considered statistically significant. Effect sizes were reported as the rank-biserial correlation (r) for non-parametric comparisons and Kendall's W for the Friedman test, and the Hodges–Lehmann median difference with 95% confidence interval (CI) was reported for between-group contrasts.

Ethics. The study was approved by the Biomedical Research Ethics Committee, Faculty of Medicine, Universitas Hasanuddin, Makassar (registration No. 650/UN4.6.4.5.31/PP36/2026).

RESULTS

Baseline characteristics. Forty-four newly diagnosed asthma patients were equally distributed into the budesonide (n = 22) and budesonide–formoterol (n = 22) groups. Sex distribution was identical (9 men, 40.9%, and 13 women, 59.1%, in each group; p = 1.000), and age did not differ (median 42.5 vs 39.5 years; p = 0.280). Baseline ACT (median 13.5 vs 14.0; p = 0.322) and baseline FEV_1 (p = 0.213) were also comparable, with all participants in the uncontrolled category (ACT < 19). The groups were therefore homogeneous at entry (Table 1).

Table 1. Demographic and clinical characteristics of the study participants

Characteristic	Budesonide (n = 22)	Combination (n = 22)	p value
Sex, n (%)			1.000[a]

Male	9 (40.9)	9 (40.9)	
Female	13 (59.1)	13 (59.1)	
Age, years — median (IQR)	42.5 (35.3–47.8)	39.5 (29.3–45.8)	0.280[c]
ACT, month 1 — median (IQR)	16.0 (15.0–18.0)	19.0 (16.3–19.8)	0.001*[c]
ACT, month 2 — median (IQR)	18.0 (16.3–19.8)	20.0 (19.3–22.0)	0.001*[c]
ACT, month 3 — median (IQR)	19.5 (17.3–21.0)	23.0 (21.0–24.0)	<0.001*[c]
FEV_1, month 1, L — median (IQR)	1.76 (1.65–1.86)	1.86 (1.77–2.06)	0.016*[c]
FEV_1, month 2, L — median (IQR)	1.85 (1.74–1.94)	2.00 (1.89–2.19)	0.001*[c]
FEV_1, month 3, L — median (IQR)	1.93 (1.84–2.00)	2.13 (2.00–2.31)	<0.001*[c]

*[a] Chi-square test; [c] Mann–Whitney U test. *Statistically significant ($p < 0.05$). ACT, Asthma Control Test; FEV_1, forced expiratory volume in one second; IQR, interquartile range.*

ACT over time. ACT increased progressively in both groups. In the budesonide group the median rose from 13.5 at baseline to 16.0, 18.0 and 19.5 at months 1, 2 and 3, whereas in the combination group it rose from 14.0 to 19.0, 20.0 and 23.0 (Table 2, Figure 1). The Friedman test confirmed significant within-group improvement over time in both arms ($p < 0.001$; Kendall's W 0.946 for budesonide and 0.975 for the combination), and Wilcoxon post-hoc tests confirmed that every successive interval was significant ($p < 0.05$).

Table 2. ACT score by time of measurement and between-group comparison

Time	Budesonide (n = 22)	Combination (n = 22)	p value
Baseline	13.5 (12.0–14.8)	14.0 (12.3–15.0)	0.322
Month 1	16.0 (15.0–18.0)	19.0 (16.3–19.8)	0.001*
Month 2	18.0 (16.3–19.8)	20.0 (19.3–22.0)	0.001*
Month 3	19.5 (17.3–21.0)	23.0 (21.0–24.0)	<0.001*
Friedman p	<0.001*	<0.001*	

*Values are median (IQR), compared between groups with the Mann–Whitney U test. *$p < 0.05$. Friedman test with Wilcoxon signed-rank post-hoc: all paired intervals significant in both groups ($p < 0.05$).*

Between-group comparison. ACT did not differ at baseline (median 14.0 vs 13.5; $p = 0.322$; $r = 0.174$), confirming group homogeneity. After one month, ACT was significantly higher with the combination (19.0 vs 16.0; $p = 0.001$; $r = 0.587$ [large]; Hodges–Lehmann median difference 2.0; 95% CI 1.0–3.0). The gap widened at month 2 (20.0 vs 18.0; $p = 0.001$; $r = 0.607$; median difference 2.0; 95% CI 1.0–4.0) and was greatest at month 3 (23.0 vs 19.5; $p < 0.001$; $r = 0.707$; median difference 3.0; 95% CI 2.0–4.0). The progressively increasing effect size ($r = 0.587 \rightarrow 0.607 \rightarrow 0.707$) indicates that the advantage of the combination strengthened with treatment duration, and the 3-point difference at month 3 reached the minimal clinically important difference (Figure 2).[15]

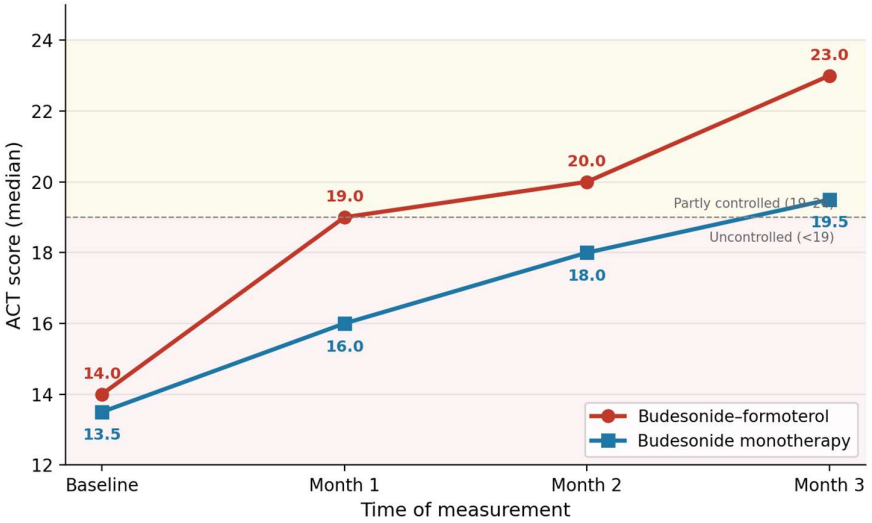

Figure 1. Median Asthma Control Test (ACT) score over three months in the budesonide-monotherapy and budesonide–formoterol groups. The combination group separated from monotherapy by month 1 and the difference widened thereafter, reaching the 3-point minimal clinically important difference at month 3.

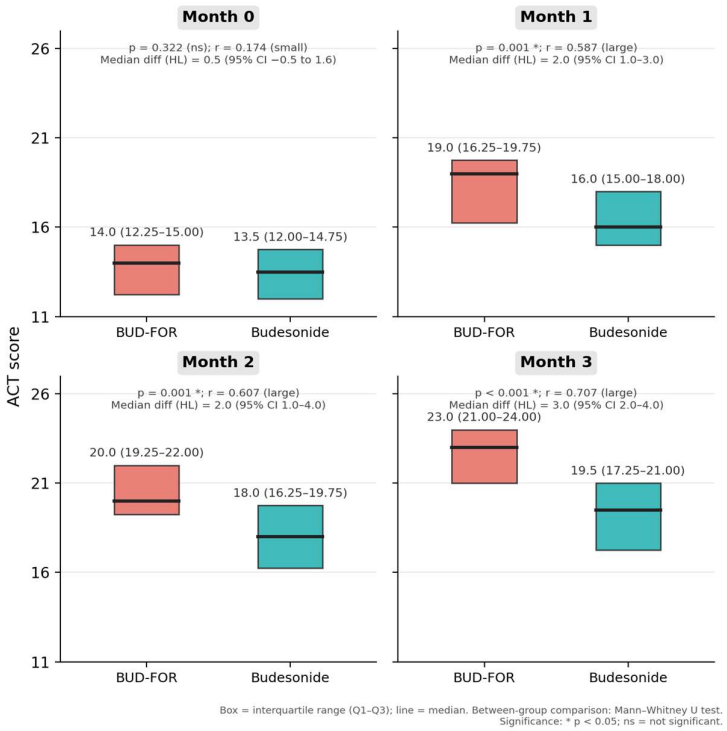

Figure 2. Distribution of ACT scores by treatment group (budesonide–formoterol [BUD-FOR] and budesonide) at baseline (Month 0) and at Months 1, 2 and 3. Each box represents the interquartile range (Q1–Q3) and the horizontal line the median, with the median (IQR) shown above each box. Annotations report the between-group p value, effect size (rank-biserial r) and Hodges–Lehmann median difference (95% CI). Groups were comparable at baseline (p = 0.322, ns) and the combination was significantly superior from Month 1 onward, with the difference greatest at Month 3 (median difference 3.0; 95% CI 2.0–4.0). Between-group comparison by the Mann–Whitney U test (*p < 0.05).

Early advantage. Analysis of ACT change between intervals showed that the increase from baseline to month 1 was significantly larger with the combination (Δ median 5 [IQR 4.0–5.0] vs 3 [IQR 2.3–3.0]; p < 0.0001; r = 0.926 [very large]), the largest effect size in the study. By contrast, the rate of change from month 1 to month 2 (p = 0.493; r = 0.116) and from month 2 to month 3 (p = 0.119; r = 0.267) did not differ between groups, indicating that the benefit of the combination was concentrated in the first month, after which both regimens improved at a comparable rate (Figure 3).

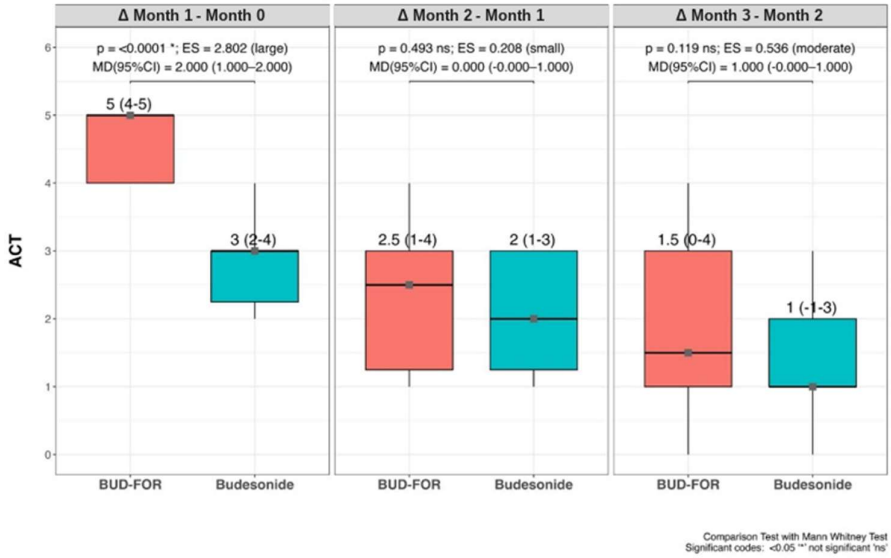

Figure 3. Box-and-whisker plots of the change in ACT score (Δ) between successive intervals (Month 1 − Month 0, Month 2 − Month 1, Month 3 − Month 2) by treatment group. The gain in the first interval was significantly greater with

budesonide–formoterol than with budesonide (median Δ 5 vs 3; p < 0.0001; MD 2.000; 95% CI 1.000–2.000), whereas the subsequent intervals did not differ significantly, illustrating the early advantage of the combination. Values are median (range); between-group comparison by Mann–Whitney U test.

Asthma control status. At month 1, more combination-group patients reached at least partial control (54.5% vs 13.6%; p = 0.011), while more budesonide-group patients remained uncontrolled (86.4% vs 45.5%; p = 0.011); none reached full control in either group (Table 3). At month 2 the proportion partly controlled was 86.4% with the combination versus 45.5% with budesonide (p = 0.011) (Table 4). At month 3, all combination-group patients had reached at least partial control (90.9% partly controlled, 9.1% fully controlled), whereas 31.8% of budesonide-group patients remained uncontrolled (p = 0.009); among patients in the same partly-controlled category, the combination still produced significantly higher ACT scores (median 22.5 vs 21.0; p = 0.008) (Table 5).

Table 3. Asthma control status at month 1

Asthma control status	Budesonide n (%)	Combination n (%)	p value
Fully controlled (ACT ≥25)	0 (0.0)	0 (0.0)	1.000
Partly controlled (ACT 19–24)	3 (13.6)	12 (54.5)	0.011*
Uncontrolled (ACT <19)	19 (86.4)	10 (45.5)	0.011*

**p < 0.05. Fisher's exact test used when an expected cell frequency was below 5.*

Table 4. Asthma control status at month 2

Asthma control status	Budesonide n (%)	Combination n (%)	p value
Fully controlled (ACT ≥25)	0 (0.0)	0 (0.0)	1.000
Partly controlled (ACT 19–24)	10 (45.5)	19 (86.4)	0.011*
Uncontrolled (ACT <19)	12 (54.5)	3 (13.6)	0.011*

**p < 0.05. Fisher's exact test used when an expected cell frequency was below 5.*

Table 5. Asthma control status at month 3

Asthma control status	Budesonide n (%)	Combination n (%)	p value
Fully controlled (ACT ≥25)	0 (0.0)	2 (9.1)	0.488
Partly controlled (ACT 19–24)	15 (68.2)	20 (90.9)	0.132
Uncontrolled (ACT <19)	7 (31.8)	0 (0.0)	0.009*

**p < 0.05. All month-3 comparisons used Fisher's exact test because of expected cell frequencies below 5.*

DISCUSSION

In this prospective real-world cohort of newly diagnosed, ICS-naïve asthma patients, both inhaled regimens significantly and progressively improved asthma control over three months, but budesonide–formoterol produced earlier, larger and clinically meaningful gains compared with budesonide monotherapy. The two groups were comparable at baseline in sex, age, ACT and FEV_1, so the divergence in outcomes can reasonably be attributed to the treatment regimen rather than to baseline differences.

The efficacy of budesonide monotherapy is consistent with the pathophysiology of asthma, in which type-2 airway inflammation mediated by mast cells, eosinophils and T lymphocytes underlies bronchial hyper-responsiveness; ICS suppress this inflammatory substrate and, with sustained use, improve symptom control.[16,17] Untreated persistent inflammation can progress to airway remodelling and fixed obstruction, underscoring the importance of early effective therapy.[18] Because the present study did not include a non-ICS comparator, the ACT improvement observed with budesonide reflects the effectiveness of ICS monotherapy in this setting rather than a direct comparison with a short-acting bronchodilator.

The superiority of the combination reflects the complementary mechanisms of its components: budesonide suppresses inflammation, while formoterol provides long-acting bronchodilatation and enhances glucocorticoid-receptor sensitivity.[9] The progressively increasing effect size (r = 0.707 at month 3) and a between-group median difference of 3.0 points — reaching the minimal clinically important difference — indicate that this advantage is both statistically and clinically relevant.[15] These findings align with the broader evidence base favouring ICS–LABA over ICS monotherapy in inadequately controlled asthma and with guideline recommendations to optimise ICS–LABA before further escalation, although those recommendations specifically address severe asthma whereas the present population comprised newly diagnosed patients with milder disease.[19]

A notable observation is the "early advantage" of the combination: the largest between-group difference occurred in the first month (r = 0.926), after which the rate of improvement became comparable. This is plausibly explained by the rapid onset of formoterol (approximately 1–3 minutes), which yields immediate symptomatic relief reflected in the ACT, whereas the anti-inflammatory effect of ICS accrues over weeks in both arms.[20] Clinically, this supports using a first-month ACT assessment as an early marker of treatment response, allowing earlier escalation

from ICS monotherapy to ICS–LABA when the response is inadequate, without waiting a full three months.

The categorical analysis reinforced these findings. By month 3, no combination-group patient remained uncontrolled, in contrast to roughly one-third of the monotherapy group, and even within the partly-controlled category the combination achieved higher ACT scores. These patterns are consistent with studies of ICS–formoterol reporting better control and fewer exacerbations than ICS monotherapy and with a treatable-traits approach that favours ICS–LABA in persistent bronchoconstriction.[11,13,21,22] Suboptimal control in real-world cohorts is largely driven by treatment-related factors such as adherence and inhaler technique, which a single-inhaler MART strategy may mitigate, and recurrent exacerbations meaningfully impair quality of life, further supporting timely optimisation of inhaled therapy.[23,24] Real-world data from Asian populations, including Indonesia, likewise report consistent control benefits from budesonide–formoterol maintenance and reliever therapy.[25]

This study has limitations. First, treatment was allocated by clinical judgment rather than randomisation, raising the possibility of confounding by indication, although measured baseline characteristics were balanced. Second, the observational design cannot exclude unmeasured confounders such as inhaler technique, environmental exposures and atopy; adherence was controlled at selection (exclusion below 80%) but not measured with a validated instrument such as the MMAS-8 or the Test of Adherence to Inhalers. Third, the sample of 22 per group, although meeting the calculated requirement, is relatively small for subgroup detection. Fourth, the three-month horizon precludes assessment of long-term outcomes such as exacerbation rate, hospitalisation and airway remodelling. Randomised controlled trials with longer follow-up and validated adherence measurement are needed to confirm these findings.

CONCLUSION

Both budesonide monotherapy and budesonide–formoterol effectively improved asthma control in newly diagnosed, ICS-naïve patients, but the budesonide–formoterol combination delivered earlier and greater improvement in ACT score, asthma control status and FEV_1, with a month-3 median difference of 3.0 ACT points that was both statistically and clinically significant. The advantage was concentrated in the first month, suggesting that a first-month ACT assessment can serve as an early marker of response and a trigger for timely escalation to ICS–LABA. Given the non-randomised allocation, these results support — but do not definitively prove — budesonide–formoterol as the more optimal initial inhaled regimen; confirmation by randomised controlled trials remains necessary.

ACKNOWLEDGEMENTS

The authors thank the staff of the Department of Internal Medicine, Faculty of Medicine, Universitas Hasanuddin Makassar, and all participants who took part in this study.

Conflict of interest: The authors declare no conflict of interest.

Funding: This research received no specific grant from any funding agency.

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