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Original Research Article

OUTCOMES OF SINGLE COMBINATION INHALER VERSUS MULTIPLE INHALER IN ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Background: The aim is to evaluate the clinical efficacy and safety outcomes of single-inhaler triple therapy (ICS/LABA/LAMA) versus multiple-inhaler dual therapy (ICS/LABA + LAMA) in patients with moderate-to-severe asthma and COPD over an 18-month treatment period. **Materials and Methods:** A prospective, open-label, comparative clinical study was conducted over 18 months involving 150 patients (75 in each group) aged 18-75 years with documented asthma-COPD overlap or moderate-to-severe COPD. Group A received single-inhaler combination therapy (budesonide/ formoterol/ glycopyrronium), while Group B received the same medications in multiple inhalers. Primary outcome measures included exacerbation rates, forced expiratory volume in 1 second (FEV_1), COPD Assessment Test (CAT) scores, and treatment adherence. Secondary outcomes included dyspnea scores (mMRC), quality of life measures (SGRQ), and adverse events. Statistical analysis employed intention-to-treat methodology with repeated measures ANOVA and logistic regression. **Result:** Single-inhaler triple therapy demonstrated superior clinical outcomes compared to multiple-inhaler therapy. Exacerbation rates were significantly reduced in the SITT group (0.45 events per patient per year vs. 1.23 in MIT, $p<0.001$). Mean FEV_1 improvement was greater in SITT (18.2% vs. 9.7%, $p=0.002$). Treatment adherence was significantly higher in SITT (86.7% vs. 64.3%, $p<0.001$). CAT scores improved by 4.2 points in SITT versus 2.1 points in MIT ($p=0.008$). Adverse event profiles were comparable between groups ($p=0.156$). **Conclusion:** Single-inhaler triple therapy significantly improves clinical outcomes, adherence, and symptom control in asthma and COPD patients compared to multiple-inhaler therapy. The simplified regimen reduces exacerbation rates and healthcare burden, making it the preferred therapeutic approach for moderate-to-severe disease requiring triple therapy.

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) represent significant global health challenges, affecting over 330 million individuals worldwide and contributing substantially to morbidity and mortality. While asthma and COPD are distinct pathophysiological entities, patients with overlapping features (asthma-COPD overlap syndrome, ACOS) present unique therapeutic challenges. Inhaled corticosteroids (ICS), long-acting beta-2 agonists (LABA), and long-acting muscarinic antagonists (LAMA) form the cornerstone of pharmacological management for moderate-to-severe disease.[1-3]

The introduction of inhaled corticosteroid/long-acting beta-2 agonist (ICS/LABA) combination inhalers represented a paradigm shift in respiratory disease management, demonstrating superior efficacy and improved adherence compared to separate component therapy. More recently, fixed-dose triple-therapy combinations incorporating ICS/LABA/LAMA in a single inhaler have emerged as increasingly relevant therapeutic options, particularly for COPD patients experiencing inadequate symptom control or frequent exacerbations on dual therapy.[4-6]

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The rationale for combining all three agents in a single inhaler extends beyond mere convenience. Multiple epidemiological and clinical studies have documented that medication adherence remains a critical determinant of therapeutic success in obstructive airway disease. With the average COPD patient requiring multiple daily medications, polypharmacy contributes to medication non-adherence, suboptimal disease control, and increased healthcare resource utilization. The transition from multiple-inhaler therapy (MIT) to single-inhaler triple therapy (SITT) addresses this fundamental barrier, providing all three classes of medications in one device, thereby simplifying the therapeutic regimen and potentially enhancing compliance.[7-9]

The pivotal randomized controlled trials establishing the efficacy of fixed triple therapy (such as the TRILOGY and TRINITY studies) demonstrated significant reductions in exacerbation rates and improvements in lung function and quality of life compared to various two-component regimens. However, most published evidence derives from controlled trial populations that may not fully represent real-world clinical practice, where patient populations are more heterogeneous and adherence patterns differ substantially from trial conditions.[10]

This study was designed to evaluate the real-world comparative effectiveness of single-inhaler triple therapy versus multiple-inhaler dual therapy (ICS/LABA combined with separate LAMA) in a diverse patient cohort with asthma-COPD overlap and moderate-to-severe COPD over an extended 18-month observation period. We hypothesized that single-inhaler triple therapy would demonstrate superior clinical outcomes through enhanced adherence, reduced exacerbation rates, improved lung function, and better symptom control.[11,12]

MATERIALS AND METHODS

Study Design and Setting: This was a prospective, open-label, non-randomized comparative clinical study conducted at a tertiary respiratory medicine department over 18 months (January 2024 to June 2025). The study was approved by the institutional ethics committee and registered with the Clinical Trials Registry (CTRI reference number pending).

Study Population: The study enrolled 150 consecutive adult patients aged 18-75 years meeting diagnostic criteria for asthma-COPD overlap syndrome (ACOS) according to GINA/GOLD guidelines or moderate-to-severe COPD (GOLD stage 2 or 3). Inclusion criteria included: (1) documented diagnosis with FEV_1 <80% predicted; (2) ≥2 exacerbations in the preceding 12 months; (3) CAT score ≥10; (4) willingness to provide informed consent. Exclusion criteria comprised: (1) acute exacerbation within 4 weeks of enrollment; (2) severe comorbidities affecting compliance; (3) pregnancy or lactation; (4) smoking <100 pack-years cessation within 6 months; (5) prior triple therapy exposure.

Intervention Group A (n=75) received single-inhaler triple therapy: budesonide160 mcg/formoterol fumarate 4.8 mcg/glycopyrronium 9 mcg per actuation, two inhalations twice daily. Group B (n=75) received the same pharmacological components in separate inhalers: formetrol 6 mcg budesonide 200 mcg twice daily plus tiotropium 18 mcg once daily via separate devices.

Outcome Measures

Primary Outcomes

- Annualized moderate-to-severe exacerbation rate
- Change in FEV_1 from baseline
- COPD Assessment Test (CAT) score change
- Treatment adherence (defined as ≥80% expected inhaler use)

Secondary Outcomes

- Modified Medical Research Council (mMRC) dyspnea scale
- Saint George's Respiratory Questionnaire (SGRQ) total score
- Adverse events and serious adverse events

RESULTS

Table 1: baseline patient characteristics and demographics

Parameter	SITT Group (n=75)	MIT Group (n=75)	P-value
Age (years, mean ± SD)	62.3 ± 8.7	61.9 ± 9.2	0.758
Male gender, n (%)	48 (64.0)	51 (68.0)	0.582
Smoking history (pack-years)	42.1 ± 18.5	44.7 ± 16.3	0.401
Current smokers, n (%)	12 (16.0)	14 (18.7)	0.631
Body Mass Index (kg/m²)	26.8 ± 4.2	27.1 ± 3.9	0.682
Baseline FEV_1 (% predicted)	54.2 ± 14.3	53.8 ± 15.1	0.834
Baseline FVC (% predicted)	72.6 ± 16.8	73.1 ± 17.4	0.872
FEV_1/FVC ratio (%)	58.3 ± 9.4	57.9 ± 10.2	0.763
COPD Assessment Test (CAT)	24.6 ± 6.2	25.1 ± 6.8	0.641
mMRC Dyspnea Score	2.4 ± 0.8	2.5 ± 0.9	0.519
SGRQ Total Score	68.4 ± 12.3	69.2 ± 13.1	0.705
Prior exacerbations (12 months)	3.2 ± 1.4	3.4 ± 1.6	0.421
Exacerbations requiring hospitalization	1.1 ± 0.9	1.2 ± 1.0	0.563

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Table 2: pulmonary function and lung function outcomes

Parameter	SITT Group	MIT Group	P-value
FEV_1 (% predicted)			
Baseline	54.2 ± 14.3	53.8 ± 15.1	0.834
6 months	62.1 ± 13.8	58.7 ± 14.2	0.087
12 months	67.3 ± 12.6	61.9 ± 13.7	0.004
18 months	72.4 ± 11.9	63.5 ± 14.3	0.001
Change from baseline (mean ± SD)	18.2 ± 8.3%	9.7 ± 7.6%	0.002
FEV_1/FVC Ratio (%)			
Baseline	58.3 ± 9.4	57.9 ± 10.2	0.763
18 months	66.2 ± 8.7	61.4 ± 9.8	0.003
Mean change	7.9 ± 5.1%	3.5 ± 4.8%	0.001
FVC (% predicted)			
Baseline	72.6 ± 16.8	73.1 ± 17.4	0.872
18 months	79.3 ± 15.2	74.8 ± 16.9	0.128

Table 3: clinical outcomes and exacerbation rates

Parameter	SITT Group	MIT Group	P-value
Exacerbation Rates (18-month period)			
Total exacerbations reported	34	92	<0.001
Mean exacerbations per patient	0.45 ± 0.8	1.23 ± 1.1	<0.001
Exacerbation rate reduction (%)	63.4%		
Moderate exacerbations (oral corticosteroids)			
Patients with ≥1 event, n (%)	15 (20.0)	38 (50.7)	<0.001
Mean events per affected patient	1.3 ± 0.6	2.1 ± 0.9	0.018
Severe exacerbations (hospitalization)			
Patients with ≥1 event, n (%)	4 (5.3)	17 (22.7)	0.003
Total hospitalizations	5	24	0.005
Hospital-free days (mean)	542 ± 15	488 ± 42	<0.001
COPD Assessment Test (CAT) Scores}			
Baseline	24.6 ± 6.2	25.1 ± 6.8	0.641
18 months	20.4 ± 5.9	23.0 ± 6.5	0.028
Mean improvement	4.2 ± 3.1	2.1 ± 2.8	0.008
CAT responders (≥2 point improvement), n (%)	63 (84.0)	48 (64.0)	0.008
Reliever Medication Use (actuations/week)			
Baseline	8.4 ± 4.2	8.1 ± 3.9	0.641
18 months	2.1 ± 1.8	4.3 ± 2.5	0.001

Table 4: adherence, quality of life, and safety profile

Parameter	SITT Group	MIT Group	P-value
Medication Adherence}			
Mean adherence rate (%)	86.7 ± 8.3	64.3 ± 14.2	<0.001
Patients with ≥80% adherence, n (%)	68 (90.7)	38 (50.7)	<0.001
Patients with ≥90% adherence, n (%)	54 (72.0)	19 (25.3)	<0.001
Mean pharmacy refill consistency	0.91 ± 0.07	0.62 ± 0.15	<0.001
Quality of Life (SGRQ Total Score)}			
Baseline	68.4 ± 12.3	69.2 ± 13.1	0.705
18 months	48.2 ± 11.6	58.7 ± 12.4	<0.001
Mean improvement (points)	20.2 ± 9.8	10.5 ± 8.3	<0.001
Clinical improvement (≥4 point drop), n (%)	69 (92.0)	52 (69.3)	0.001
Modified Medical Research Council Dyspnea Scale}			
Baseline	2.4 ± 0.8	2.5 ± 0.9	0.519
18 months	1.4 ± 0.7	1.9 ± 0.8	0.002
Mean improvement	1.0 ± 0.6	0.6 ± 0.5	0.001
Adverse Events}			
Patients with any adverse event, n (%)	18 (24.0)	21 (28.0)	0.583
Tremor/palpitations	4	5	0.738
Oral candidiasis	3	4	0.695
Headache	6	7	0.801
Cough	5	5	1.000
Serious adverse events	0	1 (pneumonia)	0.317
Patient Satisfaction (VAS 0-10 scale)}			
Device ease of use	8.7 ± 1.2	6.2 ± 2.1	<0.001
Symptom control satisfaction	8.4 ± 1.4	6.8 ± 1.9	<0.001
Overall treatment satisfaction	8.5 ± 1.3	6.9 ± 2.0	<0.001

This 18-month prospective study enrolled 150 patients with asthma-COPD overlap (n=42) or moderate-to-severe COPD (n=108). Baseline characteristics were comparable between groups [Table 1], with no significant differences in age, smoking history, baseline lung function, or symptom severity (all p>0.05).

Consistent with the primary endpoint, single-inhaler triple therapy demonstrated significantly greater improvements in forced expiratory volume in 1

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second (FEV_1) compared to multiple-inhaler therapy [Table 2]. The SITT group achieved a mean FEV_1 improvement of 18.2 ± 8.3% from baseline to 18 months, compared to 9.7 ± 7.6% in the MITT group (p=0.002). At the 18-month assessment point, absolute FEV_1 values were 72.4 ± 11.9% predicted in SITT versus 63.5 ± 14.3% predicted in MIT (p=0.001). The FEV_1/FVC ratio similarly improved more substantially in SITT patients, with mean increases of 7.9 ± 5.1% versus 3.5 ± 4.8% in MITT.

The COPD Assessment Test (CAT) demonstrated clinically meaningful improvements in symptom control favoring SITT. Mean CAT scores decreased by 4.2 ± 3.1 points in SITT patients versus 2.1 ± 2.8 points in MIT patients (p=0.008), with 84.0% of SITT patients achieving CAT score improvements of ≥2 points compared to 64.0% in MIT. The Saint George's Respiratory Questionnaire (SGRQ) total score showed substantial improvements in quality of life with SITT, with mean improvements of 20.2 ± 9.8 points compared to 10.5 ± 8.3 points in MIT (p<0.001)

A critical finding was the substantially superior adherence with single-inhaler therapy. Mean medication adherence in SITT patients was 86.7 ± 8.3% compared to 64.3 ± 14.2%. The adverse event profiles were remarkably similar between groups, with 24.0% of SITT patients experiencing at least one adverse event compared to 28.0% of MITT patients (p=0.583).

Patient satisfaction assessments revealed significantly higher satisfaction with SITT [Table 4]. Device ease of use was rated 8.7 ± 1.2 on a 0-10 visual analog scale in SITT versus 6.2 ± 2.1 in MIT (p<0.001).

Statistical Analysis: Data were analyzed using SPSS version 26.0 with intention-to-treat methodology. Continuous variables were expressed as mean ± standard deviation; categorical variables as frequencies and percentages. Comparison between groups employed independent t-tests for continuous variables and chi-square tests for categorical variables. Time-course analyses utilized repeated measures ANOVA with Bonferroni correction. Logistic regression evaluated factors predicting exacerbation reduction. P-value <0.05 denoted statistical significance.

DISCUSSION

The present 18-month prospective comparative study provides compelling real-world evidence supporting the superiority of single-inhaler triple therapy over multiple-inhaler dual therapy in patients with asthma-COPD overlap and moderate-to-severe COPD. The magnitude of clinical benefit observed, particularly in exacerbation reduction and quality of life improvement, is substantial and has important therapeutic implications.[13]

The 63.4% relative reduction in exacerbation rate with SITT compared to MIT represents the most clinically significant finding of this study. The annualized exacerbation rate of 0.45 events per patient per year in SITT patients compares favorably with landmark pivotal trials. In the TRILOGY study evaluating triple therapy, mean exacerbation rates in the triple therapy group were reported at approximately 0.50 events per patient per year, strikingly concordant with our findings. Similarly, the TRINITY study demonstrated triple therapy reduced moderate-to-severe exacerbations versus LAMA monotherapy with a hazard ratio of 0.65. Our MIT exacerbation rate of 1.23 events per patient per year exceeds rates reported in dual therapy arms of comparable trials, potentially reflecting our real-world population's greater baseline disease severity and prior exacerbation frequency.[14-16]

However, the markedly superior exacerbation reduction in SITT versus MIT cannot be attributed solely to superior pharmacology, as both groups received identical pharmacological components. Rather, the substantial difference likely reflects enhanced medication adherence with simplified regimen. This is strongly supported by our adherence data demonstrating 86.7% adherence with SITT versus 64.3% with MIT. This adherence superiority translates directly into more consistent airway inflammation suppression and smoother bronchodilation, reducing the sudden inflammation-driven exacerbations characteristic of suboptimal control.[17-19]

Vanfleteren et al. in their comprehensive 2018 review concluded that "triple therapy is the most effective treatment in moderate/severe symptomatic patients with COPD at risk of exacerbations, with marginal if any risk of side effects. Our data provide additional support for this conclusion in real-world practice settings. Furthermore, our findings extend evidence to asthma-COPD overlap patients, where exacerbation prevention is equally critical.[20]

The FEV_1 improvement of 18.2% in SITT patients versus 9.7% in MIT patients represents a differential benefit of nearly 9 percentage points—clinically meaningful by any standard. This greater FEV_1 response in SITT is consistent with several mechanisms. First, enhanced adherence allows more consistent delivery of the triple-therapy pharmacological stimulus, supporting sustained airway smooth muscle relaxation and improved elastic recoil. Second, the avoidance of medication gaps inherent in multiple-inhaler regimens means continuous LAMA effect without intermittent lapse, as missed doses of any single component (particularly the LAMA, requiring daily device preparation) are less likely with a single device.[21]

Comparative effectiveness studies examining ICS/LABA/LAMA therapy have consistently shown FEV_1 improvements in the range of 15-18% from baseline. Our SITT cohort achieved improvements within this well-established range, while our MITT comparator showed suboptimal response, likely reflecting adherence-related loss of benefit. This suggests that real-world MIT users frequently

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experience subtherapeutic FEV_1 responses due to inconsistent dosing, supporting the therapeutic rationale for SITT. The FEV_1/FVC ratio improvement in SITT (7.9% vs 3.5% in MITT) provides additional evidence of sustained bronchodilation, as this ratio is less susceptible to effort-dependent variation than FEV_1 alone. This objective measure of improved airflow dynamics further validates the clinical benefit of SITT.

The SGRQ score improvement of 20.2 points in SITT versus 10.5 points in MIT represents substantial quality of life gains. Minimal clinically important differences (MCID) for SGRQ are typically established at 4 points. By this standard, 92% of SITT patients achieved clinically meaningful improvement compared to 69.3% of MITT patients. The SGRQ encompasses diverse dimensions including symptoms, activity limitation, and psychosocial impact—all substantially improved with SITT. This real-world quality of life benefit exceeds what adherence differences alone might predict, suggesting that improved symptom control and reduced anxiety about exacerbations create psychological benefits beyond medication optimization.

The CAT score improvements are similarly impressive. The CAT is a validated, patient-friendly 8-item questionnaire specifically developed for COPD symptom assessment. The 4.2-point improvement in SITT versus 2.1-point improvement in MIT is substantial, with 84% of SITT patients achieving improvements of ≥2 points. CAT score improvements of ≥2 points are generally considered clinically significant.Dyspnea reduction, measured by the mMRC scale, favored SITT with 1.0-point improvement versus 0.6-point improvement in MIT. Given that dyspnea is the most distressing symptom for COPD and asthma patients and directly impacts exercise tolerance and quality of life, this improvement represents meaningful clinical benefit. The mMRC scale improvement correlates with healthcare utilization reduction and mortality in COPD, suggesting our findings have prognostic significance.

The reduced reliever medication use in SITT (2.1 vs. 4.3 actuations/week) objectively demonstrates improved disease control and reduced breakthrough symptoms. This reduction in SABA use is particularly important given emerging evidence suggesting frequent SABA use may be associated with adverse outcomes. The 36.4% superior adherence in SITT compared to MIT likely represents the primary mechanism driving outcome superiority. This finding aligns with the systematic literature review by Braido et al., which identified that single-inhaler combinations demonstrated greater adherence across nine observational studies, with statistical significance in seven studies. The pooled analysis by Rogliani et al. examining ICS/LABA single versus dual inhalers demonstrated adherence rates of 71-79% with single inhalers versus 48-65% with separate components, closely paralleling our findings.

Medication adherence in COPD and asthma is notoriously poor, with average adherence rates of 50-60% reported in real-world cohorts. The 86.7% adherence achieved with SITT in our study substantially exceeds typical real-world performance and approaches adherence rates achieved in controlled clinical trials. The simplified regimen reduces daily decisions, simplifies instructions, and decreases the cognitive and behavioral burden associated with multiple-device therapy.Importantly, our adherence assessment employed multiple methodologies: patient-reported adherence via device counts, pharmacy refill consistency, and direct inhaler device counters. The consistency across these independent measurement approaches strengthens confidence in the adherence findings. The adherence-exacerbation relationship is bidirectional and mutually reinforcing: improved adherence reduces exacerbations, which further enhances patient confidence and motivation to continue therapy.

Our findings are highly concordant with the existing literature. The TRILOGY study, evaluating beclometasone/ formoterol/ glycopyrronium in moderate-to-severe COPD with prior exacerbations, demonstrated rate ratio of 0.62 for moderate-to-severe exacerbations versus LAMA/LABA, remarkably similar to our findings. The TRINITY study showed similar efficacy. Both studies demonstrated FEV_1 improvements consistent with our SITT findings. However, most prior studies compared triple therapy to dual-therapy inhalers, not to multiple separate inhalers. Our study's specific comparison of SITT to MIT (receiving identical pharmacological components) isolates the effect of regimen simplification from pharmacological differences. This design strengthens conclusions about the critical role of adherence in determining clinical outcomes.

Real-world effectiveness studies examining single versus multiple-inhaler therapy directly support our findings. González-González et al. recently published data comparing SITT to MIT in COPD, documenting exacerbation rate reduction from 1.35 to 0.72 events per patient per year with SITT, CAT score improvement of 2.86 points, FEV_1 improvements, and enhanced adherence. These findings closely parallel our results. Similarly, studies from South Korea examining the transition from MITT to SITT demonstrated CAT score improvements of 1.40 points, FEV_1/FVC ratio improvements of 4.31%, and exacerbation rate reduction. Economic analyses strongly favor SITT. Braido et al.'s systematic review identified six studies documenting reduced healthcare resource use with single-inhaler therapy and five demonstrating cost-effectiveness. The substantial exacerbation reduction in our SITT cohort (from 1.23 to 0.45 events per year) would translate to significant cost savings through reduced emergency department visits,

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hospitalizations, and oral corticosteroid prescriptions.

Limitations include non-randomized design (though baseline characteristics were well-balanced), open-label design (though this reflects real-world clinical practice), single-center setting (limiting generalizability), and lack of pharmacoeconomic data (though documented exacerbation reduction would support cost-effectiveness).

Clinical Implications: These findings support modification of clinical practice toward preferential use of SITT in patients requiring triple therapy. Current GOLD guidelines recommend triple therapy for COPD patients with persistent exacerbations despite dual therapy. Our data suggest SITT is preferable to MIT when triple therapy is indicated, with substantially superior outcomes due to enhanced adherence and consistent medication delivery.For asthma patients, particularly those with overlapping COPD features or inadequate ICS/LABA control, SITT offers a therapeutic option with strong adherence and efficacy support. The simplified regimen is particularly valuable in elderly patients with multiple comorbidities and complex medication regimens, where reducing pill/device burden improves overall medication management.

Healthcare providers should actively communicate to patients the rationale for single-inhaler simplification, addressing potential concerns about "combining drugs" by explaining how the three complementary mechanisms work together to suppress airway inflammation and prevent exacerbations. Patient education about correct inhaler technique remains essential regardless of device type.

CONCLUSION

This 18-month prospective comparative study provides robust real-world evidence that single-inhaler triple therapy substantially outperforms multiple-inhaler dual therapy in patients with asthma-COPD overlap and moderate-to-severe COPD. The primary mechanism of superiority is enhanced medication adherence with the simplified single-inhaler regimen, translating into superior clinical outcomes across multiple dimensions: 63.4% reduction in exacerbation frequency, 18.2% improvement in FEV_1, 4.2-point improvement in CAT symptoms, and 20.2-point improvement in quality of life (SGRQ). These outcomes achieved with a safety profile equivalent to dual therapy.

The marked adherence advantage (86.7% vs. 64.3%) demonstrates that when patients encounter simplified medication regimens, compliance improves substantially. This improved adherence directly translates into superior disease control, fewer exacerbations, better symptom relief, and higher quality of life—outcomes that matter most to patients.Single-inhaler triple therapy should be the preferred option for patients requiring triple therapy for asthma and COPD management. The widespread adoption of SITT represents an important therapeutic advance that leverages simplified regimen design to overcome a critical barrier to treatment success: medication adherence. Future research should examine SITT efficacy in milder disease, potentially repositioning it as initial therapy rather than reserved for patients failing dual therapy.

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