Budesonide–glycopyrronium–formoterol fumarate dihydrate in uncontrolled asthma (KALOS and LOGOS): twin multicentre, double-blind, double-dummy, parallel-group, randomised, phase 3 trials

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Summary

Background Long-acting muscarinic antagonists (LAMA) can be added to inhaled corticosteroid– (ICS)–long-acting β_2-agonist (LABA) therapy for inadequately controlled asthma. We aimed to evaluate the efficacy and safety of budesonide–glycopyrronium–formoterol fumarate dihydrate (BGF) versus budesonide–formoterol fumarate dihydrate using Aerosphere co-suspension delivery technology (BFF_A) and the current suspension formulation (Symbicort, BFF_S).

Methods Two multicentre, randomised, double-blind, double-dummy, phase 3 studies (KALOS and LOGOS) recruited participants aged 12–80 years with inadequately-controlled asthma despite daily medium-dose or high-dose ICS–LABA use from across 378 sites in 20 countries (KALOS), and 324 sites in 15 countries (LOGOS). Participants were randomly assigned (1:1:1:1) to BGF 320 µg, 28·8 µg, 10 µg (BGF 28·8); BGF 320 µg, 14·4 µg, 10 µg (BGF 14·4); BFF_A 320 µg, 10 µg; or BFF_S 320 µg, 9 µg, twice a day via pressurised metered-dose inhaler for 24–52 weeks. Primary lung function endpoints were change from baseline in FEV_1 area under the curve from 0 h to 3 h ($AUC_{0–3}$) and in morning pre-dose trough FEV_1 from day 1 to week 24 (over 24 weeks; depending on regional health authority guidance). The primary pooled analysis across both studies was annualised severe exacerbations. The efficacy analysis set and safety set included all randomly assigned participants receiving any amount of study treatment but were analysed according to randomly assigned treatment and received treatment, respectively. The KALOS and LOGOS studies are registered with ClinicalTrials.gov (NCT04609878 and NCT04609904, respectively) and are complete.

Findings Between Dec 15, 2020, and March 21, 2025 (KALOS), and between March 1, 2021, and March 20, 2025 (LOGOS), 8820 participants were recruited and 4311 received treatment (1179 received BGF 28·8, 726 received BGF 14·4, 1210 received BFF_A, and 1196 received BFF_S). In each study, the pre-specified multiplicity-adjusted primary endpoints for all regulatory comparisons were met. Least squares mean differences favoured BGF 28·8 for change from baseline in trough FEV_1 and FEV_1 $AUC_{0–3}$ across all comparisons (all $p<0·05$). Least squares mean differences in change from baseline in morning pre-dose trough FEV_1 and in FEV_1 $AUC_{0–3}$ over 24 weeks for BGF 28·8 versus $BFF_{combined}$ were 76 mL (95% CI 57–94; $p<0·0001$) and 90 mL (72–108; $p<0·0001$), respectively. BGF 28·8 reduced severe exacerbation rates versus $BFF_{combined}$ (incidence rate ratio 0·86, 95% CI 0·76–0·97; $p=0·012$) and versus BFF_S (0·82, 0·71–0·94; $p=0·0043$). Exacerbation rate ratio for BGF 28·8 versus BFF_A was 0·90 (95% CI 0·78–1·03; $p=0·12$). 627 (53·2%) adverse events were observed with BGF 28·8, 436 (60·0%) with BGF 14·4, 666 (55·2%) with BFF_A, and 698 (58·4%) with BFF_S. No deaths were treatment related.

Interpretation These findings show that BGF improves lung function and reduces severe exacerbation rates in a broad population with asthma inadequately controlled despite medium-dose or high-dose ICS–LABA use. Given that these findings were observed regardless of recent exacerbation history, BGF could benefit individuals with inadequately controlled asthma without requiring a recent episode of acute deterioration on ICS–LABA before escalation.

Funding AstraZeneca.

Introduction

Global Initiative for Asthma (GINA) recommendations include an add-on long-acting muscarinic antagonist (LAMA) for patients with uncontrolled asthma despite inhaled corticosteroid (ICS)–long-acting β_2-agonist (LABA) maintenance therapy.[1] Phase 3 studies show that adding a LAMA to ICS–LABA improves lung function compared with ICS–LABA alone in people with uncontrolled

Research in context

Evidence before this study

Although previous studies have shown the benefit of inhaled corticosteroid (ICS)–long-acting muscarinic antagonist (LAMA)–long-acting β_2-agonist (LABA) triple therapy on lung function in people with asthma, evidence for the benefit of ICS–LAMA–LABA on exacerbations is inconsistent. Between Jan 2, 2020, and Oct 19, 2025, we searched Embase and Citeline using prespecified search terms related to disease state, treatment drug categories, generic treatment names (investigational and marketed), delivery methodologies, and registered clinical trial identifiers for publications published in all languages (appendix p 74). A 2021 systemic literature review summarises five phase 3 studies (ARGON, CAPTAIN, IRIDIUM, TRIGGER, and TRIMARAN) that compared single inhaler triple ICS–LAMA–LABA therapy with dual ICS–LABA therapy in participants with asthma inadequately controlled despite ICS–LABA use. Although these studies consistently showed benefit of ICS–LAMA–LABA on lung function, they did not show benefits on severe exacerbation risk due to an absence of significance and/or design considerations that prevented evaluation of severe exacerbation rates. Notably, IRIDIUM, TRIGGER, and TRIMARAN required participants to have had a severe exacerbation in the previous year, limiting the generalisability of these findings only to individuals with a history of recent exacerbations.

Added value of this study

The KALOS and LOGOS studies, which did not require participants to have persistent airflow limitation or a history of exacerbations in the previous year, are, to our knowledge, the first studies to evaluate the effect of ICS–LAMA–LABA on severe exacerbations in a broadly representative population with asthma (ie, individuals with or without persistent airflow limitation or recent exacerbation history). In a pre-specified analysis of the primary endpoint across both studies, ICS–LAMA–LABA therapy with budesonide 320 µg, glycopyrronium 28·8 µg, plus formoterol fumarate dihydrate 10 µg (BGF 28·8) showed a 10–18% relative reduction in severe exacerbation rates and significantly improved lung function versus ICS–LABA in participants with uncontrolled asthma.

Implications of all the available evidence

BGF 28·8 has the potential to benefit individuals with inadequately controlled asthma and could be an important treatment option in individuals with symptomatic asthma who are receiving ICS–LABA maintenance therapy, irrespective of whether they have a history of severe exacerbations.

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See **Online** for appendix

asthma,[2–4] but evidence on severe exacerbations for ICS–LAMA–LABA versus ICS–LABA is unclear.

Previous single-inhaler triple therapy studies have not shown significant reductions in severe exacerbation rate with triple therapy versus dual therapy; indeed, some studies used designs that prevented evaluation of severe exacerbation rates.[2–4] Moreover, although adding tiotropium to existing ICS–LABA treatment has been shown to significantly increase time to first severe exacerbation and reduce severe exacerbation risk,[5] findings are limited to individuals with persistent airflow limitation, which represents only 21% of the population with asthma.[5,6] In addition, tiotropium is not available in a single-inhaler triple combination therapy.[1]

Budesonide–glycopyrronium–formoterol fumarate dihydrate (BGF; 320 µg, 14·4 µg, and 10 µg, respectively) delivered in a fixed-dose co-suspension via a single pressurised metered-dose inhaler[7,8] has been shown to improve lung function and reduce exacerbation rates compared with an ICS–LABA comparator of budesonide–formoterol fumarate dihydrate (BFF; 320 µg and 10 µg, respectively) in people with chronic obstructive pulmonary disease.[9–11] However, evidence is needed to establish the benefits of triple therapy, including BGF, for managing asthma inadequately controlled by ICS–LABA. There is a particular need for additional evidence for the benefit of ICS–LAMA–LABA on exacerbation rates, especially in a population with asthma and without requirement of persistent airflow limitation or recent exacerbation history.[12]

The KALOS and LOGOS studies aimed to evaluate the efficacy and safety of BGF compared with BFF via a metered-dose inhaler using Aerosphere co-suspension delivery technology (BFF_A) or via Symbicort metered-dose inhaler (BFF_S) over a variable-length treatment in individuals aged 12–80 years with inadequately controlled asthma despite ICS–LABA treatment.

Methods

Study design

The KALOS and LOGOS studies were multicentre, randomised, double-blind, double-dummy, parallel-group, phase 3 trials done over a variable length of 24–52 weeks (appendix pp 10–11). The KALOS study was done at 378 sites in 20 countries and the LOGOS study at 324 sites in 15 countries. Access to the study population and ability to conduct the study at each potential study site was assessed in accordance with the clinical study protocol and regulatory requirements. Sites were primary and specialist care centres, including outpatient community and hospital clinics. Except for the embedded sub-studies, both studies had identical designs.

We performed these studies in accordance with the Declaration of Helsinki, other ethical guidelines, and applicable laws and regulations. Local or country-specific controlling institutional review boards and independent ethics committees approved the study protocols (appendix pp 102–115), which were also reviewed by a patient group. Patients were involved in the design of the study. The KALOS and LOGOS studies are registered

with ClinicalTrials.gov (NCT04609878 and NCT04609904, respectively) and are complete.

Participants

Participants were recruited through study sites' databases and advertisements. Eligible participants were aged 12–80 years with a history of physician-diagnosed asthma (per GINA 2020[13]) ≥1 year before visit 1, regularly used a stable daily medium-dose or high-dose ICS–LABA regimen for ≥4 weeks before visit 1, were non-current smokers (ie, never smoked or former smokers with <10 pack-years history who stopped smoking >6 months before visit 1), and had a 7-item Asthma Control Questionnaire (ACQ-7) total score ≥1·5 at visits 1, 3, and 5 (appendix pp 30–34). Due to recruitment difficulties associated with the COVID-19 pandemic, several inclusion and exclusion criteria were revised to ensure recruitment could continue, including amending the salbutamol reversibility definition to include salbutamol reversibility evidenced in the 12 months before visit 1, removing the conditional inclusion criterion for 50% of the population to have a pre-randomisation pre-bronchodilator FEV_1 <55% predicted normal, and removing the inclusion criterion of one or more severe exacerbations within 12 months before visit 1.

Participants were trained with placebo metered-dose inhaler devices and were required to demonstrate correct inhaler technique. Participating adults and legal guardians of participating adolescents provided written informed consent, with adolescents providing verbal assent. Sex was self-reported; options were female or male. Race and ethnicity were also self-reported. Options for race were Black or African American, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Asian, White, or other. Options for ethnicity were Hispanic or Latino, or not Hispanic or Latino.

Randomisation and masking

After a 4-week run-in on BFF_A 320 µg, 10 µg metered-dose inhaler twice daily, participants were randomly assigned (1:1:1:1) to treatment with BGF 320 µg, 28·8 µg, 10 µg (BGF 28·8; equivalent to budesonide 320 µg, glycopyrrolate 36 µg, and formoterol fumarate 9·6 µg); BGF 320 µg, 14·4 µg, 10 µg (BGF 14·4; equivalent to budesonide 320 µg, glycopyrrolate 18 µg, and formoterol fumarate 9·6 µg); BFF_A 320 µg, 10 µg; or BFF_S 320 µg, 9 µg, using restricted, fixed (non-adaptive) randomisation via interactive response technology. Given recruitment difficulties associated with the COVID-19 pandemic, recruitment to BGF 14·4 was terminated, with the expectation that approximately 450 participants would be randomly assigned to BGF 14·4 by the time the protocol amendment was approved globally. Participants were subsequently randomly assigned (1:1:1) to BGF 28·8, BFF_A, or BFF_S, and the multiple testing procedure was revised to prioritise the BGF 28·8 group's comparisons for the lung function endpoints and severe exacerbations. All decisions were made with the sponsor masked to the data. Randomisation was stratified by country, baseline pre-bronchodilator FEV_1 % predicted (adults: ≤55% or >55%; adolescents: ≤75% or >75%), severe exacerbations in the 12 months before visit 1 (adults only: 0, 1, or ≥2), and ICS dose (adults only: medium or high). Within each stratum, assignments were generated in fixed-size blocks to maintain balance across the four groups.

Although all treatments were delivered via metered-dose inhalers, there were small differences in the devices used for BGF and BFF_A compared with BFF_S; therefore, a double-blind, double-dummy design avoided accidental unmasking of participants, care providers, investigators, and outcome assessors. This involved masking the study intervention, so each participant received two devices resembling one of each type of metered-dose inhaler, with one treatment and one dummy inhaler. All active and respective placebo inhalers were designed to be indistinguishable in terms of appearance, packaging, labelling, and dosing schedule. Allocation concealment and randomisation were implemented through an interactive response technology system with role-based access. Although emergency unmasking was available for medical necessity, it was not required during the study.

Procedures

At visit 1, following a 12–24-h washout, participants switched from current ICS–LABA and started a 4-week run-in with BFF_A (budesonide 320 µg and formoterol fumarate dihydrate 10 µg twice a day) until the evening before visit 5 and were provided with albuterol or salbutamol depending on location for rescue use throughout the study. At the end of the run-in, participants were randomly assigned to treatment. BGF 28·8, BGF 14·4, and BFF_A were self-administered twice a day via metered-dose inhalers using Aerosphere co-suspension technology (AstraZeneca), and BFF_S was self-administered twice a day via a Symbicort metered-dose inhaler (AstraZeneca, Dunkerque, France), with adherence monitored via completion of a daily electronic diary. Participants in the BGF 28·8, BGF 14·4, and BFF_A groups self-administered a dummy placebo Symbicort inhaler and those in the BFF_S group self-administered a dummy Aerosphere placebo inhaler to maintain masking. Study lengths were variable, with a 24-week minimum to 52-week maximum, ending when the last randomly assigned participant completed 24 weeks of treatment and a 2-week safety follow-up. Treatment was discontinued if participants developed exclusion criteria or safety concerns.

Over the 52-week treatment period, participants attended visits at randomisation and weeks 4, 8, 12, 16, 20, 24, 28, 36, 44, and 52. Severe exacerbations were monitored throughout the treatment period, and data

were collected for pre-dose spirometry, the 5-item Asthma Control Questionnaire (ACQ-5), and ACQ-7 at each visit during the treatment period. Data were collected during the treatment period for serial spirometry (at randomisation and weeks 4, 12, 24, and 52), which was required for determining post-dose FEV_1 area under the curve from 0 h to 3 h ($AUC_{0–3}$), Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12; at randomisation and weeks 4, 12, 20, 24, 28, 36, 44, and 52), and St George's Respiratory Questionnaire (SGRQ; at randomisation and weeks 4 and 24). All staff were trained on study-related procedures.

Outcomes

Due to regional Health Authority considerations, different endpoints and comparators were assessed in four separate submission approaches to type 1 error control, which are summarised in the appendix (pp 12–16, 35–37). Data from all participants recruited across all geographies were used in the submission approaches, which differ by comparator, endpoints, and multiple testing approach used according to the Health Authority responsible for reviewing marketing authorisation, not participants' recruitment location or nationality.

The comparator to BGF for all endpoints was the combined BFF_A and BFF_S groups ($BFF_{combined}$) in the Europe submission approach, BFF_A in the USA and Japan approaches, and BFF_S in the China approach. In all four approaches, change in lung function was pre-specified as the multiplicity-adjusted primary and key secondary lung function endpoints in the individual studies—ie, change from baseline in morning pre-dose trough FEV_1 or change from baseline in FEV_1 $AUC_{0–3}$. In the Europe, China, and Japan approaches, the primary lung function endpoint was change from baseline in morning pre-dose trough FEV_1, and the key secondary endpoint was change from baseline in FEV_1 $AUC_{0–3}$, assessed from day 1 to week 24 (over 24 weeks) for the Europe and China approaches and over 12–24 weeks for the Japan approach (the KALOS study only). In the USA approach, the primary lung function endpoint was change from baseline in FEV_1 $AUC_{0–3}$ and the key secondary lung function endpoint was change from baseline in morning pre-dose trough FEV_1, both assessed at week 24.

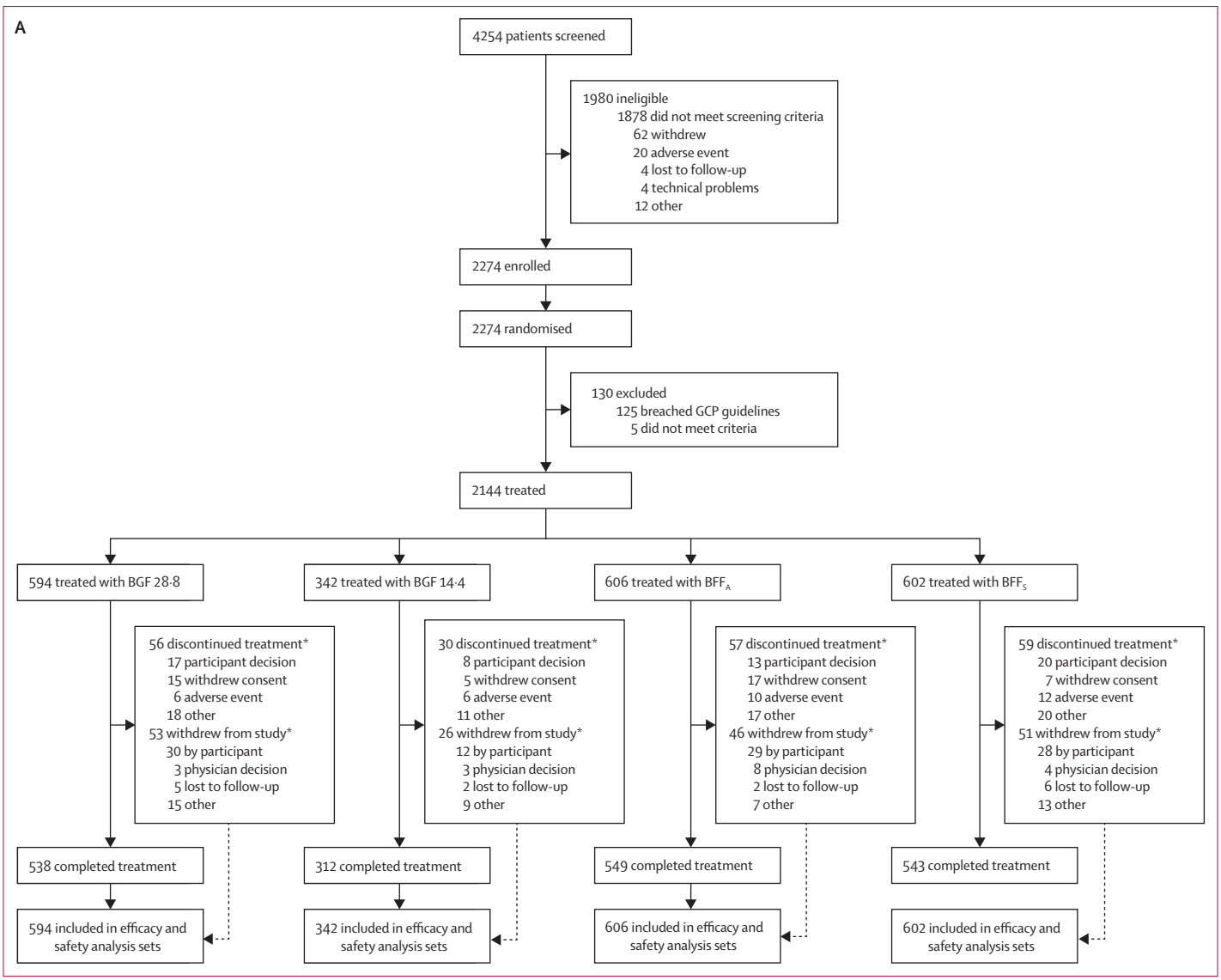
Annualised severe exacerbation rate pooled across the KALOS and LOGOS studies was a primary pooled endpoint in each submission approach. A severe asthma exacerbation was defined as: a course of systemic corticosteroids for at least 3 consecutive days to treat symptoms of asthma worsening, an emergency room or urgent care visit (defined as evaluation and treatment for <24 h in an emergency department or urgent care centre) due to asthma that required treatment with systemic corticosteroids, or an in-patient hospitalisation (defined as admission to an in-patient facility and/or evaluation and treatment in a health-care facility for ≥24 h) due to asthma or death related to asthma. Emergency room events, urgent care visits, and hospitalisations related to respiratory conditions were adjudicated by a masked independent committee to determine whether these scenarios were related to asthma worsening.

Secondary endpoints included a within-group lung function assessment of onset of action, measured as a change in FEV_1 at 5 min post-dose on day 1. Given onset of action was expected to be driven by the formoterol fumarate dihydrate component present in each treatment group, this endpoint assessed onset of action within treatment groups. Other secondary endpoints were patient-reported outcomes, including percentage of responders in ACQ-5, ACQ-7 (measured by a ≥0·5-unit decrease from baseline), AQLQ+12 (measured by a ≥0·5-unit increase from baseline), and SGRQ (measured by a ≥4·0-unit decrease from baseline) over 24 weeks (Europe and China submission approaches), at week 24 (USA submission approach), and over 12–24 weeks (Japan submission approach) in the individual studies. The programming of analyses was outsourced to Everest Clinical Research, Markham (Ontario, Canada).

Adverse events and serious adverse events were documented, recorded, and graded by investigators by Medical Dictionary for Regulatory Activities version 27.1 System Organ Class and Preferred Term. Potential relatedness to an intervention was determined by the principal investigator. An unmasked independent data monitoring committee reviewed safety data at pre-determined intervals.

Statistical analysis

Due to recruitment difficulties associated with the COVID-19 pandemic, the original sample size of 2800 participants per study (700 per group) was reassessed and reduced. For the primary and key secondary lung function endpoints, a target sample size of 2200 participants per study (550 per group) was required to provide 93% power to detect a significant difference in change from baseline in morning pre-dose trough FEV_1 at week 24, assuming a true difference of 65 mL (SD ≤280) for BGF 28·8 versus BFF_A or BGF 28·8 versus BFF_S, and more than 99% power to detect a significant difference for change from baseline in FEV_1 $AUC_{0–3}$ at week 24, assuming a true difference of 100 mL (≤330) for BGF 28·8 versus BFF_A or BGF 28·8 versus BFF_S. The target sample size provided equal or additional power over 24 weeks and 12–24 weeks. For the primary pooled endpoint, a target sample size of 1100 participants per group was required to provide 80% probability to detect a 26·5% reduction in severe exacerbation rate, assuming annualised rates of 0·35 for BFF_A and BFF_S based on previous reports,[2–4] a dispersion parameter of 1·2, and average exposure time of 0·8 years. The minimum reduction to achieve significance under



(Figure 1 continues on next page)

these assumptions is 17% for BGF versus BFF$_A$ or BFF$_S$ and 15% versus BFF$_{combined}$ (appendix p 6).

The efficacy analysis set included all randomly assigned participants receiving any amount of study treatment and was analysed according to assigned treatment, regardless of the treatment received. We analysed change from baseline in FEV$_1$ AUC$_{0–3}$ and in morning pre-dose trough FEV$_1$ in the individual studies using repeated measures analysis of covariance models, including treatment, visit, previous ICS dose (medium *vs* high), and treatment-by-visit interaction as categorical covariates and baseline trough FEV$_1$ and percentage reversibility as continuous covariates. Pooled analyses were conducted as pre-specified in the statistical analysis plan, adjusting for study as a fixed effect and without robust SEs (given the protocols were identical, with respect to main study conduct).

We controlled type I error at a two-sided α level of 0·05 in the multiple testing procedures for each of the four regional submission approaches (appendix pp 12–16). In each approach, multiplicity was controlled for the primary, key secondary, and secondary endpoints in the individual studies using a mix of sequential, Hochberg, and recycling approaches. Annualised severe exacerbation rates pooled across studies were included in the multiple testing procedures. As results for all primary and key secondary lung function analyses were significant for BGF 28·8 in both studies, we present data pooled across the studies for the Europe approach. Data for the individual studies and the USA, China, and Japan approaches are provided in the appendix (pp 44–59). The pooled lung function endpoints were not in multiple testing procedures but were pre-specified in the statistical

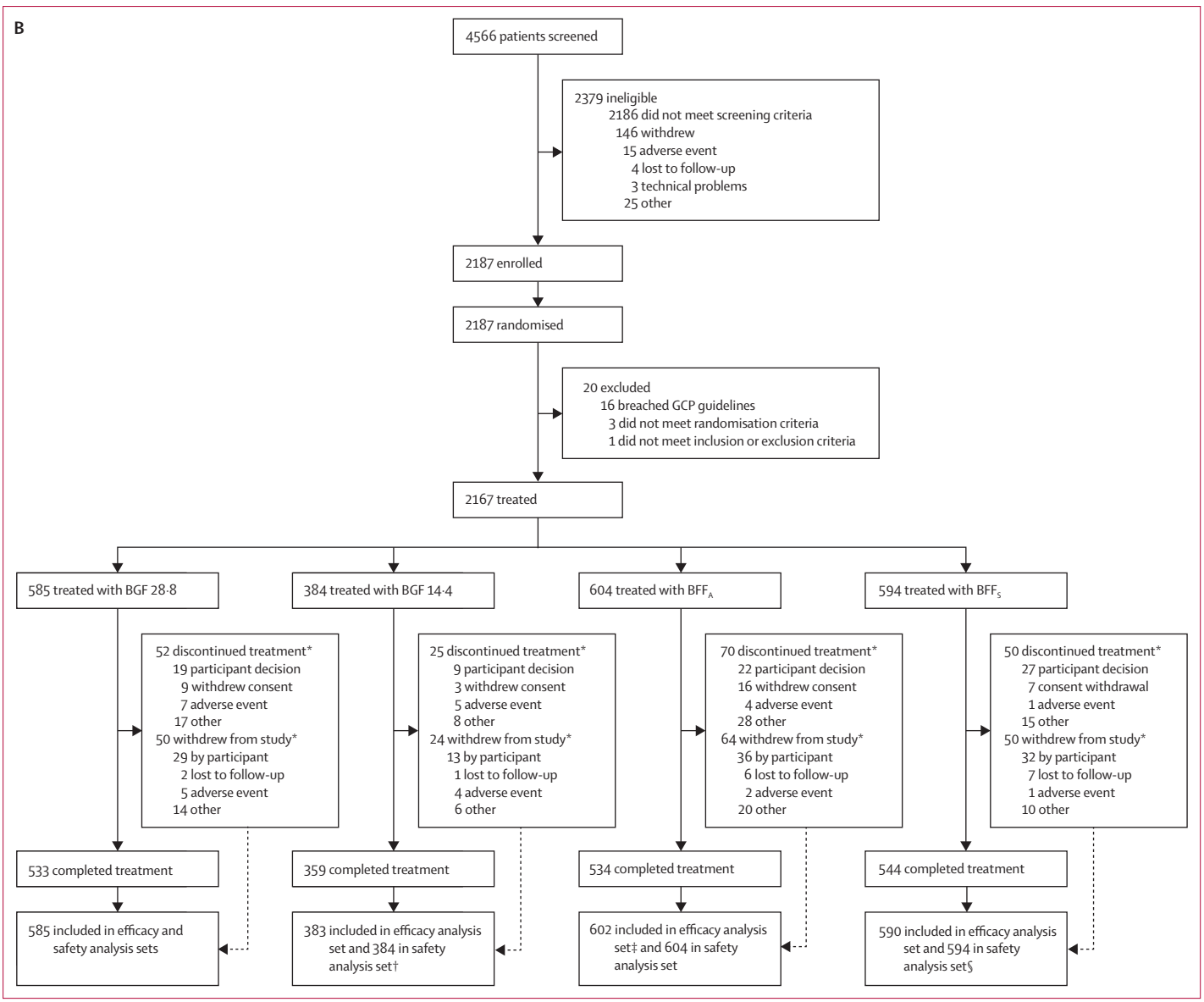


Figure 1: **Trial profiles**
Trial profiles for the KALOS study (A) and LOGOS study (B). BFF$_A$=budesonide 320 µg and formoterol fumarate dihydrate 10 µg via Aerosphere metered-dose inhaler. BFF$_S$=budesonide 320 µg and formoterol fumarate dihydrate 9 µg via Symbicort metered-dose inhaler. BGF 14·4=budesonide 320 µg, glycopyrronium 14·4 µg, and formoterol fumarate dihydrate 10 µg. BGF 28·8=budesonide 320 µg, glycopyrronium 28·8 µg, and formoterol fumarate dihydrate 10 µg. GCP=Good Clinical Practice. *Patients who withdrew from study were a subset of the total number of patients who discontinued treatment. †One patient was randomised multiple times at sites or studies, and one patient did not receive study intervention (excluded from safety set). ‡Two patients were randomised multiple times at sites or studies. §Four patients were randomised multiple times at sites or studies, and two patients did not receive study intervention (excluded from safety set).

analysis plan. p values for endpoints outside of the multiple testing procedure are considered descriptive in nature. Safety results are summarised descriptively in the safety set, which is similar to the efficacy set, except participants were analysed according to the treatment received; pooled percentages across studies were adjusted by study.

Data processing, statistical screening, descriptive reporting, and analysis of the efficacy and safety data were performed using SAS version 9.4 or higher. Interim analyses were not planned or conducted.

Role of the funding source
The funder of the study had a role in the study design, data analysis, interpretation, and writing of the report.

Results
Between Dec 15, 2020, and March 21, 2025, 4254 participants were screened in the KALOS study (figure 1A), and between March 1, 2021, and March 21, 2025, 4566 participants were screened in the LOGOS study (figure 1B). Across studies, 4311 participants were randomly assigned and received

	BGF 28·8 (n=1179)	BGF 14·4 (n=725)	BFF_A (n=1208)	BFF_S (n=1192)	$BFF_{combined}$ (n=2400)
Age, years					
Mean	52·4 (14·7)	51·6 (14·9)	51·7 (14·7)	52·4 (14·9)	52·1 (14·8)
≥12 to <18	30 (2·5%)	19 (2·6%)	39 (3·2%)	40 (3·4%)	79 (3·3%)
≥18	1149 (97·5%)	706 (97·4%)	1169 (96·8%)	1152 (96·6%)	2321 (96·7%)
Sex					
Female	725 (61·5%)	451 (62·2%)	758 (62·7%)	771 (64·7%)	1529 (63·7%)
Male	454 (38·5%)	274 (37·8%)	450 (37·3%)	421 (35·3%)	871 (36·3%)
Race					
Black or African American	47 (4·0%)	20 (2·8%)	49 (4·1%)	38 (3·2%)	87 (3·6%)
Native Hawaiian or Pacific Islander	0	0	1 (0·1%)	0	1 (0·0%)
American Indian or Alaska Native	9 (0·8%)	13 (1·8%)	10 (0·8%)	13 (1·1%)	23 (1·0%)
Asian	369 (31·3%)	242 (33·4%)	372 (30·8%)	387 (32·5%)	759 (31·6%)
White	652 (55·3%)	365 (50·3%)	666 (55·1%)	640 (53·7%)	1306 (54·4%)
Other	102 (8·7%)	85 (11·7%)	110 (9·1%)	114 (9·6%)	224 (9·3%)
BMI, kg/m²	27·45 (5·13)	27·30 (5·14)	27·65 (5·12)	27·59 (5·25)	27·62 (5·18)
Smoking status					
Former smoker	213 (18·1%)	133 (18·3%)	207 (17·1%)	200 (16·8%)	407 (17·0%)
Never smoked	966 (81·9%)	592 (81·7%)	1001 (82·9%)	992 (83·2%)	1993 (83·0%)
ACQ-7 score	2·58 (0·56)	2·57 (0·56)	2·58 (0·56)	2·59 (0·57)	2·59 (0·57)
Severe exacerbation history in previous year					
0	514 (43·6%)	244 (33·7%)	527 (43·6%)	506 (42·4%)	1033 (43·0%)
1	500 (42·4%)	359 (49·5%)	495 (41·0%)	507 (42·5%)	1002 (41·8%)
≥2	165 (14·0%)	122 (16·8%)	186 (15·4%)	179 (15·0%)	365 (15·2%)
Baseline severe asthma exacerbation history within previous year	0·7 (0·8)	0·9 (0·8)	0·8 (0·8)	0·8 (0·8)	0·8 (0·8)
Pre-bronchodilator FEV_1, mL	1664 (581)	1675 (559)	1715 (568)	1661 (555)	1688 (562)
Pre-bronchodilator FEV_1 % predicted	58·1 (12·7)	58·6 (12·4)	59·4 (12·2)	58·9 (12·4)	59·2 (12·3)
Post-bronchodilator FEV_1/FVC <0·7	727 (61·7%)	433 (59·7%)	711 (58·9%)	709 (59·5%)	1420 (59·2%)
Percentage reversibility	22·7 (18·9)	23·3 (19·0)	22·1 (17·3)	22·1 (17·2)	22·1 (17·2)
Blood eosinophil count, cells per mm²	222·4 (185·5)	223·3 (175·1)	233·8 (193·3)	215·9 (164·9)	224·9 (179·9)
Previous ICS dose*					
Low	7 (0·6%)	9 (1·2%)	5 (0·4%)	6 (0·5%)	11 (0·5%)
Medium	784 (66·5%)	459 (63·3%)	781 (64·7%)	772 (64·8%)	1553 (64·7%)
High	388 (32·9%)	256 (35·3%)	421 (34·9%)	413 (34·6%)	834 (34·8%)
Missing	0	1 (0·1%)	1 (0·1%)	1 (0·1%)	2 (0·1%)

Data are n (%) or mean (SD). Baseline percent reversibility was calculated as (post-salbutamol FEV_1 − pre-salbutamol FEV_1)/(pre-salbutamol FEV_1) × 100, using visit 2 data if non-missing and visit 3 data otherwise. ACQ-7=7-item Asthma Control Questionnaire. BFF_A=budesonide 320 µg plus formoterol fumarate dihydrate 10 µg via Aerosphere pressurised metered-dose inhaler. $BFF_{combined}$=combined treatment groups of BFF_A and BFF_S. BFF_S=budesonide 320 µg plus formoterol fumarate dihydrate 9 µg via Symbicort pressurised metered-dose inhaler. BGF 14·4=budesonide 320 µg, glycopyrronium 14·4 µg, and formoterol fumarate dihydrate 10 µg. BGF 28·8=budesonide 320 µg, glycopyrronium 28·8 µg, and formoterol fumarate dihydrate 10 µg. ICS=inhaled corticosteroid. *Low-dose budesonide was 200–400 µg/day; medium-dose budesonide was more than 400 to 800 µg/day or equivalent; and high-dose budesonide was more than 800 µg/day or equivalent.

Table 1: **Baseline demographics and clinical characteristics in the pooled KALOS and LOGOS studies (pooled efficacy set)**

treatment, of whom 4304 participants constituted the efficacy set (1179 in the BGF 28·8 group, 725 in the BGF 14·4 group, 1208 in the BFF_A group, and 1192 in the BFF_S group). Pooled demographic and clinical characteristics were balanced across treatments (table 1). Mean age was 52·1 years (SD 14·8). 2705 (62·8%) of 4304 participants were female and 1599 (37·2%) were male. 2323 (54·0%) of 4304 participants were White (individual study data are presented in the appendix pp 38–43). Concomitant medications were used by similar proportions of participants across treatment groups.

The primary and key secondary lung function endpoints in each regional submission approach were met. In the individual studies, change from baseline in morning pre-dose trough FEV_1 and change from baseline in FEV_1 $AUC_{0–3}$ was significantly higher ($p<0·05$) for BGF 28·8 compared with all comparators (BFF_A, BFF_S, and $BFF_{combined}$; appendix pp 49–59). In pre-specified analyses of these endpoints using data from the pooled KALOS and LOGOS studies, least squares mean differences for BGF 28·8 versus $BFF_{combined}$ were 76 mL (95% CI 57–94; $p<0·0001$) for change from baseline in morning pre-dose trough

	BGF 28·8 (n=1179)	BGF 14·4 (n=725)	$BFF_{combined}$ (n=2400)
Change from baseline in morning pre-dose trough FEV_1 over 24 weeks (mL)			
N	1175	721	2387
LS mean (SE)	166 (8)	156 (10)	90 (6)
LS mean difference (95% CI); p value†	76 (57 to 94); <0·0001	65 (43 to 88); <0·0001	Comparator
Change from baseline in FEV_1 AUC_{0-3} over 24 weeks (mL)			
N	1175	723	2391
LS mean (SE)	328 (8)	319 (10)	238 (5)
LS mean difference (95% CI); p value†	90 (72 to 108); <0·0001	81 (60 to 103); <0·0001	Comparator
Onset of action: change in FEV_1 (mL) at 5 min post dose on day 1			
N	1114	692	2289
LS mean change from baseline (95% CI); p value†‡	170 (158 to 182); <0·0001	143 (128 to 158); <0·0001	136 (127 to 144); <0·0001
Severe exacerbations: primary pooled			
n (%) with exacerbations; event number	398 (33·8); 612	257 (35·4); 422	914 (38·1); 1444
Time at risk, participant years	1077·9	723·6	2188·7
Adjusted annualised exacerbation rate (SE)	0·54 (0·028)	0·53 (0·034)	0·63 (0·022)
Absolute rate reduction (95% CI); p value	−0·09 (−0·16 to −0·02); 0·0096	−0·10 (−0·18 to −0·02); 0·013	Comparator
Time to first severe asthma exacerbation, HR (95% CI); p value§	0·84 (0·75 to 0·95); 0·0051	0·86 (0·75 to 0·99); 0·030	Comparator
Treatment incidence rate ratio (95% CI); p value	0·86 (0·76 to 0·97); 0·012	0·84 (0·73 to 0·97); 0·017	Comparator

AUC_{0-3}=area under the curve from 0 h to 3 hours. BFF_A=budesonide 320 µg plus formoterol fumarate dihydrate 10 µg via Aerosphere pressurised metered-dose inhaler. $BFF_{combined}$=combined treatment groups of BFF_A and BFF_S. BFF_S=budesonide 320 µg plus formoterol fumarate dihydrate 9 µg via Symbicort pressurised metered-dose inhaler. BGF 14·4=budesonide 320 µg, glycopyrronium 14·4 µg, and formoterol fumarate dihydrate 10 µg. BGF 28·8=budesonide 320 µg, glycopyrronium 28·8 µg, and formoterol fumarate dihydrate 10 µg. HR=hazard ratio. LS=least squares. *All observed data were used unless participants discontinued prematurely in conjunction with asthma therapy or prohibited medication potentially impacting efficacy, in which case treatment failure was imputed. †Nominally significant due to absence from multiple testing procedures. ‡p value measured by a within-group *t* test to show that mean change from baseline in FEV_1 at 5 min post dose on day 1 is statistically greater than 100 mL. §A Cox regression model was used to compare time to exacerbation between treatment groups, adjusted for baseline severe asthma exacerbation history (0, 1, ≥2), previous inhaled corticosteroid dose (medium *vs* high), region, study, baseline trough FEV_1, and percentage reversibility.

Table 2: **Lung function and severe exacerbation endpoints for BGF 28·8 and BGF 14·4 versus $BFF_{combined}$ in the pooled KALOS and LOGOS studies (Europe submission approach; pooled efficacy set*)**

FEV_1 and 90 mL (72–108; p<0·0001) for change from baseline in FEV_1 AUC_{0-3} over 24 weeks (table 2). Similar findings were observed for BGF 28·8 versus BFF_A at week 24 (USA submission approach), BGF 28·8 versus BFF_S at 24 weeks (China submission approach), and BGF 28·8 versus BFF_A over 12–24 weeks (Japan submission approach; appendix pp 44–59). Change from baseline in FEV_1 AUC_{0-3} and morning pre-dose trough FEV_1 were evaluated to contextualise the data from the KALOS and LOGOS studies relative to previously reported asthma therapy efficacy results at 24 weeks. In the pooled analysis, least squares mean differences in change from baseline in FEV_1 AUC_{0-3} at week 24 for BGF 28·8 versus BFF_S was 105 mL (95% CI 80–130) and 103 mL (78–127) for BGF 28·8 versus $BFF_{combined}$. For the change from baseline in morning pre-dose trough FEV_1 in pooled KALOS and LOGOS studies, least squares mean differences at week 24 for BGF 28·8 versus BFF_S was 87 mL (60–114), and BGF 28·8 versus $BFF_{combined}$ was 80 mL (57–104).

BGF 28·8 treatment effects were observed from day 1 and were sustained to week 52 (figure 2). BGF 14·4 findings for the primary and key secondary endpoints in the BGF 14·4 group are reported for the individual studies in the appendix (pp 49–59) and for the analyses of the pooled studies in table 2 and the appendix (pp 44–48). Although change from baseline in trough FEV_1 was significant with BGF versus $BFF_{combined}$ over 24 weeks in the LOGOS study, significance was not observed in the KALOS study, in which BGF 14·4 had a lower magnitude of effect. Despite this, in pooled analyses across both studies, the magnitude of effect for BGF 14·4 versus the ICS–LABA comparators was similar to BGF 28·8 for lung function endpoints and severe exacerbations (figures 2, 3A).

For the primary pooled endpoint, severe exacerbation rate for BGF 28·8 was 18% lower than for BFF_S (incidence rate ratio 0·82, 95% CI 0·71–0·94; p=0·0043) and 14% lower for BGF 28·8 than $BFF_{combined}$ (0·86, 0·76–0·97; p=0·012). The severe exacerbation rate for BGF 28·8 versus BFF_A was 0·90 (0·78–1·03, p=0·12; figure 3A; appendix pp 44–48). Analyses of time to first severe exacerbation were supportive of the exacerbation rate reductions observed compared with the ICS–LABA comparators, with hazard ratios (HRs) favouring BGF 28·8 versus $BFF_{combined}$ (0·84, 95% CI 0·75–0·95) and BFF_S (0·81, 0·71–0·93). The HR for time to first severe exacerbation for BGF 28·8 versus BFF_A was 0·88 (95% CI 0·77–1·01; appendix pp 60–61). For BGF 28·8 and BGF 14·4, treatment benefits in extending time to first severe exacerbation were observed up to week 52 (figure 3B).

Pre-specified subgroup analyses of the primary, key secondary, and pooled primary endpoints, evaluated by

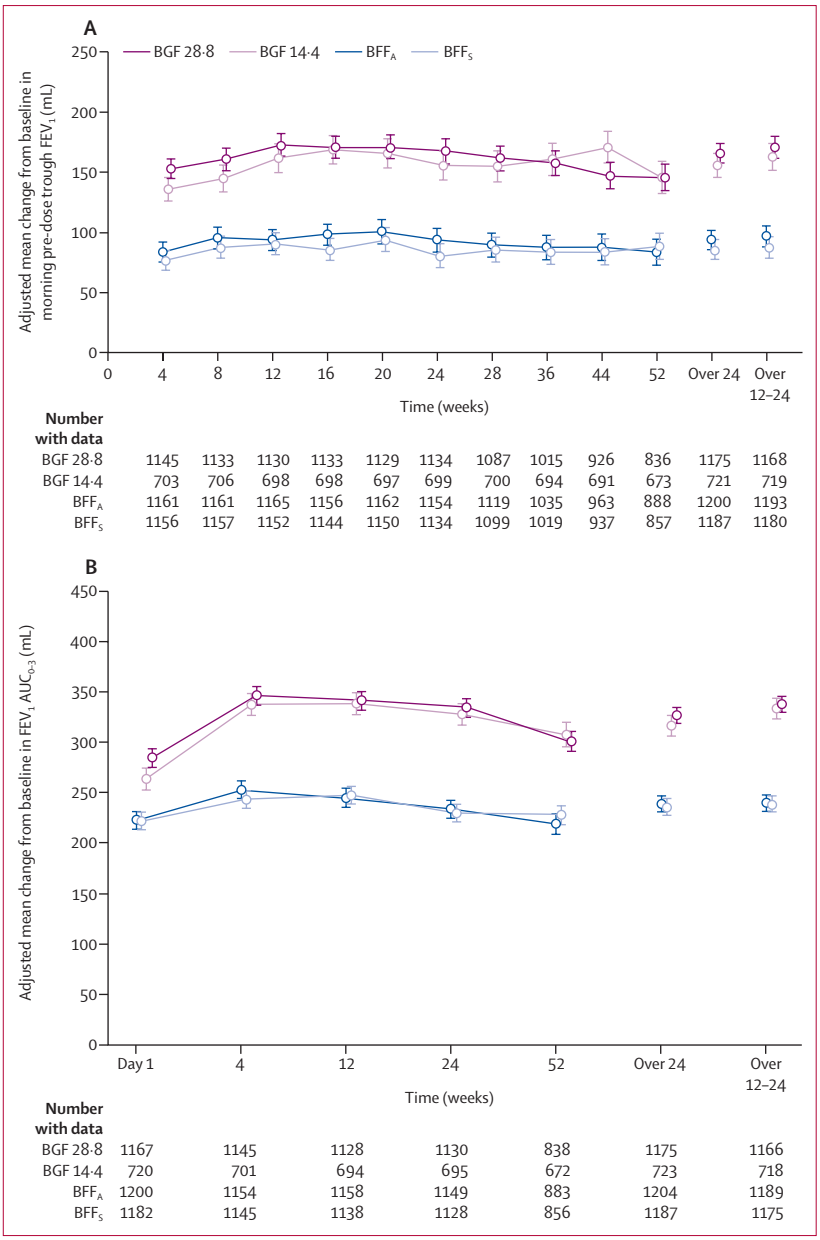


Figure 2: **Lung function over time in the pooled KALOS and LOGOS studies (pooled efficacy set*)**
Error bars indicate SE. Baseline is day 1. AUC_{0-3}=area under the curve from 0 h to 3 h. BFF_A=budesonide 320 µg and formoterol fumarate dihydrate 10 µg via Aerosphere metered-dose inhaler. BFF_S=budesonide 320 µg and formoterol fumarate dihydrate 9 µg via Symbicort metered-dose inhaler. BGF 14·4=budesonide 320 µg, glycopyrronium 14·4 µg, and formoterol fumarate dihydrate 10 µg. BGF 28·8=budesonide 320 µg, glycopyrronium 28·8 µg, and formoterol fumarate dihydrate 10 µg. *All observed data were used unless participants discontinued prematurely in conjunction with asthma therapy or prohibited medication potentially impacting efficacy, in which case treatment failure was imputed.

sex, race, severe exacerbation history, previous ICS dose, percentage reversibility, and region, supported the primary findings, with largely similar treatment effects favouring BGF 28·8 over $BFF_{combined}$ for change from baseline in lung function over 24 weeks and severe exacerbation rates, irrespective of baseline characteristics (appendix pp 17–20).

Rapid onset of action was observed for all treatment groups, all of which contained formoterol fumarate dihydrate (table 2; appendix pp 44–48). Findings for the pre-specified individual and pooled studies for all comparators and findings on BGF 28·8 and BGF 14·4 for individual studies are presented in the appendix (pp 21–22 and 49–59, respectively). For the patient-reported outcomes, most participants improved in all treatment groups, with only nominal differences in the percentage of responders for BGF 28·8 versus $BFF_{combined}$ in SGRQ in the KALOS study and ACQ-7 in the LOGOS study (appendix pp 23–26). Across all treatment groups, an improvement from baseline in ACQ-5, ACQ-7, and AQLQ+12 scores was observed over 52 weeks (appendix pp 27–29). No clinically relevant differences were observed between BGF 28·8, BGF 14·4, BFF_A, and BFF_S for change from baseline in ACQ-5, ACQ-7, AQLQ+12, and SGRQ scores.

No substantive differences were observed for safety assessments, with a similar occurrence of on-treatment adverse events, serious adverse events, or adverse events leading to discontinuation between groups (table 3; appendix pp 64–69). 627 (53·2%) adverse events occurred with BGF 28·8, 436 (60·0%) with BGF 14·4, 666 (55·2%) with BFF_A, and 698 (58·4%) with BFF_S. Most adverse events were mild or moderate, and only 184 (4·3%) were considered possibly treatment related (table 3). The incidence of adverse events related to LAMA was generally consistent across treatment groups (appendix pp 64–66). Of 12 deaths that occurred during the study, ten occurred during treatment, but none were attributed to treatment (table 3).

Discussion

Across individual and pooled analyses, single-inhaler ICS–LAMA–LABA therapy with BGF 28·8 was superior to ICS–LABA comparators BFF_A, BFF_S, or $BFF_{combined}$ on lung function, with greater improvements observed across several lung function parameters. BGF 28·8 also showed 10–18% relative reductions in severe exacerbation rate versus ICS–LABA comparators.

The benefits of BGF on lung function are consistent with previously published phase 3 studies on ICS–LAMA–LABA that evaluated lung function as a primary endpoint.[2–4] In the KALOS and LOGOS studies, improvements in least squares mean differences for change from baseline in morning pre-dose trough FEV_1 and in FEV_1 AUC_{0-3} at 24 weeks and over 24 weeks with BGF 28·8 and BGF 14·4 were similar to previous studies evaluating triple therapy against ICS–LABA in asthma. In the IRIDIUM study, adding glycopyrrolate to medium-dose or high-dose mometasone furoate–indacaterol acetate improved change from baseline in trough FEV_1 at 26 weeks by 76 mL and 65 mL, respectively. Likewise, adding glycopyrrolate to beclomethasone dipropionate–formoterol fumarate dihydrate significantly improved change from baseline

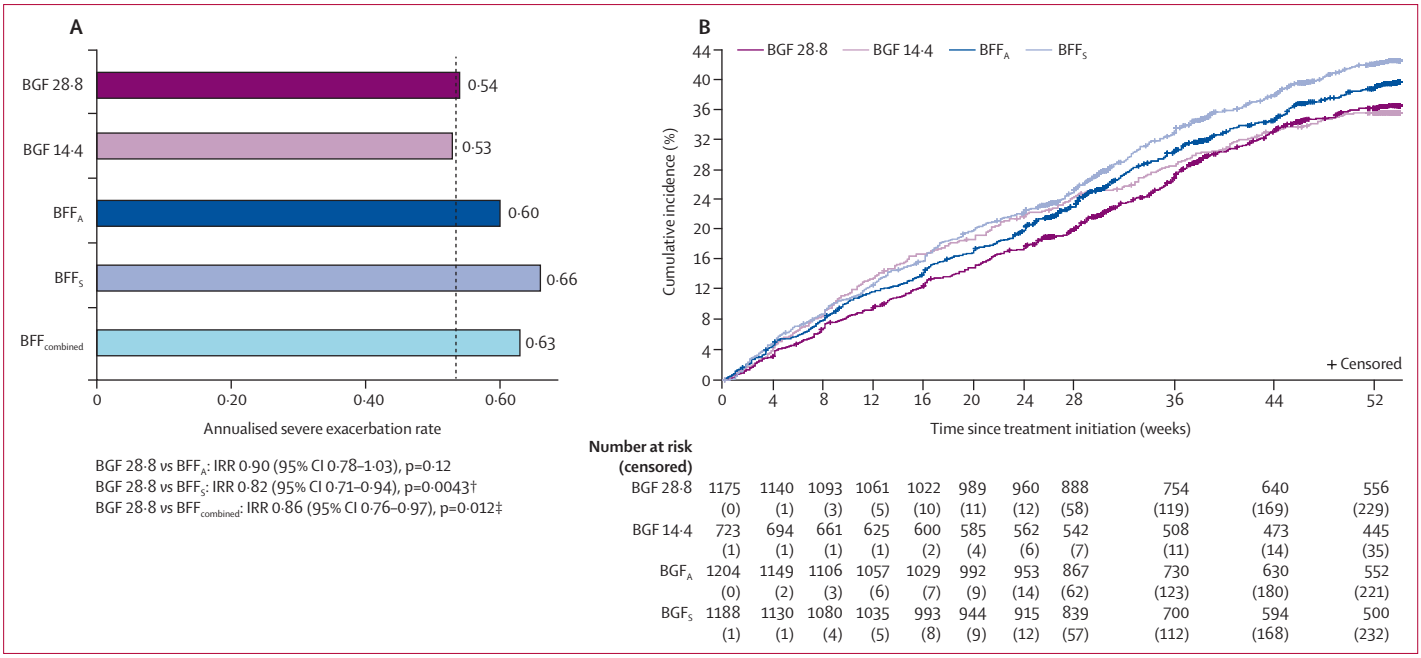


Figure 3: **Severe exacerbation in the pooled KALOS and LOGOS studies (pooled efficacy set*)**
(A) Severe exacerbation rates in the pooled KALOS and LOGOS studies. (B) Time to first severe exacerbation. BFF$_A$=budesonide 320 µg and formoterol fumarate dihydrate 10 µg via Aerosphere metered-dose inhaler. BFF$_{combined}$=combined treatment groups of BFF$_A$ and BFF$_S$. BFF$_S$=budesonide 320 µg and formoterol fumarate dihydrate 9 µg via Symbicort metered-dose inhaler. BGF 28·8=budesonide 320 µg, glycopyrronium 28·8 µg, and formoterol fumarate dihydrate 10 µg. BGF 14·4=budesonide 320 µg, glycopyrronium 14·4 µg, and formoterol fumarate dihydrate 10 µg. IRR=incidence rate ratio. *All observed data were used unless participants discontinued prematurely in conjunction with asthma therapy or prohibited medication potentially impacting efficacy, in which case treatment failure was imputed. †Significant per multiple testing procedure for the China submission approach. ‡Significant per multiple testing procedure for the Europe submission approach.

	BGF 28·8 (n=1179)	BGF 14·4 (n=726)	BFF$_A$ (n=1208)	BFF$_S$ (n=1196)
Adverse events	627 (53·2%)	436 (60·0%)	666 (55·2%)	698 (58·4%)
Mild	279 (23·7%)	181 (24·8%)	287 (23·8%)	333 (27·9%)
Moderate	300 (25·4%)	222 (30·7%)	317 (26·2%)	309 (25·8%)
Severe	48 (4·1%)	33 (4·5%)	62 (5·1%)	56 (4·7%)
Serious adverse events	73 (6·2%)	49 (6·7%)	83 (6·9%)	68 (5·7%)
Serious adverse events with death as outcome	2 (0·2%)	1 (0·1%)	4 (0·3%)	3 (0·2%)
Adverse events leading to investigational product discontinuation	13 (1·1%)	9 (1·2%)	11 (0·9%)	11 (0·9%)
Possibly treatment-related adverse event	63 (5·4%)	34 (4·6%)	42 (3·5%)	45 (3·8%)
Possibly treatment-related serious adverse event	1 (0·1%)	2 (0·3%)	3 (0·3%)	2 (0·2%)

BFF$_A$=budesonide 320 µg plus formoterol fumarate dihydrate 10 µg via Aerosphere pressurised metered-dose inhaler. BFF$_S$=budesonide 320 µg plus formoterol fumarate dihydrate 9 µg via Symbicort pressurised metered-dose inhaler. BGF 14·4=budesonide 320 µg, glycopyrronium 14·4 µg, and formoterol fumarate dihydrate 10 µg. BGF 28·8=budesonide 320 µg, glycopyrronium 28·8 µg, and formoterol fumarate dihydrate 10 µg. *Percentages adjusted by study were calculated as the sum of the KALOS and LOGOS weighted percentages of participants with an adverse event within the treatment group, in which the respective study weight is the total number of participants in the study divided by the total number of participants across both studies.

Table 3: **Adverse events in the pooled KALOS and LOGOS studies (pooled safety set, on-treatment)***

in pre-dose FEV$_1$ at 26 weeks by 73 mL in the TRIGGER trial and by 57 mL in the TRIMARAN trial. Similarly, in the CAPTAIN study, significant improvements in change from baseline in trough FEV$_1$ at week 24, ranging from 82 mL to 110 mL, were observed when adding umeclidinium to medium or high-dose fluticasone–vilanterol.

However, previous evidence for benefits of ICS–LAMA–LABA versus ICS–LABA on severe exacerbation reductions is sparse and inconsistent, with few studies prioritising the evaluation of severe exacerbations.[2–4] Although in the IRIDIUM study, a nominal reduction in severe exacerbation rates was observed when adding glycopyrrolate to high-dose (but not medium-dose) mometasone furoate–indacaterol acetate, it was not powered to compare exacerbation rates, and these comparisons were not adjusted for multiplicity.[3] In the pooled analysis of the TRIGGER and TRIMARAN trials, a treatment effect on severe exacerbations was not conclusive and methodologically suboptimal as the studies included

different ICS doses and requirements for previous ICS–LABA use.[2] Importantly, the IRIDIUM, TRIGGER, and TRIMARAN trials required individuals to have had severe exacerbations in the previous year, limiting generalisability of results to only these individuals. Conversely, approximately 40% of the population in the KALOS and LOGOS studies did not have a severe exacerbation in the year preceding study entry. In addition, in a pooled analysis of the TRIGGER and TRIMARAN studies, reductions in severe exacerbation rate over 52 weeks were only nominally significant due to a failure higher up in the pre-specified hierarchical testing precedure.[2] In the CAPTAIN study, a reduction in severe exacerbation rates over 52 weeks was not observed.[4] In the PrimoTinA-asthma 1 and 2 studies, which assessed time to first severe exacerbation as a pooled co-primary endpoint, adding tiotropium to existing ICS–LABA therapy significantly reduced severe exacerbation risk.[5] However, these studies only included participants with persistent airflow limitation, substantially limiting generalisation to the wider asthma population.[5] Furthermore, tiotropium is not available in a single-inhaler triple therapy.[1]

To our knowledge, the KALOS and LOGOS studies are the first studies designed to evaluate effects of triple therapy on severe exacerbations in participants with asthma uncontrolled by ICS–LABA, without requiring persistent airflow limitation or a history of exacerbations in the previous year. The 18% reduction in severe exacerbation rates with BGF 28·8 versus BFF_S gives an effect magnitude for escalating to treatment with BGF in clinical practice in the setting of a standard therapeutic option (ie, Symbicort),[14] providing an opportunity to reduce the substantial burden associated with severe asthma exacerbations.[15] A smaller effect was observed for BGF versus BFF_A, which outperformed BFF_S on exacerbations; BFF_A is not approved for asthma treatment and was included because it was a regulatory requirement for certain regions. Given that comparisons of BGF with both ICS–LABA comparators are relevant, this study focuses on the $BFF_{combined}$ comparator, which was provided for European submission.

Substantial improvements in patient-reported outcomes were observed across treatments with no differences seen among comparators, suggesting that the main benefits for BGF versus ICS–LABA are on lung function and exacerbations. The benefit of adding LAMA to ICS–LABA on patient-reported outcomes in previous studies has been variable. In the TRIGGER and TRIMARAN trials, no significant differences in ACQ-7 response rates were observed when adding glycopyrrolate to beclomethasone dipropionate and formoterol fumarate.[2] However, despite not showing any benefit on exacerbations in the CAPTAIN study, adding high-dose umeclidinium to fluticasone furoate–vilanterol improved response rates at a nominal level (ie, not adjusted for multiplicity) in ACQ.[4] In the KALOS and LOGOS studies, potentially due to the inclusion of formoterol fumarate dihydrate, all treatments showed a rapid onset of action, which is a valuable aspect of inhaled therapy as it might facilitate treatment adherence.[16] The safety and tolerability profile of BGF was similar to that of the ICS–LABA comparators, including with regard to adverse events generally considered related to LAMA, with no new or unexpected findings.

The 4-week run-in is a strength of the KALOS and LOGOS studies that ensured inadequate asthma control despite adherence to ICS–LABA therapy such that patients were considered safe to enter and were committed to the study requirements before randomisation. In addition, these studies had broad inclusion criteria, with no requirement for exacerbations in the previous 12 months. Subsequently, the results of these studies are generalisable to a wider population with uncontrolled asthma despite ICS–LABA treatment, which is often seen in primary care. However, most participants in the KALOS and LOGOS studies were White, with Black or African American participants comprising only a small percentage of the study populations. Notably, the budesonide dose (320 µg) included in the BGF groups is considered a medium ICS dose, which is consistent with the treatment pathway recommended by GINA for add-on LAMA.[1] Although this aspect could be considered to limit the potential options for fixed-dose ICS therapy in asthma, the alternate view is that BGF could align with a treatment strategy as a maintenance therapy used in combination with ICS–formoterol or ICS with short-acting β_2-agonist reliever.[1]

Recruitment difficulties associated with the COVID-19 pandemic prompted termination of recruitment to the BGF 14·4 group to ensure sufficient sample size for the BGF 28·8, BFF_A, and BFF_S groups. Given that the effect size for the BGF 28·8 group was greater than for the BGF 14·4 group in the phase 2 evaluation, especially for trough FEV_1, we prioritised the BGF 28·8 group by continuing recruitment in this group over BGF 14·4 and prioritising it in the testing heirarchy.[17,18]

When pooling data across studies to increase statistical power, effect sizes for lung function and severe exacerbations for BGF 28·8 and BGF 14·4 were generally similar. Numerical differences were observed for some endpoints between the KALOS and LOGOS studies, despite sharing mostly identical designs. Although numerical differences are expected when comparing any two studies, these differences might be attributable to regional differences. Indeed, the KALOS and LOGOS studies were conducted at different sites globally during the COVID-19 pandemic, which might have magnified differences attributable to regional disparities, leading to the observed treatment effect variability across doses, endpoints, and studies. Lastly, as with other clinical studies in asthma,[2] we did not observe significant incremental symptomatic benefit after the addition of the LAMA glycopyronium to ICS–LABA combination therapy. Nonetheless, the KALOS and LOGOS studies showed

benefits in lung function and a reduction in severe asthma exacerbations. These findings highlight that treating symptoms is complex in asthma. Given the well-recognised, clinically significant, symptomatic benefit with budesonide and formoterol,[19,20] these results support a combination approach for BGF use in individuals with uncontrolled asthma on ICS–LABA therapy to gain the composite benefits of all three pharmacological_agents, administered as one inhaled therapy.

In conclusion, these findings indicate single-inhaler triple therapy with BGF 28·8 is superior to a standard ICS–LABA therapeutic option for improving lung function and exacerbation rates in individuals aged 12–80 years with asthma inadequately controlled by ICS–LABA. Importantly, including people without an exacerbation history over the previous year indicates that BGF 28·8 benefits are observed in a broad population, irrespective of recent asthma exacerbation history.

Contributors

AP, CM, KK, and MP were responsible for study conceptualisation. TT, CO, KS, MB, MS, KK, KB, HP, AM, and MP were responsible for data curation. TT, CO, JH, KB, AM, and MP were responsible for formal analysis. KK, KB, AM, and MP were responsible for funding acquisition. AP, RAW, RC, TT, CO, CM, KK, KS, MB, MS, KB, AM, and MP were responsible for the investigation. RC, TT, CO, CM, JH, KK, KB, AM, and MP were responsible for the methodology. RC, TT, CO, CM, KK, KS, MB, MS, KB, HP, AM, and MP were responsible for project administration. RC was responsible for resources. TT, CO, JH, KB, AM, and MP were responsible for software. AP, RAW, RC, CO, KK, KB, MS, HP, AM, and MP were responsible for supervision. RC, TT, CM, JH, KS, MB, KB, AM, and MP were responsible for validation. RC, TT, CO, CM, JH, KS, MB, KB, AM, and MP were responsible for visualisation. AP, RAW, TT, JH, KB, AM, and MP verified the data. All authors critically reviewed and provided feedback on all manuscript versions and, along with the sponsor, agreed to manuscript submission. All authors had full access to the data, contributed to data interpretation, and vouch for the accuracy and completeness of the data and for the fidelity of the studies to the protocols. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

AP reports grants from Chiesi, AstraZeneca, GSK, and Sanofi; consultancy fees from Chiesi, AstraZeneca, GSK, Sanofi, Avillion, Moderna, Roche, Regeneron, Zambon, and Zentiva; and honoraria for lectures from Chiesi, AstraZeneca, GSK, Zambon, Sanofi, Avillion, Regeneron, Moderna, and Roche. RAW reports research grant support from AstraZeneca, Verona, Chiesi, and Sanofi-Regeneron and consulting fees for serving on a data safety monitoring board or Clinical Endpoint Committees from AbbVie, AstraZeneca, BioNTech, Boehringer-Ingelheim, BristolMyersSquibb, Chiesi, GSK, Pulmonx, and Kamada. DJJ reports advisory board, speaker fees, and research grants from AstraZeneca and GSK. NL reports consulting fees from AbbVie, Amgen, Apogee, AstraZeneca, Avillion, Foresee, Genentech, GSK, Niox, Novartis, Regeneron, Sanofi, and Teva; honoraria for non-speakers bureau presentations from GSK, Teva, Sanofi/Regeneron, and AstraZeneca; travel support from AstraZeneca, Sanofi, Teva, Regeneron, and GSK; institutional research support from Amgen, AstraZeneca, Avillion, Bellus, Evidera, Gossamer Bio, Genentech, GSK, Janssen, Regeneron, Roche, Sanofi, Novartis, and Teva; and being an honorary faculty member of the Observational and Pragmatic Research Institute (OPRI) but does not receive compensation for this role. RC reports research grants and speaker's fees from AstraZeneca, GSK, Genrix Bio, Novartis, and Sanofi. TT, CO, CM, JH, PS, KS, MB, MS, KK, KB, HP, AM, and MP are employees of AstraZeneca and might hold stock or stock options in the company.

Data sharing

Data collected for the study, including de-identified individual participant data and the data dictionary, will be made available in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform. The AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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