Functional respiratory imaging assessment of budesonide/glycopyrrolate/formoterol fumarate and glycopyrrolate/formoterol fumarate metered dose inhalers in patients with COPD

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Introduction

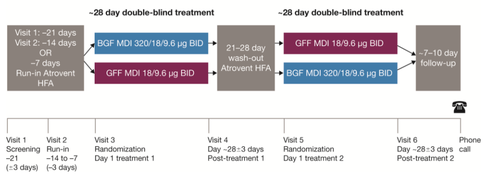
- Triple therapy with inhaled corticosteroids/long-acting muscarinic antagonists/long-acting β_2-agonists (ICS/LAMA/LABA) is recommended for patients with chronic obstructive pulmonary disease (COPD) who experience continued symptoms or exacerbations, despite treatment with LAMA/LABA or ICS/LABA.[1]
- The ICS/LAMA/LABA fixed-dose combination budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler (BGF MDI) was shown to significantly improve lung function and symptoms, and significantly reduce moderate/severe exacerbations versus glycopyrrolate/formoterol fumarate (GFF) MDI and budesonide/formoterol (BFF) MDI in symptomatic patients with COPD in the ETHOS (NCT02465567) study.[2]
- BGF MDI was also shown to be deposited throughout the large and small airways of healthy male patients, during both a standard breath-hold (10 seconds) and a 3-second breath-hold when delivered via a single Aerosphere inhaler.[3] While deposition was evident throughout the lung, neither deposition studies or traditional spirometry are able to assess regional effects on lung function.
- Functional respiratory imaging (FRI; a computed tomography-based, quantitative post-processing technology) can be used to evaluate regional airway changes following treatment, including parameters of airway volume and airway resistance, which has previously been demonstrated for the LAMA/LABA dual therapy GFF MDI.[4]
- This study was the first to assess the effect of adding an ICS to LAMA/LABA dual therapy using FRI to evaluate the effects of fixed-dose triple therapy with BGF MDI 320/18/9.6 µg compared with dual therapy with GFF MDI 18/9.6 µg on specific (i.e., corrected for lobar volume) image-based volume (siVaw) and resistance (siRaw) in patients with moderate-to-severe COPD.

Methods

Study design

- This randomized, double-blind, Phase-IIIb, 4-week, crossover study (NCT03836677) evaluated the effects of BGF MDI 320/18/9.6 µg and GFF MDI 18/9.6 µg, both administered as two inhalations, twice-daily, via an Aerosphere inhaler, on FRI parameters and pulmonary function in patients with moderate-to-severe COPD.
- Patients were randomized into one of two treatment sequences: BGF MDI followed by GFF MDI, or GFF MDI followed by BGF MDI (Figure 1).

Figure 1. Study design.



BGF, budesonide/glycopyrrolate/formoterol fumarate; BID, twice-daily; GFF, glycopyrrolate/formoterol fumarate; HFA, hydrofluoroalkane; MDI, metered dose inhaler.

Patients

- The key inclusion criteria were as follows:
  - Patients 40–80 years of age
  - A diagnosis of COPD with a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity <0.70 and a post-bronchodilator FEV_1 30-80% predicted normal
  - Receiving ≥1 inhaled maintenance therapies (including ≥1 LAMA or LABA) for management of their COPD for at least four weeks prior to screening
  - Patients with ICS use in the 3 months prior to screening were excluded
  - Current or former smokers with a history of at least 10 pack-years
  - Blood eosinophil count >150 cells/mm³
- Key exclusion criteria:
  - Respiratory diseases other than COPD (inclusive of asthma) or other significant diseases (cardiac, renal, etc.) other than COPD that could increase patient risk or influence results
  - Patients with poorly controlled COPD, identified by acute worsening of COPD requiring oral corticosteroid treatment and antibiotics in the 3 months prior to Visit 1, or during the run-in period (Visit 1–Visit 3)

Assessments

- The primary FRI endpoints were siVaw and siRaw.
- Secondary endpoints of image-based airway volume (iVaw) and resistance (iRaw) were measured, in addition to endpoints based upon spirometry (FEV_1) and plethysmography (functional residual capacity [FRC]).
- All endpoints were based on post-dose assessments performed within 150 minutes of dosing on Day 29 (±3 days), with high-resolution computed tomography (HRCT) scans performed 90 minutes ±30 minutes post-dose, followed by spirometry and body plethysmography.
  - HRCT scans were performed on Day 1 of period 1 (baseline) and at Day 29 of each treatment period, at total lung capacity (TLC) and FRC.
  - Spirometry and plethysmography were performed pre-dose on Day 1 of each treatment period and post-dose on Day 29.
- Adverse events were monitored throughout the study.

Statistical analysis

- The intent-to-treat (ITT) population was defined as all patients who were randomized to treatment. The modified ITT (mITT) population was defined as all patients who completed both treatment periods and had FRI data at baseline and after approximately 4 weeks of treatment, with data judged to be impacted by important protocol deviations excluded. The primary analysis used the ITT population.
- The safety population included all patients who received ≥1 dose of study drug.
- FRI parameters used data averaged across all lung lobes, and separately for each lobe to estimate differences in effects between treatments. Baseline was recorded as Day 1 of Treatment Period 1 (Visit 3).
- Comparisons between treatments were also conducted. P-values (2-sided) were reported to a significance level of 0.05.
- Primary efficacy analyses (siVaw and siRaw) consisted of a within-treatment comparison of change from baseline data with Day 29 and used a paired t-test. This was performed separately for each primary endpoint within each treatment group.
  - "Untrimmed" data used in primary analysis were based on generations visible for each segment at that particular study visit.
  - "Trimmed" data used in sensitivity analyses were based on generations visible in both the baseline scan and the Day 29 scan in each period.
  - Estimates were produced for the difference between BGF and GFF treatment groups, by lobe and across all lobes. A multilevel model was used to incorporate the repeated measurements from the lobes for each patient, including fixed effects for period, treatment, lobe, and treatment-by-lobe interaction. Lobe was included as a random effect within each patient. FRI data were logarithmically transformed before analysis with treatment effect estimates, then exponentiated and presented as ratios.
- Secondary endpoint analysis was similar to the analysis of the primary endpoints.
  - iVaw and iRaw at TLC were additionally analyzed across lobes, with untrimmed data being used without correction for lobe volume.
- For spirometric and plethysmographic endpoints at Day 29, paired tests were compared with assessments at Visit 3 and Visit 5 (Day 1 of each treatment period) with averaging over –60 and –30 minute values for spirometry. For comparisons between treatments, a subject-level baseline for a given endpoint was defined as the average of the corresponding period-dependent baselines.
- For the primary efficacy endpoints, Hochberg's step-up procedure was used to adjust for multiplicity. It was applied once for siVaw and siRaw endpoints of BGF, and separately again for GFF. There was no multiplicity adjustment for secondary endpoints.

Results

Study population

- A total of 23 patients were randomized and received ≥1 dose of the study drug, and 17 patients were included in the mITT population (Table 1).
- The modified ITT analysis set was defined as all subjects in the ITT analysis set who completed both treatment periods and had functional respiratory imaging data at baseline and after approximately 4 weeks of treatment. Data judged to be impacted by important protocol deviations was excluded.
- Baseline demographics and characteristics are shown in Table 1.

FRI

- Both BGF and GFF showed statistically significant improvements from baseline in the primary endpoints of airway volume (siVaw; 72% [p<0.0001] and 53% [p<0.0001] increases, respectively) and airway resistance (siRaw; 50% [p<0.0001] and 48% [p<0.0001] reductions, respectively) at Day 29 (Table 2, Figure 2).
  - On average, siVaw was 9% higher (p=0.0061) and siRaw was 3% lower (p=0.6094) with BGF versus GFF (Table 2).
  - Improvements in siVaw and siRaw were observed across all lobes for BGF and GFF.
  - Sensitivity analyses based on trimmed siVaw and siRaw values showed similar trends as the primary analyses based on untrimmed values.
- Representative images from one patient for siVaw and siRaw, respectively, are shown in Figure 3.
- For iVaw and iRaw endpoints, statistically significant differences from baseline were observed for both BGF and GFF, consistent with primary endpoints (Table 2).
  - On average, iVaw was 10% higher (LSM ratio 1.10; p=0.0051) and iRaw was 4% lower (LSM ratio 0.96; p=0.5346) with BGF versus GFF (Table 2).

Mass of deposited particles

- Deposition as determined by using computational fluid dynamics and formulation characteristics was 38.1% of budesonide, 40.5% of glycopyrrolate, and 39.8% of formoterol fumarate.

Table 1. Baseline demographics and characteristics (ITT population).

Patient disposition, n (%)	Total (N=23)
Treated Treated with BGF 320/18/9.6 µg Treated with GFF 18/9.6 µg	23 (100.0) 22 (95.7) 23 (100.0)
Completed study	21 (91.3)
ITT population mITT population	23 (100.0) 17 (73.9)
Baseline demographics	
Mean age, years (SD)	64.9 (7.6)
Male, n (%)	18 (78.3)
Current smoker, n (%) Median pack-years smoked[a] (range)	10 (43.5) 41.0 (15–100)
Severity of COPD (GOLD)[c], n (%) Moderate Severe	 17 (73.9) 6 (26.1)
COPD exacerbations per subject (past 12 months), mean (SD)	0.2 (0.5)
Total CAT score (0–40)[b], mean (SD)	17.3 (5.6)
FEV_1 at screening (% predicted) Pre-bronchodilator, mean (SD) Post-bronchodilator, mean (SD)	 58.4 (13.1) 63.6 (13.7)
FEV_1/FVC post-bronchodilator at screening, mean (SD)	51.7 (10.5)
% predicted RV, mean (SD)	173.1 (43.9)
Baseline TLC (L), mean (SD)	7.4 (1.4)
% predicted FRC, mean (SD)	149.8 (26.2)

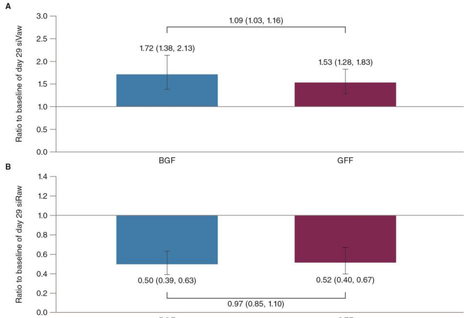
[a]Number of pack-years smoked = (number of cigarettes per day / 20) x number of years smoked.
[b]The total score was the sum of 8 CAT item scores. A higher score denotes a more severe impact of COPD.
[c] One subject was reported with very severe COPD on the electronic case report form; however, all FEV_1 values at Visit 1 and Visit 3 fell within the inclusion criteria (30-80%) and the subject was correctly randomized in the severe COPD group
BGF, budesonide/glycopyrrolate/formoterol fumarate; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; GOLD, global initiative for COPD; GFF, glycopyrrolate/formoterol fumarate; ITT, intent-to-treat; mITT, modified intent-to-treat; RV, residual volume; SD, standard deviation; TLC, total lung capacity.

Table 2. Comparison with baseline for primary and secondary efficacy endpoints at Day 29 (ITT population).

	BGF 320/18/9.6 µg (N=22)	GFF 18/9.6 µg (N=23)	Treatment difference BGF vs GFF
Primary FRI endpoints			
siVaw at TLC, mL/L Geometric mean Ratio to baseline (95% CI)	 2.05 1.72 (1.38, 2.13)****	 2.00 1.53 (1.28, 1.83)****	 LSM ratio 1.09 (1.03, 1.16)**
siRaw at TLC, kPa·s/L Geometric mean Ratio to baseline (95% CI)	 0.21 0.50 (0.39, 0.63)****	 0.20 0.52 (0.40, 0.67)****	 LSM ratio 0.97 (0.85, 1.10)
Secondary endpoints			
FRI			
iVaw at TLC, mL Geometric mean Ratio to baseline (95% CI)	 2.74 1.70 (1.37, 2.11)****	 2.71 1.51 (1.26, 1.80)****	 LSM ratio 1.10 (1.03, 1.17)**
iRaw at TLC, kPa·s/L Geometric mean Ratio to baseline (95% CI)	 0.18 0.50 (0.40, 0.63)****	 0.16 0.52 (0.40, 0.68)****	 LSM ratio 0.96 (0.85, 1.09)
Spirometry			
Post-dose FEV_1, L Mean change from baseline (95% CI)	 0.35 (0.18, 0.51)**	 0.27 (0.14, 0.41)**	LSM difference 0.060 (–0.014, 0.133)
Body plethysmography			
FRC, L Mean change from baseline (95% CI)	 –0.28 (–0.77, 0.21)	 –0.50 (–0.81, –0.18)**	LSM difference 0.15 (–0.23, 0.53)

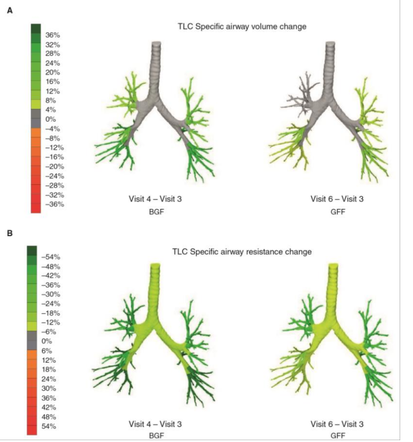
**statistically significant, p<0.01; ****statistically significant, p≤0.0001.
BGF, budesonide/glycopyrrolate/formoterol fumarate; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; FRI, functional respiratory imaging; GFF, glycopyrrolate/formoterol fumarate; iRaw, image-based airway resistance; ITT, intent-to-treat; iVaw, image-based airway volume; LSM, least squares mean; siRaw, specific image-based airway resistance; siVaw, specific image-based airway volume; TLC, total lung capacity.

Figure 2. Geometric mean ratio to baseline for A) siVaw and B) siRaw at Day 29.



BGF, budesonide/glycopyrrolate/formoterol fumarate; CI, confidence interval; GFF, glycopyrrolate/formoterol fumarate; siRaw, specific image-based airway resistance; siVaw, specific image-based airway volume.

Figure 3. Example patient images for % change from baseline to Day 29 for siVaw at TLC (mL/L) and siRaw at TLC (kPa·s). Green coloring represents A) an increase in airway volume and B) a decrease in airway resistance. Orange coloring indicates the converse.



BGF, budesonide/glycopyrrolate/formoterol fumarate; GFF, glycopyrrolate/formoterol fumarate; siRaw, specific image-based airway resistance; siVaw, specific image-based airway volume; TLC, total lung capacity.

Spirometry and body plethysmography

- A significant improvement was observed for change from baseline in post-dose FEV_1 with BGF (p=0.0003) and GFF (p=0.0004) (Table 2).
  - The LSM difference between treatments in the change from baseline for FEV_1 (BGF vs GFF) was 60 mL, but the difference was not significant (Table 2).
- Improvements from baseline in FRC were observed for both groups, which were numerical for BGF (p=0.2515) and statistically significant for GFF (p=0.0040) (Table 2).
  - The LSM difference between treatments in the change from baseline in FRC (BGF vs GFF) was 0.15 (p=0.4256). Median improvements in FRC were –0.36 L for BGF and –0.26 L for GFF.

Safety

- Safety findings were consistent with the known safety profiles of both treatments in patients with moderate-to-severe COPD (Table 3).
- Four patients (18.2%) and six patients (26.1%) experienced any AE in the BGF and GFF treatment groups, respectively (Table 3).

Table 3. Overall summary of adverse events, safety analysis set.[a]

	BGF 320/18/9.6 µg (N=22)	GFF 18/9.6 µg (N=23)
Any AEs, n (%)	4 (18.2)	6 (26.1)
Any AEs related to study treatment[b], n (%)	1 (4.5)	3 (13.0)
Any AE leading to early discontinuation, n (%)	0	1 (4.3)
Any serious TEAEs, n (%)	1 (4.5)	0
Any serious AEs related to study treatment[b], n (%)	0	0
Deaths (all causes)	0	0

[a]Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories. Total number of patients in the safety analysis set = 23.
[b]Investigator assessed.
AE, adverse event; BGF, budesonide/glycopyrrolate/formoterol fumarate; GFF, glycopyrrolate/formoterol fumarate; TEAE, treatment-emergent adverse event.

Conclusions

- Both BGF and GFF demonstrated clinically meaningful improvements in FRI parameters, increasing airway volume, and reducing airway resistance in patients with moderate-to-severe COPD.
- The ICS component of BGF resulted in significant incremental improvement in airway volume relative to GFF alone.
- Improvements in lung function observed by spirometry and plethysmography were directionally consistent with FRI endpoints; however, no significant differences were shown between BGF MDI and GFF MDI, indicating the increased sensitivity of the FRI parameters to detect differences between treatments in a small number of subjects.
- Both treatments were well tolerated with no unexpected safety findings.
- These results are consistent with the scintigraphy findings (NCT03906045), which show efficient delivery and deposition of BGF throughout the large and small airways.
- Overall, the results of this study confirm the beneficial effects of BGF on airway volume and resistance throughout the lungs, complementing recent scintigraphy findings showing that BGF is deposited throughout the large and small airways of the lung.[3]

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Disclosures

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JDB is the Chief Executive Officer and founder of FLUIDDA and holds shares in the company.

CVH is an employee of FLUIDDA.

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RT, MJ, PD, and MA are employees of AstraZeneca and hold stock and/or stock options in the company.

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