

In Silico Lung Deposition Profiles of Three Single-Inhaler Triple Therapies in Patients with COPD Using Functional Respiratory Imaging

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Introduction: Inhalation is the foundational route for administering pharmacological treatments for chronic obstructive pulmonary disease (COPD). Given the relevance of both large and small airways in COPD, lung distribution deposition characteristics of different inhaler options could influence treatment effects. This study evaluated the total deposition of 3 single-inhaler triple therapies in the large and small airways.

Methods: This study assessed lung deposition of different inhalers using in silico functional respiratory imaging from 20 patients with COPD. The first part evaluated budesonide/glycopyrronium/formoterol fumarate dihydrate (BGF) pressurized metered-dose inhaler (pMDI), beclomethasone dipropionate/glycopyrronium/formoterol fumarate dihydrate (BDP/G/F) pMDI, and fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) dry powder inhaler (DPI) at 30 L/min. The second part assessed BGF pMDI and FF/UMEC/VI DPI at 60 L/min.

Results: All 3 inhalers had different in silico total lung and large and small airways deposition profiles at 30 L/min, with BGF pMDI (54.8% to 57.7%) demonstrating a higher deposition profile across each therapeutic component versus BDP/G/F pMDI (38.6% to 40.5%) and FF/UMEC/VI DPI (24.0% to 36.1%), respectively. Similarly, at 60 L/min, the total deposition of all 3 components of BGF pMDI (57.2% to 58.5%) remained higher compared with FF/UMEC/VI DPI (19.8% to 34.1%).

Conclusion: These findings provide quantitative insights into relative lung deposition distribution profiles and efficiency of delivery for 3 inhaler options. Further research is needed to understand if these deposition patterns could translate into real-world clinical effectiveness differences.

Keywords: functional respiratory imaging, chronic obstructive pulmonary disease, small airways, single-inhaler triple therapy

Introduction

Inhaled drugs are the mainstay of pharmacological treatment for people with chronic obstructive pulmonary disease (COPD). Delivering drugs to the lungs via inhalation presents inherent challenges due to the complex anatomy and physiology of the respiratory system, especially when there are varying degrees of obstruction.¹ With many inhalers, a substantial amount of the administered dose is deposited in the mouth and throat.¹ This may result in little or no clinical benefit to the lungs and poses risks, including local side effects, such as oral candidiasis, and systemic exposure through swallowing, for drugs with limited first-pass effect.² Therefore, it is important to understand the performance and efficiency of inhalers at delivering the appropriate dose of treatment to the lungs.

COPD affects both large and small airways (also known as the central and peripheral airways, respectively), and each may require treatment. With COPD, the large airways undergo structural changes characterized by airway narrowing, mucus

hypersecretion, and mucus plugging, which compromise airflow and facilitate infection.¹ Studies have also demonstrated the crucial role of the small airways in COPD as a region of inflammation and a major cause of airway obstruction resulting in air trapping and lung hyperinflation.^{3,4} Expiratory flow limitation, characterized by small airway collapse during expiration, exacerbates gas trapping, and static and dynamic hyperinflation.⁵ This leads to increased dyspnea and a higher impact on daily living,⁵ leading to poor health outcomes.⁶ Thus small airways may be a critical treatment target for inhaled bronchodilators and anti-inflammatory medications.⁶ Therefore, it is not only important to understand the overall lung deposition of inhaled treatments, but also the relative distribution throughout large and small airways.

In vivo gamma scintigraphy is the gold standard for assessing lung deposition of inhaled medications. However, it is often impractical or impossible to compare multiple inhaled medications using this technique due to the technical challenges of radio-labeling different inhaled formulations. Additionally, the significant radiation exposure to patients associated with this technique limits the ability to conduct multiple assessments on the same individuals.⁷ One alternative technique is an in silico method, referred to as functional respiratory imaging (FRI), that utilizes computed tomography (CT) scans from patients to develop 3-dimensional (3D) anatomical models of the lungs. Computational fluid dynamics models based on particle size distribution, inhalation flow profile, and lung anatomy are then used to simulate particle flow and estimate deposition in the lungs. Despite the inherent limitations of any modeling technique, this method has been validated in several studies, showing that it corresponds well with in vivo scintigraphy.^{7,8}

Currently, 3 single-inhaler triple therapies consisting of inhaled corticosteroid/long-acting muscarinic antagonist/long-acting β_2 -agonist (ICS/LAMA/LABA) are available for the treatment of COPD. In the European Union, budesonide/glycopyrronium/formoterol fumarate dihydrate (BGF) pressurized metered-dose inhaler (pMDI), beclomethasone dipropionate/glycopyrronium/formoterol fumarate dihydrate (BDP/G/F), which is available in both a pMDI and dry powder inhaler (DPI) device, and fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) DPI (specifically the Ellipta[®] device) are currently approved for the maintenance treatment of COPD.^{9–11} In the United States, BGF and FF/UMEC/VI are the single-inhaler triple therapies currently approved for the maintenance treatment of COPD.^{9,10} Different inhaler types and formulations may exhibit varying abilities to deposit drugs in the lungs and may be characterized by different deposition profiles. Notably, the particle size distribution of inhaler devices plays a critical role in these deposition patterns, influencing the efficiency of drug delivery to both large and small airways.¹² Understanding these deposition patterns may help optimize delivery of medication to both large and small airways.

The objectives of this study were to understand the overall deposition patterns of the 3 single-inhaler triple therapies (BGF pMDI, BDP/G/F pMDI, and FF/UMEC/VI DPI) in the lungs, as well as the distribution in the large and small airways using in silico FRI. The study compared all 3 products at a low flow rate (30 L/min) recommended for pMDIs. This flow rate is also suitable for some DPIs, including the Ellipta[®],¹³ and can be generated by patients with COPD who struggle to inhale forcibly enough to deagglomerate dry powder formulations into respirable particles. Additionally, BGF was compared with FF/UMEC/VI at a higher flow rate (60 L/min), which is typically recommended for DPIs, but is less suitable for pMDIs. This analysis provides insights on the efficiency of these 3 treatments to deliver medication to the large and small airways of the lung.

Methods

Study Design

This study was conducted in 2 phases to assess the lung deposition performance of different inhaler devices. The first phase evaluated all 3 devices—BGF pMDI (2 actuations of 160/7.2/5 μ g), BDP/G/F pMDI (2 actuations of 87/9/5 μ g), and FF/UMEC/VI DPI (1 actuation of 92/55/22 μ g)—using a mean flow rate of 30 L/min. The second phase focused on BGF pMDI and FF/UMEC/VI DPI at a higher mean flow rate of 60 L/min. Because this higher flow rate is less suitable for pMDI devices, BDP/G/F was not included in this second phase. The study employed in silico FRI, combining high-resolution CT (HRCT) scans with computational fluid dynamics (CFD) to provide quantitative insights into patient-specific respiratory pathways. The FRI technique consists of 4 main components: (1) HRCT scanning to produce 3D airway models; (2) determination on inhaler characteristics; (3) setting the inhalation profiles; and (4) in silico lung deposition modeling using CFD simulations.^{8,14,15}

3D Airway Modeling

HRCT lung scans were retrospectively obtained from 20 patients with moderate-to-very severe COPD using the FLUIDDA database.¹⁶ All patients provided written informed consent for their HRCT scans to be included in the FLUIDDA database, and ethics approval was granted by the Institutional Review Board (2015–001743-36) of the University Hospital in Antwerp, Belgium. This study adhered to the ethical principles outlined in the Declaration of Helsinki. Lung segmentation data obtained from HRCT scans of patients in the FLUIDDA database are the exclusive property of FLUIDDA and did not require additional patient consent for use in this study. Patient models were selected to resemble the type of patients encountered in clinical trials and real-world settings, based on forced expiratory volume in 1 second (FEV₁). HRCT scans were taken at total lung capacity and functional residual capacity. The process to develop the 3D airway models has been previously described.¹⁴

Inhaler Characteristics

The in vitro aerosol characteristics used for modeling, including aerodynamic particle size distribution (APSD) at flow rates of 30 L/min and 60 L/min, are presented in [Supplementary Table 1](#).^{13,17} Plume or spray characteristics including cone angle, velocity measurements, and injection duration are described in [Supplementary Table 2](#). The velocity values for BGF at 3 different distances from the inhaler nozzle were used to extrapolate the velocity magnitude at the inhaler nozzle, following a previously outlined method.¹⁸

Lung Deposition Modeling

The patient HRCT scans were used to generate 3D computer-aided design models of each inhaler by reverse-engineering the inhaler's geometry from the HRCT images. The correct position of the lips on the mouthpiece was determined to ensure proper insertion depth, and the inhaler was virtually coupled with upper airway models to direct airflow toward the mouth opening, avoiding the hard palate and tongue. However, in real life, variations in individual patient anatomy and differences in inhaler technique may result in deviations from these idealized conditions. Simulations were governed by conservation of mass, momentum, and energy equations, with airflow coupled to aerosols using source terms. Large eddy simulation turbulence model was applied for turbulence effects.¹⁹

In silico FRI technology applied patient-specific boundary conditions in CFD simulations using HRCT data by extracting lobe volumes and airway geometries from inspiratory and expiratory HRCT scans. Additionally, ventilated air from each lobe was determined and applied as the flow rate from the airways, capturing peripheral resistance and regional compliance.

APSD data were integrated into CFD simulations to predict particle motion and airway deposition across various inhalation profiles. Lung deposition evaluated in intrathoracic airways (total lung) divided into large airways (up to ~9th-generation bronchioles, ~2 mm diameter) and small airways (beyond HRCT limit).⁶ Particles not deposited in extra-thoracic regions or large airways were assumed to deposit in small airways, considering no particle exhalation with a recommended breath-hold.

Reported data include the percentage of the delivered dose of BGF, BDP/G/F, or FF/UMEC/VI overall and for each individual ICS, LAMA, and LABA component.

Inhalation Profiles

The study was conducted in 2 parts with 2 separate inhalation profiles. In both parts there was a single flow profile with 1 inhalation cycle for the DPI and 2 inhalation cycles for the pMDIs to represent the treatment instructions provided to patients.

Part 1: 30 L/min

The flow characteristic for each cycle included a mean flow rate of 30 L/min, a peak inspiratory flow of 32.4 L/min, and a total inhalation time and total inhaled volume of 5 seconds and 2.5 L, respectively, and are characteristic of a pMDI profile.¹⁴ All 3 products were tested under these conditions ([Supplementary Figure 1A](#)).

Part 2: 60 L/min

Using a similar single flow profile, the flow characteristics for the second phase included a mean flow rate of 60 L/min and a peak inspiratory flow of 90 L/min. The total inhalation time was 2.5 seconds and the total inhaled volume was 2.5 L, and both are characteristic of a DPI profile ([Supplementary Figure 1B](#)).¹⁴

Statistics Analysis

Statistical analyses were conducted using R version 3.2.5 or higher (The R Foundation for Statistical Computing). Lung deposition, expressed as a percentage of the delivered dose, is shown as mean $\pm$ standard deviation (SD).

Statistical comparisons were conducted using paired *t* tests to compare BGF, BDP/G/F, and FF/UMEC/VI for total lung, large airway, and small airway deposition. These comparisons were made for each treatment component (ICS, LAMA, and LABA) and the overall average of the components. Results included mean differences and 95% confidence intervals (CIs) for lung deposition between treatments, along with nominal *P* values for these differences.

Results

Baseline Characteristics

Data from 20 patients (11 male and 9 female) diagnosed with moderate-to-severe COPD were used to create 3D airway models to assess in silico lung deposition with FRI ([Supplementary Table 3](#)). Patients had a mean (SD) age of 64.9 (4.9) years and a mean (SD) body mass index of 27.6 (5.3) kg/m². Respiratory characteristics included a mean (SD) FEV₁ of 1.3 (0.5) L and mean (SD) FEV₁ percentage of predicted value of 47.4 (15.9).

Part I: 30 L/min

The distribution profiles of all 3 inhalers in the mouth and throat, the large airways, and the small airways are shown in [Figure 1](#). More detailed data, broken down for each individual component of the medication and showing total deposition and absolute delivered deposition within each zone of the lungs, are presented in [Figure 2](#). Additionally, [Figure 3](#) provides visual depictions of the deposition across all 3 products in the same representative single subject.

The majority of the BGF dose reached the lungs (54.8% to 57.7%). There was higher deposition in the small airways (31.2% to 32.8%) versus large airways (23.3% to 24.8%) with a central:peripheral (C:P) ratio of 0.75 overall ([Table 1](#)), and $\geq 50\%$ of the dose for BDP/G/F and FF/UMEC/VI was deposited in the mouth and throat. A greater proportion of the dose for BDP/G/F was deposited in the small airways (C:P ratio = 0.49), and the majority of the dose for FF/UMEC/VI was deposited in the large airways (C:P ratio = 1.03).

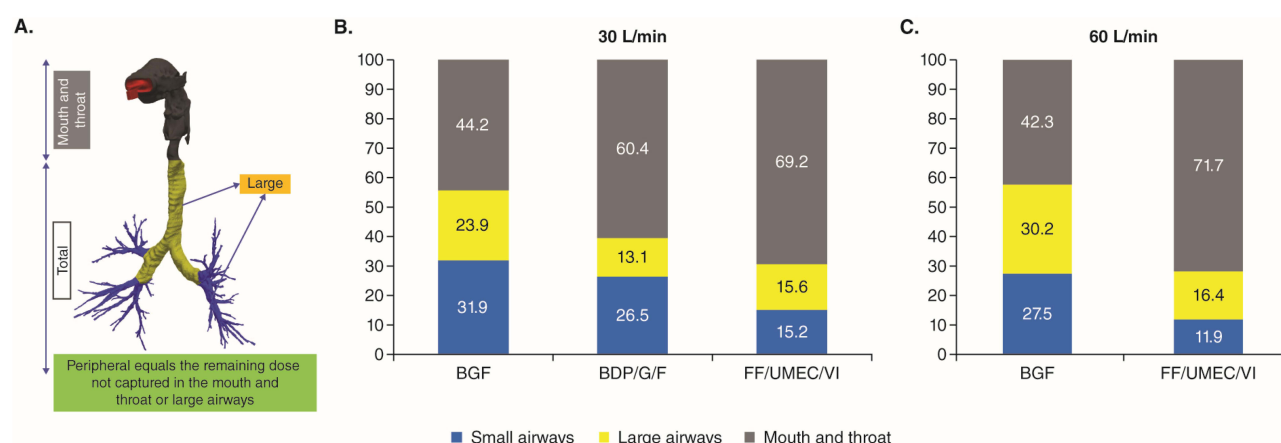


Figure 1 Anatomy and Overall Distribution Profiles (A) Lung Structures and Zones, (B) Distribution at 30 L/min, and (C) Distribution at 60 L/min.

Abbreviations: BDP/G/F, beclomethasone dipropionate/glycopyrronium/formoterol fumarate dihydrate; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol.

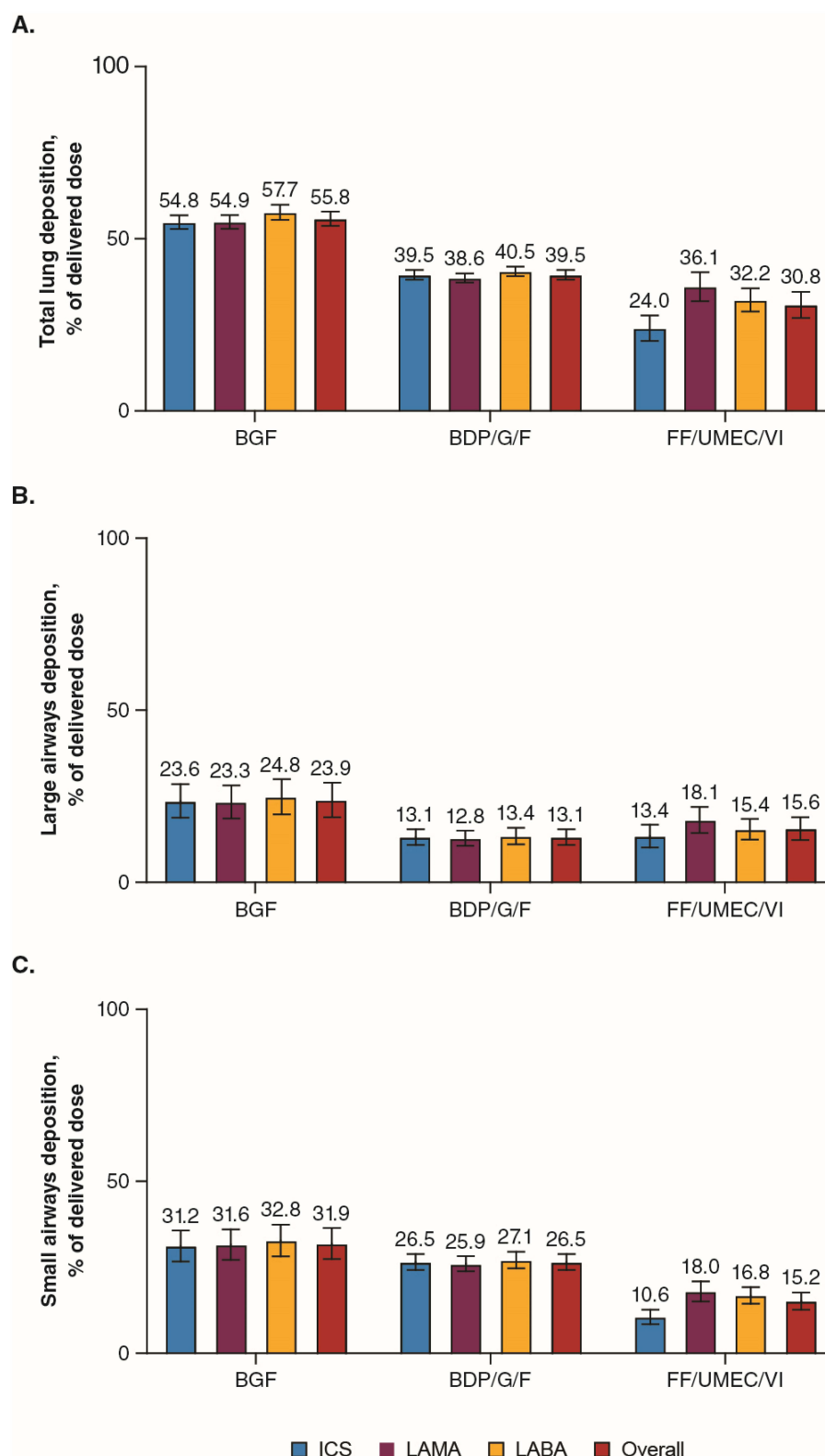


Figure 2 Deposition for All Components of BGF, BDP/G/F, and FF/UMEC/VI at 30 L/min by Location for (A) Total Lung, (B) Large Airways, and (C) Small Airways.^{a,b}
Notes: ^aData labels represent the mean $\pm$ SD. ^bThe absolute delivered dose was calculated using the percentage of delivered dose multiplied by the delivered dose label claim, then multiplied again by the number of actuations, if applicable. For example, for BGF: 54.8% of the ICS component was delivered in the total lung, therefore $54.8\% \times 160 \mu\text{g} \times 2 \text{ actuations} = 175.4 \mu\text{g}$ absolute delivered drug dose.
Abbreviations: BDP/G/F, beclomethasone dipropionate/glycopyrronium/formoterol fumarate dihydrate; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; SD, standard deviation.



Figure 3 Representative Deposition Visualization (% Delivered Dose) of 3D Airway Model of the Same Participant Using the 30 L/min Flow Rate.
Abbreviations: 3D, 3-dimensional; BDP/G/F, beclomethasone dipropionate/glycopyrronium/formoterol fumarate dihydrate; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; DPI, dry powder inhaler; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; pMDI, pressurized metered-dose inhaler.

The greatest total lung deposition was observed with BGF and on average demonstrated a ratio $\pm$ 95% CI of 1.41 ± 0.01 times ($P < 0.001$) greater deposition as a percent of delivered dose than BDP/G/F and 1.81 ± 0.07 times ($P < 0.001$) greater than FF/UMEC/VI (Table 2). Both pMDIs had a greater small airway deposition of the ICS component versus the DPI (BGF vs FF/UMEC/VI ratio: 2.95 ± 0.17 , $P < 0.001$; BDP/G/F vs FF/UMEC/VI ratio: 2.50 ± 0.15 , $P < 0.001$), and there was less difference between the 2 pMDI devices across all 3 components (BGF vs BDP/G/F ratio: 1.20 ± 0.04 , $P < 0.001$). In the large airways, BGF exhibited a 1.53 ± 0.06 times greater deposition compared with FF/UMEC/VI and 1.83 ± 0.06 times greater than BDP/G/F (both $P < 0.001$). Conversely, BDP/G/F showed reduced deposition in the large airways relative to the DPI by a ratio of 0.84 ± 0.04 ($P < 0.001$).

The 3 components of BGF showed similar deposition to each other in both large and small airways. For BDP/G/F, total lung deposition was 38.6% to 40.5% with similar deposition seen for all 3 components in both large (12.8% to 13.4%) and small airways (25.9% to 27.1%).

Table 1 Large to Small Airway Deposition Ratio

	Treatment (Device)	BGF (pMDI)				BDP/G/F (pMDI)				FF/UMEC/VI (DPI)			
	Component	ICS	LAMA	LABA	Overall	ICS	LAMA	LABA	Overall	ICS	LAMA	LABA	Overall
30 L/min	C:P ratio	0.75	0.74	0.76	0.75	0.49	0.49	0.49	0.49	1.27	1.00	0.91	1.03
60 L/min	C:P ratio	1.14	1.08	1.08	1.10	–	–	–	–	1.80	1.43	1.13	1.38

Note: Yellow cells indicate overall data and grey cells indicate no data available.
Abbreviations: BDP/G/F, beclomethasone dipropionate/glycopyrronium/formoterol fumarate dihydrate; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; C:P, central:peripheral; DPI, dry powdered inhaler; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; pMDI, pressurized metered-dose inhaler.

Table 2 Relative Deposition Based on Percent of Delivered Dose

	Treatment (Device)	BGF (pMDI) vs BDP/G/F (pMDI)				P value	BGF (pMDI) vs FF/UMEC/VI (DPI)				P value	BDP/G/F (pMDI) vs FF/UMEC/VI (DPI)				P value
	Component	ICS	LAMA	LABA	Overall		ICS	LAMA	LABA	Overall		ICS	LAMA	LABA	Overall	
30 L/min	Total , ratio $\pm$ 95% CI	1.39 $\pm$ 0.01	1.42 $\pm$ 0.01	1.42 $\pm$ 0.01	1.41 $\pm$ 0.01	<0.001	2.29 $\pm$ 0.13	1.52 $\pm$ 0.06	1.79 $\pm$ 0.06	1.81 $\pm$ 0.07	<0.001	1.65 $\pm$ 0.09	1.07 $\pm$ 0.04	1.26 $\pm$ 0.04	1.29 $\pm$ 0.05	<0.001
	% of delivered dose	54.8	54.9	57.7	55.8		24.0	36.1	32.2	30.8		39.5	38.6	40.5	39.5	
	Large airways , ratio $\pm$ 95% CI	1.81 $\pm$ 0.06	1.83 $\pm$ 0.05	1.86 $\pm$ 0.06	1.83 $\pm$ 0.06	<0.001	1.76 $\pm$ 0.10	1.29 $\pm$ 0.04	1.61 $\pm$ 0.05	1.53 $\pm$ 0.06	<0.001	0.97 $\pm$ 0.07	0.71 $\pm$ 0.03	0.87 $\pm$ 0.03	0.84 $\pm$ 0.04	<0.001
	% of delivered dose	23.6	23.3	24.8	23.9		13.4	18.1	15.4	15.6		13.1	12.8	13.4	13.1	
	Small airways , ratio $\pm$ 95% CI	1.18 $\pm$ 0.04	1.22 $\pm$ 0.04	1.21 $\pm$ 0.04	1.20 $\pm$ 0.04	<0.001	2.95 $\pm$ 0.17	1.75 $\pm$ 0.09	1.95 $\pm$ 0.09	2.10 $\pm$ 0.10	<0.001	2.50 $\pm$ 0.15	1.43 $\pm$ 0.06	1.61 $\pm$ 0.06	1.75 $\pm$ 0.08	<0.001
	% of delivered dose	31.2	31.6	32.8	31.9		10.6	18.0	16.8	15.2		26.5	25.9	27.1	26.5	
60 L/min	Total , ratio $\pm$ 95% CI	–	–	–	–	–	2.89 $\pm$ 0.17	1.69 $\pm$ 0.07	1.87 $\pm$ 0.04	2.03 $\pm$ 0.07	<0.001	–	–	–	–	–
	% of delivered dose	57.2	57.5	58.5	57.7		19.8	34.1	31.2	28.4						
	Large airways , ratio $\pm$ 95% CI	–	–	–	–	–	2.40 $\pm$ 0.12	1.49 $\pm$ 0.05	1.84 $\pm$ 0.03	1.84 $\pm$ 0.05	<0.001	–	–	–	–	–
	% of delivered dose	30.4	29.8	30.4	30.2		12.7	20.1	16.5	16.4						
	Small airways , ratio $\pm$ 95% CI	–	–	–	–	–	3.78 $\pm$ 0.22	1.97 $\pm$ 0.09	1.92 $\pm$ 0.08	2.31 $\pm$ 0.10	<0.001	–	–	–	–	–
	% of delivered dose	26.7	27.7	28.1	27.5		7.1	14.0	14.7	11.9						

Note: Yellow cells indicate overall data and grey cells indicate no data available.

Abbreviations: BDP/G/F, beclomethasone dipropionate/glycopyrronium/formoterol fumarate dihydrate; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; CI, confidence interval; DPI, dry powdered inhaler; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; pMDI, pressurized metered-dose inhaler.

For FF/UMEC/VI, deposition was not consistent across the 3 components with 24.0% of the ICS component compared with 36.1% of the LAMA component and 32.2% of the LABA component reaching the lungs. Slightly higher amounts, especially the ICS component, deposited in the large airways (13.4% to 18.1%) than the small airways (10.6% to 18.0%). The C:P ratio was higher for the ICS component, but similar for the LAMA and LABA components (ICS: 1.27; LAMA: 1.0; LABA: 0.91).

For the total delivered dose component, BGF pMDI showed higher ICS deposition compared with the other treatments at 30 L/min. Specifically, BGF pMDI deposited 175.4/320 µg (54.8%) of ICS, versus 68.8/174 µg (39.5%) deposited by BDP/G/F pMDI and 22.1/92 µg (24.0%) by FF/UMEC/VI DPI (Table 3 and Figure 2B). LAMA and LABA deposition were relatively consistent across the devices.

Part 2: 60 L/min

At a higher flow rate, total lung deposition was also consistently greater for all 3 components of BGF than for the respective components of FF/UMEC/VI (BGF: 57.2% to 58.5%; FF/UMEC/VI: 19.8% to 34.1%; ratio: 2.03; Figure 4). This was evidenced by higher deposition in the large airways for all 3 components versus FF/UMEC/VI DPI (BGF: 29.8% to 30.4%; FF/UMEC/VI: 12.7% to 20.1%; ratio: 1.84 ± 0.05) and a greater small airway deposition (BGF: 27.5%; FF/UMEC/VI: 11.9%; ratio: 2.31 ± 0.10), particularly for the ICS component (BGF: 26.7%; FF/UMEC/VI: 7.1%; ratio: 3.78 ± 0.22). Supplementary Figure 2 provides visual depictions of the deposition between both products in the same representative single subject.

The ratio of total lung deposition between 60 L/min to 30 L/min was similar for BGF (1.03; Table 4). BGF was observed to have slightly greater deposition in the large airways at 60 L/min (average, 30.2% vs 23.9%; ratio, 1.26), and slightly reduced deposition in the small airways (average: 27.5% vs 31.9%; ratio: 0.86).

With FF/UMEC/VI, total lung deposition and large airway deposition remained mostly similar at both flow rates (0.92 and 1.05, respectively), but there was greater reduction in small airway deposition (0.79), with most marked reduction for the ICS component at the higher flow rate (0.67).

For the total delivered dose component at 60 L/min, BGF pMDI deposited 182.9/320 µg (57.2%) of ICS, higher than the 18.2/92 µg (19.8%) observed with FF/UMEC/VI DPI (Table 3). LAMA and LABA deposition were 8.3/14.4 µg (57.5%) and 5.9/10 µg (58.5%), respectively for BGF pMDI, and 18.8/55 µg (34.1%) and 6.7/22 µg (31.2%), respectively for FF/UMEC/VI at the higher flow rate.

Discussion

This FRI study has demonstrated notably different deposition profiles of 3 single-inhaler triple therapies approved for the maintenance treatment of COPD. At the typical flow rate for pMDI (30 L/min), BGF showed the highest overall lung deposition (>50%) with the lowest deposition in the mouth and throat as measured by percentage of the delivered dose. This lung deposition was significantly greater than the deposition achieved by both BDP/G/F and FF/UMEC/VI. Notably, BGF also exhibited the highest fraction of deposition in the small airways compared with the large airways, indicating a favorable deposition profile for targeting small airways.

Table 3 Absolute Deposition Based on Delivered Dose Label Claim

	Treatment (Device)	BGF (pMDI) ^a			BDP/G/F (pMDI) ^a			FF/UMEC/VI (DPI)		
	Component	ICS	LAMA	LABA	ICS	LAMA	LABA	ICS	LAMA	LABA
30 L/min	Total (µg)	175.4	7.9	5.8	68.8	7.0	4.0	22.1	19.9	7.1
60 L/min	Total (µg)	182.9	8.3	5.9	–	–	–	18.2	18.8	6.9

Notes: ^a2 actuations. Grey cells indicate no data available.
Abbreviations: BDP/G/F, beclomethasone dipropionate/glycopyrronium/formoterol fumarate dihydrate; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; DPI, dry powdered inhaler; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; pMDI, pressurized metered-dose inhaler.

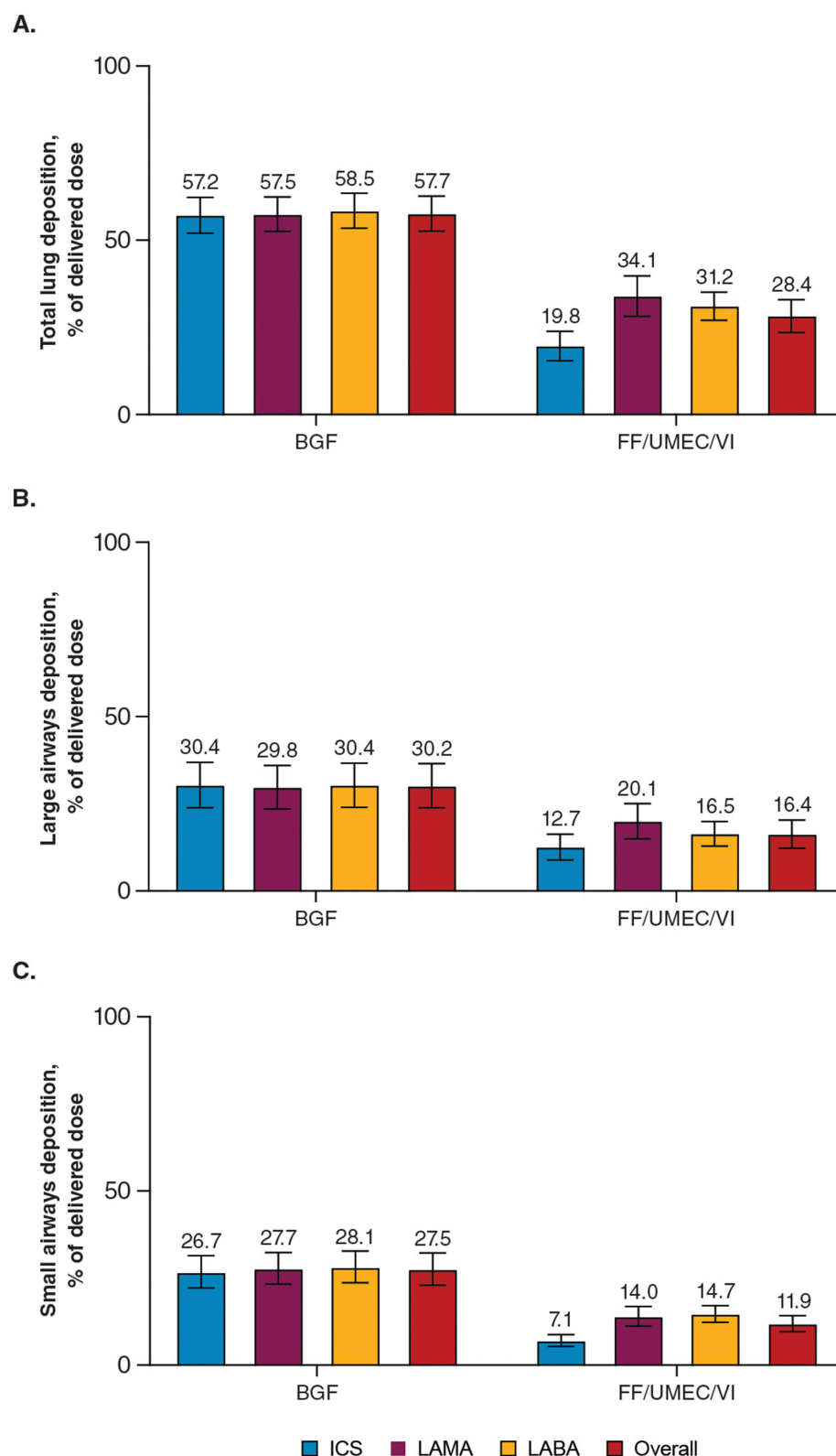


Figure 4 Deposition for All Components of BGF, BDP/G/F, and FF/UMEC/VI at 60 L/min by Location for (A) Total Lung, (B) Large Airways, and (C) Small Airways.^{a,b}
Notes: ^aData labels represent the mean $\pm$ SD. ^bThe absolute delivered dose was calculated using the percentage of delivered dose multiplied by the delivered dose label claim, then multiplied again by the number of actuations, if applicable. For example, for BGF: 54.8% of the ICS component was delivered in the total lung, therefore 54.8% $\times$ 160 μ g $\times$ 2 actuations = 175.4 μ g absolute delivered drug dose.

Abbreviations: BDP/G/F, beclomethasone dipropionate/glycopyrronium/formoterol fumarate dihydrate; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; DPI, dry powder inhaler; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; SD, standard deviation.

Table 4 Relative Deposition Comparing 60 L/min With 30 L/min

	Treatment (Device)	BGF (pMDI)				FF/UMEC/VI (DPI)			
	Component	ICS	LAMA	LABA	Overall	ICS	LAMA	LABA	Overall
60 L/min:30 L/min ratio	Total	1.04	1.05	1.01	1.03	0.82	0.94	0.97	0.92
	Large airways	1.29	1.28	1.22	1.26	0.95	1.11	1.08	1.05
	Small airways	0.86	0.88	0.86	0.86	0.67	0.78	0.87	0.79

Note: Yellow cells indicate overall data.

Abbreviations: BGF, budesonide/glycopyrrolate/formoterol fumarate dihydrate; DPI, dry powdered inhaler; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; pMDI, pressurized metered-dose inhaler.

Both the BGF and BDP/G/F inhaler demonstrated superior small airway deposition compared with FF/UMEC/VI. The large airway deposition of BGF was notably higher than BDP/G/F and FF/UMEC/VI. Regarding the individual components, the ICS lung deposition was significantly higher with BGF. The lung deposition dose of the LAMA and LABA components were similar across the 3 single-inhaler triple therapy devices. At 30 L/min, these findings suggest that BGF offers a distinct advantage in terms of total lung and small airway deposition of the ICS component.

At a higher inspiratory flow rate of 60 L/min, BGF also demonstrated the highest total lung deposition as a percentage of the delivered dose among the studied devices. This superior deposition profile for BGF was consistent across all 3 components of the medication. Likewise, BGF achieved greater large and small airway deposition compared with FF/UMEC/VI. The ratio of total lung deposition between the 60 L/min and 30 L/min flow rates was similar for BGF, indicating consistent performance across varying flow rates. In clinical practice, individual differences in patient anatomy and inhaler technique may lead to variations from these optimized conditions. Of note, there was a slight change in the profile with slightly more drug deposited in the large airways and less in the small airways, presumably due to increased inertia and less ability for particles at high velocity to navigate the twists and turns of the bronchial tree. This observation highlights that although a slow and long inhalation of 4 to 5 seconds (approximately 30 L/min for an inhalation volume of 2.5 L) is recommended by the European Respiratory Society and the International Society for Aerosols in Medicine for using a pMDI,²⁰ modern pMDIs remain efficient and deliver medication effectively to the small airways even with the use of faster and shorter inhalation profiles.

The high deposition achieved with BGF may relate to the Aerosphere™ (AstraZeneca) cosuspension technology of the formulation, where the medication is carried by low-density porous phospholipid particles.¹² These phospholipid particles help to ensure a stable suspension and consistent dosing and are aerodynamically efficient, thereby optimizing drug delivery throughout the large and small airways. Furthermore, all 3 active components are carried by the porous phospholipid particles to deposit in the airways, releasing the medication on the mucosal surface and facilitating codeposition of all 3 active components. This explains the similar percent deposition for all 3 components in each zone of the lungs.

BDP/G/F also had high levels of total lung deposition (approximately 40%). Like BGF, delivery of all 3 components was similar, suggesting codeposition. This codeposition relates to the formulation as a solution, as all 3 components would be initially released together and dissolved in droplets that evaporate in transit through the lungs before depositing all 3 components together on the epithelial surface. Codeposition may facilitate synergistic interactions between the components. Recently, synergistic effects have been suggested for triple therapy between all 3 active components, ICS, LAMA, and LABA.²¹ A proportionally smaller amount of the BDP/G/F lung dose was deposited in the large airways, with a correspondingly higher deposition in the small airways. Consequently, BDP/G/F had the smallest C:P ratio, as expected, due to the extrafine particle formulation. However, perhaps contrary to expectations, this did not translate into the greatest amount of small airways deposition as less of the delivered dose reached the lungs compared with BGF.

Although no head-to-head in vivo deposition data using scintigraphy exist, separate studies in healthy volunteers allow for an indirect comparison. For BGF, a phase 1 scintigraphy study showed 37.7% lung deposition with a C:P ratio of 0.75,²² whereas BDP/G/F showed 22.7% lung deposition with a C:P ratio of 0.94.²³ Differences in deposition may be

attributed to patient population variations and inhalation behaviors, despite BDP/G/F having an extrafine particle size.¹⁴ In addition to particle size, other factors such as fine particle fraction (FPF), geometric SD (GSD), and plume characteristics significantly influence deposition. FPF represents the proportion of drug mass in an aerosol that is small enough to penetrate the lungs and exert a therapeutic effect, typically referring to particles with an aerodynamic diameter of $\leq 5 \mu\text{m}$. GSD measures the variability in particle diameter within an aerosol; a higher GSD value indicates a wider distribution of particle sizes, whereas a lower GSD value indicates a narrower distribution. Plume characteristics also play a critical role. A high-velocity plume can cause greater medication impaction at the back of the mouth and throat, whereas a low-velocity plume may be beneficial because it can increase the dose that can bypass the bend of the throat and reach the lungs. Additionally, formulations with a mass median aerodynamic diameter (MMAD) $>2 \mu\text{m}$ still contain a portion of the dose that is $<2 \mu\text{m}$, which contributes to small airways deposition. Despite BGF having a larger MMAD than BDP/G/F and FF/UMEC/VI, BGF has a greater FPF ([Supplementary Table 1](#)), suggesting that FPF may be a better indicator of total lung deposition than MMAD.⁷ In addition to MMAD, FPF and GSD characteristics for each study treatment are listed in [Supplementary Table 1](#) and plume characteristics for the pMDI inhalers are listed in [Supplementary Table 2](#).

In a recent study, the impact of different inhalation profiles on lung deposition were assessed with varying durations and flow rates (peak and mean) to reflect the different pattern of real-world use and the abilities of patients with obstructive lung disease.¹⁴ BGF was tested with peak flow rates of 32–104 L/min and inhalation durations of 1.6–6.2 s. The study found that the total lung deposition and small airways deposition were relatively consistent with BGF irrespective of the profile used, which may be due to the AerosphereTM formulation and use of aerodynamic porous particles.

Of the 3 inhalers tested, FF/UMEC/VI had the least overall lung deposition at the flow rate of 30 L/min, with most of the lung fraction deposited in the large airways. Furthermore, the 3 components of FF/UMEC/VI did not deposit similarly, with the ICS component having the lowest deposition. This difference was most marked in the small airways, which is most likely due to the large particle size and lower FPF for the ICS component.

A low flow rate is not suited for most DPIs as they require high inhalation force to deagglomerate the powder into drug particles. However, the Ellipta[®] device is claimed to be less dependent on the need for high inhalation force and can tolerate lower inhalation flow rates.¹³ To ensure a lack of bias against the DPI, FF/UMEC/VI underwent further testing at the higher flow rate of 60 L/min. Total deposition at the higher flow rate was similar to the total deposition observed at 30 L/min, supporting the position that the Ellipta[®] device is less flow rate-dependent than many other DPIs. However, there were some differences. Notably, lower deposition was observed in the small airways at the higher flow rate, specifically with the ICS component.

The findings in this study do suggest that irrespective of the device type, optimal deposition to the small airways is achieved with slower, more prolonged inhalation profiles. Consequently, the ICS component of FF/UMEC/VI has a larger particle size and a lower FPF compared with the other 2 components resulting in lower deposition characteristics.

The results of this study highlight fundamental differences between triple therapies in the drug delivery to the various regions of the lungs. However, the study does not provide any insight into whether any of these inhalers provide greater clinical benefit than the others. There are no head-to-head clinical or real-world efficacy studies of these triple therapies, and most indirect treatment comparisons have shown similar efficacy. However, the importance of treating the small airways in COPD, and other respiratory diseases, is increasingly recognized.²⁴ The small airways are crucial in the pathophysiology of COPD, and inadequate drug deposition, particularly with anti-inflammatory medication, in the small airways could lead to suboptimal treatment outcomes, as patients with COPD impacted by small airway disease often have poorer health status.⁶

FRI has limitations that must be considered. FRI is a modeled in silico technique and it cannot fully replicate all factors of the in vivo setting that could influence deposition as measured with scintigraphy, such as physiological factors including airway humidity or the complex aerosolization process and secondary droplet aging.^{7,25} Due to the limited resolution of CT scans, FRI cannot model deposition within the small airways, but instead treats small airways as a singular region. Since the model considers exhalation of medication within the extrathoracic zone and large airways, it neglects the fraction exhaled from the small airways, which may be important when assessing the submicron particles

that make up greater proportions of extrafine formulations.²⁶ Specifically, submicron particles typically deposit by sedimentation and diffusion, so if insufficient breath-hold after inhalation, they may be exhaled before depositing on the mucosal surface.²⁷ FRI can also be an idealized view and may reflect the maximal deposition possible in any given setting. Even though patients are extensively trained in scintigraphy studies to inhale optimally, they may still make errors. In real-world clinical practice, individual differences in patient anatomy and inhaler technique, including inhalation profile, may lead to variations from these optimized conditions. In FRI, the inhalation profile is the same for each individual, timing of actuation and inhalation is precise, and there are no other patient-related errors unless specifically modeled with the technique. This may explain why results from FRI in this study seem higher than those seen with scintigraphy. Lastly, it was not feasible to compare the 3 inhalers across multiple flow rates in this study. Future research is needed to compare the 3 inhalers across different profiles mimicking real-world use to provide a more comprehensive understanding of their performance in diverse patient populations.

Despite these limitations, FRI offers several advantages over traditional techniques. Unlike with scintigraphy, there is no need for complex radio-labeling of the formulations, and patients have reduced exposure to radiation.⁸ Another advantage includes the ability to test different formulations under the same conditions in the same sets of lungs, thereby allowing robust comparisons in relatively small numbers of patients. Also, FRI can model each component individually, which is not possible with scintigraphy.

Conclusions

This study showed differences in the deposition profiles of 3 single-inhaler triple therapies in patients with COPD. Both pMDI combinations showed consistent deposition in the small airways, with BGF demonstrating the highest deposition for all components. However, the ICS component in FF/UMEC/VI had the least deposition in these airways, which decreased further with faster inhalation. These findings may be particularly relevant for treating patients with COPD who have small airway inflammation and obstruction.

Abbreviations

3D, 3-dimensional; APSD, aerodynamic particle size distribution; BDP/G/F, beclomethasone dipropionate/glycopyrronium/formoterol fumarate dihydrate; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; C:P, central: peripheral; CFD, computational fluid dynamics; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DPI, dry powder inhaler; FEV₁, forced expiratory volume in 1 second; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; FPF, fine particle fraction; FRI, functional respiratory imaging; GSD, geometric standard deviation; HRCT, high-resolution computed tomography; ICS/LAMA/LABA, inhaled corticosteroid/long-acting muscarinic antagonist/long-acting β_2 -agonist; MMAD, mass median aerodynamic diameter; NGI, next generation impactor; pMDI, pressurized metered-dose inhaler; SD, standard deviation.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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