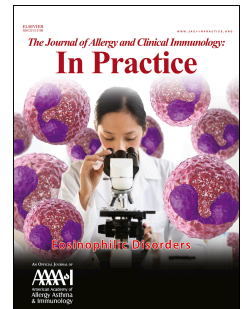


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ELLIPTA dry powder versus metered-dose inhalers in an optimized clinical trial setting

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28

29 **Conflicts of interest:**

30 A. Preece, D. Brintziki, K. Collison, R. Sharma, are employees of GlaxoSmithKline plc.

31 K. Collison owns stocks in GlaxoSmithKline plc.

32 E. Kerwin has participated in consulting, advisory boards, speaker panels, or received travel
33 reimbursement for Amphastar, Astra Zeneca, Forest, GlaxoSmithKline plc., Mylan, Novartis, Oriel,
34 Pearl, Sunovion, Teva and Theravance. He has conducted multicenter clinical research trials for
35 approximately forty pharmaceutical companies.

36

Abstract [246/250 words]

Background: Reduced error rates have been demonstrated with the ELLIPTA inhaler versus other commonly used devices.

Objective: This phase IV, randomized, crossover study evaluated correct use of ELLIPTA compared with two commonly prescribed metered-dose inhalers (MDIs) in adults with asthma and optimized inhaler technique.

Methods: The study comprised two crossover sub-studies (ELLIPTA vs MDI-1 and ELLIPTA vs MDI-2). Inhaler use was assessed at the start of each period, following instruction from a healthcare professional, and after 28 days of use without instruction. Data for each inhaler were pooled within sub-studies, irrespective of treatment sequence; study objectives were addressed in each sub-study. The primary endpoint, percentage of participants making zero errors after 28 days of use, was analyzed separately for each sub-study using a Mainland-Gart test for each ELLIPTA versus MDI comparison.

Results: Correct use rates after 28 days were higher with ELLIPTA than with MDI-1 and MDI-2 (ELLIPTA vs MDI-1: 96% vs 84%; ELLIPTA vs MDI-2: 98% vs 91%). Among discordant cases, statistically significantly more participants correctly used ELLIPTA but made ≥ 1 overall error with MDIs than those who correctly used the MDIs but made ≥ 1 overall error using ELLIPTA (87% vs 13% in both sub-studies; $p < 0.001$ and $p = 0.007$ for ELLIPTA vs MDI-1 and ELLIPTA vs MDI-2, respectively). More participants made multiple device errors with MDIs than with ELLIPTA.

Conclusion: Inhaler technique can be optimized in trial settings. In such settings, ELLIPTA is associated with higher rates of correct use and lower error rates than MDIs.

Highlights box:

1. What is already known about this topic? Inhaler errors can lead to reduced medication delivery and reduced clinical efficacy in asthma patients. The ELLIPTA inhaler device is associated with fewer critical and overall errors than other dry powder or metered-dose inhalers.
2. What does this article add to our knowledge? A significant proportion of participants demonstrated correct use of ELLIPTA and incorrect use of metered-dose inhalers versus the opposite outcome (87% vs 13% for both sub-studies; $p < 0.001$ for sub-study 1 and $p = 0.007$ for sub-study 2).
3. How does this study impact current management guidelines? Our study indicates that high rates of correct inhaler use are achievable with training by healthcare professionals and ELLIPTA may represent the preferred device choice versus tested metered-dose inhalers in patients with optimized technique.

Keywords: ELLIPTA, dry powder inhaler, metered-dose inhaler, inhaler technique, inhaler errors, optimized technique, inhaler training, clinical trial

Abbreviations:

ACT: Asthma Control Test

AE: adverse Event

COPD: chronic obstructive pulmonary disease

DPI: dry powder inhalers

HCP: healthcare professional

ICS: inhaled corticosteroid

- 82 ITT: intent-to-treat
- 83 LABA: long-acting β_2 -adrenergic agonist
- 84 MDI: metered-dose inhaler
- 85 MITT: modified intent-to-treat
- 86 PIL: patient information leaflet
- 87 SABA: short-acting β_2 -adrenergic agonist
- 88 SD: standard deviation

Introduction

Inhaled medications (i.e., short-acting and long-acting β_2 -adrenergic agonists [SABAs and LABAs, respectively], anticholinergics, and inhaled corticosteroids [ICSs] are cornerstone to the management of asthma [1, 2]. Short-acting bronchodilators (e.g. SABAs and short-acting muscarinic antagonists) are given as quick-relief medications to alleviate acute attacks, while ICSs and ICS/LABA combinations, which target the underlying inflammatory pathology of the disease, are given as regular maintenance therapy to control symptoms and reduce the risk of exacerbations [1].

There are several devices available for the delivery of inhaled asthma medications, with dry powder inhalers (DPIs) and metered-dose inhalers (MDIs) being the most commonly used [3]. While MDIs require good hand-lung coordination to optimize delivery, propellant-free DPIs were later introduced as a user-friendly alternative free from ozone-depleting substances [4, 5]. Nevertheless, errors remain unacceptably frequent with both DPIs and MDIs in real-world practice [6]. A systematic review of 54,354 patients reported that the most common errors associated with MDIs are no breath-hold post-inhalation (46%), problems with coordination of inhalation and actuation (45%), and speed/depth of inspiration (44%); and those associated with DPIs are an absence of full expiration before inhalation (46%), no breath-hold post-inhalation (37%), and incorrect preparation (29%) [6]. Such errors are associated with reduced medication delivery [4], and decreased efficacy and symptom control [1, 3, 6, 7].

The ELLIPTA DPI was developed for the treatment of asthma and chronic obstructive pulmonary disease (COPD), and has been designed to simplify use versus MDIs [8]. Patients with asthma or COPD make fewer critical errors (errors likely to result in no or significantly reduced medication being inhaled) and overall errors (any error in inhaler technique) with the ELLIPTA DPI than with other DPIs and MDIs [9]. Furthermore, patient preference for the ELLIPTA DPI has been demonstrated previously versus other DPIs and MDIs for many attributes, including ease of use [11, 12]. The current clinical study was conducted to evaluate correct use of the ELLIPTA DPI compared

with correct use of two commercially available MDIs in adults with asthma in an optimized inhaler technique setting.

Methods

Study design

This phase IV, multicenter, randomized, open-label, crossover study (ClinicalTrials.gov identifier: NCT02794480; GlaxoSmithKline plc. study number: 204980) assessed correct inhaler use with ELLIPTA versus two commonly prescribed MDIs manufactured by GlaxoSmithKline plc. and AstraZeneca (FLOVENT HFA and SYMBICORT, referred to as MDI-1 and MDI-2, respectively). Key features of these inhalers and differences between them are highlighted in **Figure 1**. The crossover design enabled participants to serve as their own control regarding their ability to use either device. The inhalers contained placebo to remove any bias due to treatment effects. Both MDIs were of traditional design and spacers were not utilized. Participants continued to take their current asthma medication(s) as prescribed and continued to follow up with their regular physician for asthma care during the study.

Within the study were two sub-studies. Sub-study one compared ELLIPTA with MDI-1; sub-study two compared ELLIPTA with MDI-2. In each sub-study, participants were randomized 1:1 to one of two inhaler sequences (ELLIPTA then MDI or MDI then ELLIPTA). The duration of each assessment period was 28 ± 2 days and inhalers were used as per the patient information leaflet (PIL).

Participants

Participants were adults (≥ 18 years old) with a documented history of well-controlled asthma (Asthma Control Test [ACT] score ≥ 20) requiring a SABA for symptom control ≤ 2 days per week. Participants also had to have been receiving maintenance therapy for ≥ 3 months, and at a stable dose in the month prior to inclusion. Participants who had received maintenance therapy via an MDI

or ELLIPTA in the past 6 months were excluded; however, other inhaler types such as DISKUS or TWISTHALER were acceptable and were continued unchanged throughout the study. Participants continued their MDI quick-relief therapies as needed.

Further exclusion criteria included a concurrent diagnosis of COPD or other respiratory disorders; current smoker or a smoking history of ≥ 10 pack years; a history of life-threatening asthma; >1 exacerbation that required oral/systemic corticosteroids in the 12 months prior to Visit 1; known hypersensitivity to any components of the study inhaler; evidence of clinically significant or rapidly progressing/unstable cardiovascular, neurologic, renal, hepatic, immunologic, endocrine (including uncontrolled diabetes or thyroid disease), or hematologic abnormalities that are uncontrolled; and inability to read, comprehend, and record information in English.

All participants provided written, informed consent prior to inclusion. The study was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice and the ethical principles outlined in the Declaration of Helsinki 2013.

A total of 324 participants (162 in each sub-study) were enrolled and randomized (intent-to-treat [ITT] population) at 20 investigational sites in the USA between August 22, 2016 and December 15, 2016. Of these, 315 participants (97%) completed the study. Reasons for study withdrawal included withdrawal of consent ($n=5$), lost to follow up ($n=2$), adverse event (AE; $n=1$), and protocol deviation ($n=1$). A total of 310 participants from the ITT population provided inhaler use data after 28 days for both inhalers (modified ITT [MITT] population), including 157/162 (97%) and 153/162 (94%) participants in sub-studies 1 and 2, respectively.

Study objectives

The primary objective of the study was to evaluate the proportions of participants who correctly used an ELLIPTA inhaler compared with those who correctly used MDI-1 or MDI-2 after 28 days of use. Secondary objectives included the frequency of errors by type for each inhaler, the number of

errors per participant for each inhaler, and the number of errors for each inhaler in participants with ≥ 1 error after 28 days of use.

Study procedures

At the start of each assessment period (Day 1, Day 28 ± 2 days), participants received their assigned inhaler per the randomization schedule and, after reviewing the written instructions in the PIL, were asked to demonstrate correct use. If they were unable to demonstrate correct use, they were given verbal instructions from the present healthcare professional (HCP) and had up to two further attempts to use the inhaler correctly. Physician principle investigators (medical doctors) oversaw staff training and data collection at each site. Thereafter, participants were requested to use the assigned inhaler at home for 28 days as instructed (ELLIPTA, one inhalation, once daily in the morning; MDI, two inhalations, twice daily).

At the end of each assessment period (Day 28 ± 2 days; Day 56 ± 2 days), participants returned to the study site and were asked to repeat the demonstration of inhaler use without instruction from study staff. The HCP noted any errors.

Outcomes and assessments

Correct use of the assigned inhaler was assessed by study HCPs at the beginning and end of each assessment period against a checklist developed per the exact PIL instructions. Overall, 11 possible types of error were identified for ELLIPTA; 13 possible error types were identified for both MDI-1 and MDI-2 (shown in **Table 1** alongside the observed error rates). Adherence was assessed based on the dose counter reading at the start and end of the assessment period on each inhaler.

Despite there being no active drugs studied, safety was still assessed; endpoints included monitoring of AEs, cardiovascular and death events, and assessment of asthma exacerbations. All AEs were treated per the clinical judgement of the principle investigators at each site overseeing care.

Statistical analyses

Sample size calculations were driven by the difference of interest between inhalers in the error rate, and the percentage of participants making ≥ 1 error with one inhaler and zero errors for the other inhaler (known as the discordance). Based on results from previous studies [10], the percentage of participants making zero errors with ELLIPTA was assumed to be 90%; a difference in the error rate between inhalers of 20% was considered to be of interest. Therefore, the percentage of participants making zero errors with each MDI was assumed to be 70%. A McNemar test and two-sided 5% significance level were used in the calculations, assuming that no period effects exist. The rate of discordance was assumed to be 40% for each MDI versus ELLIPTA comparison and, for the purposes of this calculation, no participants were assumed to make errors with both inhalers. Alternative assumptions for sample size calculation were then a difference in the error rate between inhalers of 20%, with 85% of participants making zero errors with ELLIPTA and 65% of participants making zero errors with their MDI; a discordance of 40% and an error rate of 5% across both inhalers were assumed here.

For each sub-study, 129 participants provided $\geq 94.9\%$ power to detect a difference of 20% in the proportion of participants who made zero errors at Day 28, given a discordance of 40%. Thus, the total number of evaluable participants required for 90% power overall was 258. Allowing for 15% withdrawal, it was anticipated that approximately 304 randomized participants were required.

The MITT population was used for all summary statistics and analysis of primary and secondary endpoints. Study objectives were addressed in each crossover sub-study separately. Data for each inhaler were pooled within the sub-studies, irrespective of treatment sequence. Overall conclusions were based on the results of both sub-studies.

The primary endpoint, percentage of participants having zero errors in inhaler use after 28 days of use, was analyzed separately for each sub-study using a Mainland–Gart test for each ELLIPTA versus MDI comparison. The Mainland-Gart test is an extension of the McNemar test that allows accounting for treatment sequence (period) effects. Analyses were based on participants in the MITT

213 population who made zero errors with one inhaler and ≥ 1 error with the other (i.e., discordant
214 cases). For secondary endpoints, the number of errors per participant was summarized as
215 continuous data by inhaler for each ELLIPTA versus MDI comparison for all evaluable participants,
216 and separately for those with ≥ 1 error. Frequency counts and percentages were used to summarize
217 the total number of errors per participant and the occurrence of each type of error by inhaler for
218 each ELLIPTA versus MDI comparison.

Results

Participants

Baseline characteristics of participants were similar in the two sub-studies (**Table 2**). The majority were female (70%) and the mean age was 50.9 (standard deviation [SD] 15.39) years. The majority of participants (92%) had an asthma duration ≥ 5 years (**Table 2**); only 6% had experienced an asthma exacerbation requiring medical intervention in the year prior to screening, none of which required hospitalization. The most frequently used asthma medications prior to, during, and after the study were fluticasone propionate plus salmeterol xinafoate (73%), albuterol (66%), and albuterol sulfate (23–24%).

Exposure and adherence

Mean exposure in sub-study 1 was 29.0 and 28.8 days for ELLIPTA and MDI-1, respectively. Similarly, in sub-study 2, mean exposure was 29.0 and 29.4 days for ELLIPTA and MDI-2, respectively. The adherence rate was higher with ELLIPTA than with both comparator MDIs: mean (SD) 95.2% (6.13) versus 87.9% (16.14) for ELLIPTA versus MDI-1 and 93.4% (8.99) versus 85.9% (18.12) for ELLIPTA versus MDI-2.

Correct inhaler use at baseline

In both sub-studies, more participants in the ITT population demonstrated correct use of the ELLIPTA inhaler than MDI-1 or MDI-2 during their first attempt following the PIL written instructions. Overall, 93–95% of participants used the ELLIPTA inhaler correctly at the first attempt versus 84–85% using MDIs.

Primary endpoint

After 28 days of use, more participants were able to demonstrate correct use of ELLIPTA than MDI-1 and MDI-2, with 96–98% demonstrating correct use of ELLIPTA and 84–91% demonstrating correct use of MDIs (**Table 3**). The number of discordant cases was $n=24$ and $n=15$ in sub-studies 1 and 2,

respectively. Among discordant cases, a statistically significantly higher proportion of participants correctly used the ELLIPTA inhaler and made ≥ 1 error with comparator inhalers than those who correctly used the comparator inhalers and made ≥ 1 error using the ELLIPTA inhaler (87% vs 13% for ELLIPTA vs MDI in both sub-studies; $p < 0.001$ and $p = 0.007$ for ELLIPTA vs MDI-1 and ELLIPTA vs MDI-2, respectively; Table 3).

Secondary endpoints

After 28 days of use, the mean [SD] number of errors per participant was lower with ELLIPTA than with MDI-1 and MDI-2 in the MITT population (sub-study 1: 0.07 [0.39] with ELLIPTA versus 0.35 [0.14] with MDI-1; sub-study 2: 0.04 [0.30] with ELLIPTA versus 0.21 [0.84] with MDI-2). While 3% and 1% of participants made a single error with the ELLIPTA inhaler in sub-studies 1 and 2, respectively, the rates for MDI-1 and MDI-2 were 8% and 5%, respectively. Only two participants made ≥ 2 errors with ELLIPTA in both sub-studies versus 12 participants with MDI-1 and 7 participants with MDI-2.

Among participants who made ≥ 1 error after 28 days of use, the mean number of errors made with ELLIPTA in sub-studies 1 and 2 was 1.57 and 2.00, respectively, compared with 2.20 with MDI-1 and 2.29 with MDI-2.

In sub-study 1, the most common error with ELLIPTA was shaking the inhaler (2% of participants); the most common error with MDI-1 was not checking the mouthpiece for foreign objects (9%). In sub-study 2, the most common errors with ELLIPTA were not exhaling while holding the inhaler away from the mouth (1%) and not breathing out slowly and gently (1%); the most common error with MDI-2 was not checking the mouthpiece for foreign objects (6%; **Table 1**). Other common errors (occurring in $\geq 3\%$ of participants when using an MDI) were not shaking the inhaler (3%, MDI-1 and MDI-2), not breathing out fully (3%, MDI-1), and not breathing in and pressing down on top of the inhaler (3%, MDI-1).

267 **Safety**

268 The incidence of AEs was 16% in both sub-studies and was similar between inhalers. In sub-study 1,
269 the most common AEs were headache (3%), bronchitis, nasopharyngitis (2% each), and upper
270 respiratory tract infection (1%). In sub-study 2, these were headache, nasal congestion (4% each),
271 back pain, cough, oropharyngeal pain, and upper respiratory tract infection (1% each). No AEs were
272 related to the treatment given or devices used.

Discussion

Poor inhaler technique is a common cause of treatment failure in asthma [1, 3]. Participants who incorrectly use MDIs and DPIs demonstrate a significantly increased risk of hospitalization ($p=0.001$) and emergency room visits ($p<0.001$), an increased need for oral steroids ($p<0.001$), and a reduced ACT score ($p<0.0001$) compared with participants who use their inhalers correctly [3]. Thus, poor inhaler technique leads to reduced disease control [13] and an increase in healthcare resource utilization [3].

Inhaler errors are common in real-world practice and are more frequent with MDIs than DPIs [14]; a meta-analysis of patients with asthma or COPD found that the estimated overall error frequency (95% confidence interval) was 86.8% (74.9–91.1) for MDIs and 60.9% (39.4–79.0) for DPIs [14]. While a number of factors have shown significant association with such errors, including older age and a lower degree of education, a lack of instruction from HCPs appears to be the most significant [3]. As such, participant education on device usage has been highlighted as an effective route to optimize correct inhaler technique [3, 15].

In the current study, we aimed to compare the ability of adults with asthma to correctly use the ELLIPTA inhaler versus two commonly used MDIs in an optimized technique setting. A greater number of participants demonstrated correct inhaler use with ELLIPTA than with MDI-1 or MDI-2 after 28 days of use, which is consistent with previous data and expectations [10]. Human factor validation tests have previously demonstrated similar success rates of $\geq 97\%$ with ELLIPTA [8]. The MDIs also performed well in the current study, with 84% and 91% of participants demonstrating correct use of MDI-1 and MDI-2, respectively, after 28 days of use, which is higher than anticipated [14].

Possible reasons for the smaller observed difference in error rates between ELLIPTA and MDIs in this study than anticipated based on previous findings include: (1) recruited participants had intermittent MDI experience through their quick-relief inhaler; (2) participants were better trained

than expected in using the MDIs; or (3) participants were trained when assigned the inhalers and studied in a highly regulated trial setting. Approximately 90% of participants correctly used the MDIs at baseline, which may have contributed to the high success rate observed at the error assessment after 28 days of use. In contrast to clinical trials, where inhaler training is often provided and the Hawthorne effect contributes to improved inhaler technique, there is a large body of evidence showing that some MDIs are incorrectly used in a more pragmatic real-world setting [16]. Therefore, the higher rates of correct inhaler use observed here could be related to participants making more of an active effort when enrolled in a study focused specifically on inhaler use. Previous data in MDI-naïve participants have shown more substantial differences in favor of ELLIPTA versus MDI than seen in the current study [10].

The total number of errors made when using ELLIPTA was lower than the number of errors made with MDI-1 and MDI-2 in the current study. In addition, users were more likely to make multiple device errors when using one of the MDIs than when using ELLIPTA. Similarly, in a randomized study comparing ELLIPTA with commonly used inhaler devices (DISKUS, MDI, Turbuhaler, HandiHaler, Breezhaler) in 567 patients with COPD and 162 patients with asthma, significantly fewer patients made ≥ 1 critical error or ≥ 1 overall error with ELLIPTA than with the other inhalers after reading written instructions ($p < 0.001$ for all comparisons) [10]; the most common critical error with ELLIPTA in this study was exhalation directly into the mouthpiece (4% of participants) [10]. This was also one of the most common errors reported for ELLIPTA in the current study. There were, however, discrepancies in the common errors with ELLIPTA between the sub-studies, most likely due to the overall low frequency of errors with this device.

The most common errors observed with the two MDIs were similar; however, since the PILs were different for the two MDIs based on approved dosing directions, this led to some differences in specific errors. Not breathing out fully and not breathing in while pressing down on top of the inhaler, reported as common errors with MDIs in the current study, have also been reported as

common errors in other studies [6, 7]. For instance, Ramadan and Sarkis reported that 81.4% of 246 MDI users found difficulty in coordinating their inhalation with pressing the canister [13].

International guidelines recommend that HCPs educate patients on inhalation techniques, with repeated checking to ensure correct use of inhalers [1]. Yet, in reality, this practice may be poorly implemented [17]. The ELLIPTA PILs are designed to be simple to understand and the device use entails fewer steps than other inhalers. This may explain the observation of numerically fewer errors and better adherence with ELLIPTA when compared with other devices in this study and previous work [10]. These features are useful for HCPs who often do not have enough time to demonstrate correct inhaler technique and sometimes also lack the skills [17, 18]. Indeed, previous studies have provided evidence that HCPs including physicians, pharmacists, and nurses may struggle to provide the correct teaching to patients regarding inhaler technique [19-24]. In a study of inhaler technique in 1664 patients with mostly asthma or COPD by Melani et al (2011), only 34% reported receipt of a practical demonstration using a placebo inhaler; one third of patients reported receiving no inhaler education, including 7% who read the PIL with no further instruction, and another third reported receipt of only verbal instruction [3].

Strengths of the current study include its randomized, crossover design and the large number of participants, while a limitation is its unavoidable open-label design. Taken together with the subjective assessment of inhaler use by investigators in this study, the use of an open-label design may have facilitated the introduction of bias to error assessments. Furthermore, this study was unable to obtain truly device-naïve participants due to quick-relief medication, predominantly available in MDIs. The number of discordant cases was low in both sub-studies, and this led to the inclusion of data from a smaller number of participants in the primary analyses than expected. Nevertheless, there were still observable differences in favor of the ELLIPTA DPI over the two MDIs, including better adherence and a reduced risk of errors. A final, notable limitation of this study was a

lack of error stratification by level of consequence beyond overall errors, which may have enhanced our understanding of the impact of these errors on treatment receipt in everyday clinical practice.

This study shows that high levels of correct use can be achieved with the tested inhalers in an optimized clinical trial setting with active HCP training. Here, ELLIPTA, a relatively new DPI, was correctly used by the vast majority of participants and the results of analyses among discordant cases highlighted a statistically significant advantage for ELLIPTA versus the tested MDIs ($p < 0.001$ for sub-study 1; $p = 0.007$ for sub-study 2) regarding the number of participants making zero device errors.

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Data interpretation: all authors

Writing/reviewing of the manuscript: all authors

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434 **Figure legends**

435 **Figure 1.** Key features of ELLIPTA, MDI-1 and MDI-2

436 BUD/FOR, budesonide/formoterol; DPI, dry powder inhaler; FF/UMEC/VI, fluticasone

437 furoate/umeclidinium/vilanterol; MDI, metered-dose inhaler; NA, not applicable

438

439 **Tables**440 **Table 1:** Summary of errors by type for each inhaler after 28 days of use (MITT population; N=310)

Error type from checklists	Sub-study 1 (N=157) n (%N)	Sub-study 2 (N=153) n (%N)
ELLIPTA		
1. Trained HCP provided instructions and demonstration prior to the attempt	0	0
2. Did not slide the cover completely down until a “click” was heard	0	0
3. Did shake the inhaler	3 (2)	0
4. Did not breathe out (exhale) while holding inhaler away from mouth	2 (1)	2 (1)
5. Breathed into the mouthpiece	2 (1)	0
6. Did not place mouthpiece between lips, and close lips around it	1 (<1)	0
7. Did not take one long steady deep breath	1 (<1)	1 (<1)
8. Participant blocked air vent with fingers	0	0

9. Did not remove inhaler from mouth and hold breath	1 (<1)	1 (<1)
10. Did not breathe out slowly and gently	1 (<1)	2 (1)
11. Did not close the inhaler completely	0	0
MDIs		
	MDI-1 (N=157) n (%N)	MDI-2 (N=153) n (%N)
1. Trained HCP provided instructions and demonstration prior to the attempt	0	0
2. Did not shake the inhaler	5 (3)	5 (3)
3. Did not remove the mouthpiece (MDI-1); Did not remove the mouthpiece cover (MDI-2)	0	0
4. Did not check the mouthpiece for foreign objects	14 (9)	9 (6)
5. Did not hold the inhaler with the mouthpiece down (MDI-1); Did not breathe out fully (MDI-2)	1 (<1)	0
6. Did not breathe out fully	5 (3)	0

(MDI-1); Did not place mouthpiece in mouth, and close lips around (MDI-2)		
7. Did not place mouthpiece in mouth, and close lips around it (MDI-1); Inhaler was not upright with the mouthpiece opening towards the back of the throat (MDI-2)	2 (1)	0
8. Did not press the top of the canister all the way down (MDI-1); Did not press down firmly on top of the counter to release the medication (MDI-2)	2 (1)	2 (1)
9. Did not demonstrate the ability to breathe in and press down on top of the inhaler	4 (3)	2 (1)
10. Did not take finger off the canister (MDI-1); Did not continue to breathe in (inhale) for 10 sec (MDI-2)	3 (2)	2 (1)
11. Did not remove inhaler from mouth and close mouth (MDI-1); Did not release finger	2 (1)	2 (1)

before exhaling (MDI-2)		
12. Did not hold breath for 10 seconds and breathe out slowly (MDI-1); Did not keep the inhaler upright and remove from mouth (MDI-2)	3 (2)	2 (1)
13. Did not snap the cap firmly into place (MDI-1); Did not close the mouthpiece cover until it clicks in place (MDI-2)	2 (1)	0
14. Did not close inhaler completely (MDI-2)		1 (<1) ^a

HCP, healthcare professional; MDI, metered-dose inhaler; MITT, modified intent-to-treat
 Note: Errors recorded at Visits 2 (Day 28 ± 2 days) and 3 (Day 58 ± 2 days) after 28 days of use are summarized. Participants could be counted more than once depending on the reasons for incorrect use. The table is based on the inhaler sequence the participants were randomized to. Errors are numbered per the order of their presentation on the inhaler errors checklists used by HCPs to assess correct use in this study.

^aOne participant was randomized to inhaler sequence ELLIPTA/MDI-2, but the actual inhaler sequence received was MDI-2/ELLIPTA. The participant used ELLIPTA in Assessment Period 2 and made an error with this inhaler. However, as the study was reported based on the treatments that participants were randomized to, the error was summarized as it was made on the randomized inhaler for that period (MDI-2; n=1 [<1%]).

Table 2. Participant demographics and clinical characteristics (ITT population; N=324)

	Sub-study 1 (N=162)	Sub-study 2 (N=162)	Total (N=324)
Mean (SD) age, years	51.0 (15.92)	50.8 (14.89)	50.9 (15.39)
Sex, n (%N)			
Male	51 (31)	47 (29)	98 (30)
Female	111 (69)	115 (71)	226 (70)
Mean (SD) BMI, kg/m ²	32.2 (7.84)	31.6 (7.64)	31.9 (7.74)
Duration of asthma, n (%N)			
<10 years	28 (17)	28 (17)	56 (17)
≥10 to <25 years	55 (34)	62 (38)	117 (36)
≥25 years	79 (49)	72 (44)	151 (47)

BMI, body mass index; ITT, intent-to-treat; SD, standard deviation.

Sub-study 1: ELLIPTA vs MDI-1; Sub-study 2: ELLIPTA vs MDI-2.

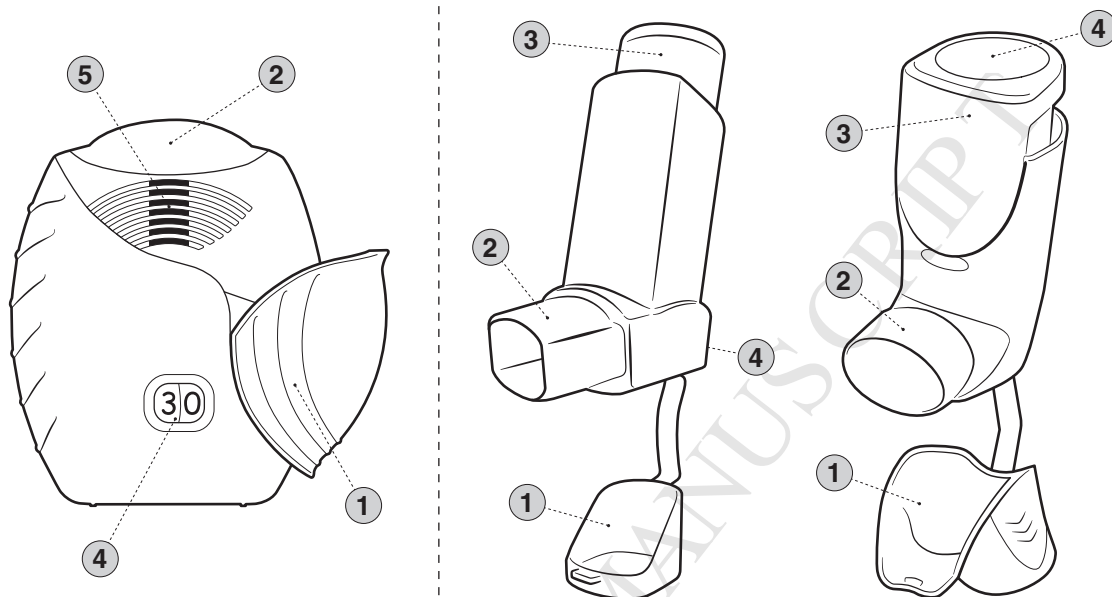
Table 3. Comparison of error rates (0 versus ≥ 1) between participants using the ELLIPTA inhaler versus MDI-1 or MDI-2 after 28 days of use (MITT population; N=310).

ELLIPTA versus MDI, n (%N)		ELLIPTA		
		Zero errors	At least one error	Total
MDI-1 (Sub-study 1; N=157)	Zero errors	129 (82)	3 (2)	132 (84)
	At least one error	21 (13)	4 (3)	25 (16)
	Total	150 (96)	7 (5)	157 (100)
MDI-2 (Sub-study 2, N=153)	Zero errors	137 (90)	2 (1)	139 (91)
	At least one error	13 (8)	1 (1)	14 (9)
	Total	150 (98)	3 (2)	153 (100)

MDI, metered-dose inhaler; MITT, modified intent-to-treat.

Note: Statistical analysis was based on the discordant cases (participants from the MITT population who made ≥ 1 error on one inhaler and no errors on the other inhaler). The numbers of discordant cases were n=24 and n=15 for sub-studies 1 and 2, respectively. Sub-study 1; 21/24 (87%) of the discordant subjects used ELLIPTA correctly but encountered at least one error with MDI-1, versus 3/24 (13%) who encountered at least one error with ELLIPTA but correctly used MDI-1. ELLIPTA vs MDI-1, $p < 0.001$ (Mainland-Gart test). Sub-study 2; 13/15 (87%) of the discordant cases used ELLIPTA correctly but encountered at least one error with the MDI-2, versus 2/15 (13%) who encountered at least one error with ELLIPTA but correctly used MDI-2. ELLIPTA vs MDI-2, $p = 0.007$ (Mainland-Gart test).

ELLIPTA DPI	MDIs	
	MDI-1 (GlaxoSmithKline plc.)	MDI-2 (AstraZeneca)



Inhaler component /action	Key differences			Number on diagram
	ELLIPTA	MDI-1	MDI-2	
Mouthpiece cover	Non-detachable mouthpiece cover slid back until “click” is heard	Mouthpiece cover must be detached for use		1
Mouthpiece	At the top of the device, under the mouthpiece cover	Found at the bottom of the device, under the mouthpiece cover		2
Canister	No canister	Canister top visible at the top of the device	Dose counter acts as the top of the canister	3
Dose counter	Remaining doses shown clearly on the front of the device	Located at the back of the device at the bottom	A gauge on the top of the device	4
Air vent	Air vent should not be blocked by fingers during use	No air vent		5
Shake prior to use	No	Yes		NA
Exhalation prior to use	Breathe out with inhaler away from mouth	Breathe out fully		NA
Medication release mechanism	Breathe in through the mouthpiece steadily and deeply	Top of the canister must be pushed all the way down while inhaling	Press down firmly on top of the dose counter while inhaling	NA