A randomized, cross-over study comparing critical and overall errors, learning time, and preference of the ELLIPTA versus BREEZHALER dry powder inhalers in patients with asthma

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Title: A randomized, cross-over study comparing critical and overall errors, learning time, and preference of the ELLIPTA versus BREEZHALER dry powder inhalers in patients with asthma

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Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhalers; GINA, Global Initiative for Asthma; HCP, healthcare professional; ICS, inhaled corticosteroids; IQR, interquartile range; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; OR, odds ratio; PIL, patient information leaflet; SABA, short-acting β2-agonist; SD, standard deviation.
Abstract

Background

Many patients with asthma make errors using inhalers, affecting the amount of medication received. Previous evidence demonstrated that patients with asthma or chronic obstructive pulmonary disease make fewer critical errors with the ELLIPTA inhaler after reading the patient information leaflet (PIL) versus other dry powder inhalers. We assessed errors made by patients with asthma using placebo ELLIPTA or BREEZHALER inhalers.

Methods

This randomized, multicenter, open-label placebo inhaler-handling study (ClinicalTrials.gov: NCT04813354) with 2x2 complete block crossover design was conducted at three centers in the Netherlands and enrolled patients aged ≥18 years with mild-to-moderate asthma. Inclusion criteria were inhaler use for ≥12 weeks prior to enrollment and naivety to ELLIPTA and BREEZHALER inhalers. Patients were randomized to ELLIPTA or BREEZHALER inhaler first and were assessed for errors in use of both inhalers after 1) reading PIL instructions, 2) receiving further instruction from a healthcare professional (HCP) if they made an error.

Results

114 patients with asthma (57% female; mean age of 55.3 years) were assessed. After reading the PIL, 6% of patients made ≥1 critical error with ELLIPTA versus 26% with BREEZHALER (odds ratio [OR]: 0.11 [95% confidence interval (CI): 0.01–0.40]; p < 0.001). With ELLIPTA, 27% of patients made ≥1 overall error after reading the PIL versus 41% with BREEZHALER (OR: 0.25 [95% CI: 0.03–0.74]; p = 0.005). Fewer patients required HCP instruction with ELLIPTA than BREEZHALER (25% versus 32%).

Conclusions

Fewer patients made critical and overall errors using the ELLIPTA inhaler versus BREEZHALER after reading the PIL.
Keywords: Asthma, ELLIPTA, BREEZHALER, dry powder inhaler, error rate, inhaler technique, patient preference
**Background**

Inhaled medications are the typical standard of care in the treatment of asthma, including inhaled corticosteroids (ICS), short- and long-acting β₂-agonists (SABAs, LABAs, respectively), and long-acting muscarinic antagonists (LAMAs) [1]. SABAs are used for quick relief of acute attacks, while ICS and ICS/LABA ± LAMA combination treatments are used as regular maintenance therapies to control symptoms and reduce the risk of attacks, as they prevent bronchoconstriction and target the underlying inflammatory pathology of asthma [1]. The Global Initiative for Asthma (GINA) advises that, as inhalers are key for asthma management, the most appropriate inhaler should be chosen and, if there are several suitable options, the patient should be involved in the choice. GINA also recommends that inhaler technique be checked at every opportunity, to ensure any errors are identified and corrected, as errors in inhaler technique can reduce the amount of medication received and hinder effective asthma management [1].

ELLIPTA and BREEZHALER are dry powder multi-dose inhalers which have been developed for the delivery of inhaled medication [2, 3]. Previous evidence showed that after reading the patient information leaflet (PIL), patients with chronic obstructive pulmonary disease (COPD) made significantly fewer critical errors (errors which most likely result in no or significantly reduced amounts of medication being inhaled) with the ELLIPTA inhaler than with other dry powder inhalers (DPIs), including BREEZHALER [4]. However, the ELLIPTA inhaler has not yet been assessed against BREEZHALER in patients with asthma. Given that up to 25% of patients with asthma do not receive verbal inhaler technique instruction [5], it is important for healthcare professionals (HCPs) to choose an inhaler which patients can use correctly after only reading the PIL. In this study, (GSK study number 213306; ClinicalTrials.gov: NCT04813354), we assessed errors made by patients with asthma when using placebo ELLIPTA or BREEZHALER DPIs, to provide data to assist HCPs when choosing an inhaler with their patients.
Methods

Study design

This was a randomized, multi-center, open-label, placebo inhaler-handling study with a 2x2 complete block crossover design. The study assessed critical errors, overall errors, training/teaching time, ease-of-use, willingness to continue use, and preference for attributes of ELLIPTA and BREEZHALER DPIs. This single-visit study was conducted at three centers in the Netherlands, between April 14, 2021 and July 8, 2021.

The study design is shown in Fig. 1. Adult patients (≥18 years old) with confirmed mild-to-moderate asthma, according to GINA 2021 [1], were randomly assigned to receive either the placebo ELLIPTA inhaler or placebo BREEZHALER first, and to receive preference questionnaire Version 1 or 2 at the end of the assessment. The randomization schedule was generated using the randomization software RandAll NG. Eligible participants were assigned to study treatment randomly using RAMOS NG, an interactive web response system. There were four possible patient groups; ELLIPTA followed by BREEZHALER, and preference questionnaire Version 1, or questionnaire Version 2 (groups 1 and 2), and BREEZHALER followed by ELLIPTA, and preference questionnaire Version 1, or questionnaire Version 2 (groups 3 and 4 [Fig. 1]). To be included, patients must have been taking asthma maintenance therapy (ICS or ICS/LABA combination therapy) for ≥12 weeks prior to study participation, and had to be naïve to both the ELLIPTA and BREEZHALER DPIs. Patients continued to take their own prescribed asthma medication and other concomitant medication(s) during the study, as the inhalers contained placebo only. Exclusions were made if patients had a concurrent diagnosis of COPD, a history of allergy or hypersensitivity to lactose/milk protein or to any other component of the placebo inhalers, and any known or suspected drug/alcohol abuse.
Fig. 1. Study design schematic.

Step 1
Patients ≥ 18 years old with mild-moderate asthma and naïve to both DPIs randomized to 1 of 4 sequences (A, B, C, D)

A  B  C  D

Procedure
1) Patients assessed for critical and overall errors after:
   - Reading the PIL
   - Up to 3x instructions from HCP as needed
2) Patients assessed for teaching and training time to use correctly
3) Patients complete ‘Ease-of-Use’ questionnaire for current DPI
4) Patients asked willingness to continue with current DPI

Step 2
1) Patients receive 1st DPI as per sequence arm A, B, C or D
2) Procedure as in procedure box below

ELLIPTA

Step 3
1) Patients receive 2nd DPI as per sequence arm A, B, C or D
2) Procedure as in procedure box below

BREEZHALER

Step 4
Patients complete preference questionnaire as per treatment arm A, B, C or D

Version 1
Version 2

DPI, dry powder inhaler; HCP, healthcare professional; PIL, patient information leaflet.
Study procedures

The error assessment steps are summarized in Fig. 2. The error criteria used for critical and overall errors were aligned with the correct use information from the respective PILs, and were provided to the HCPs to use during the study. A critical error was defined as one which was likely to result in no or significantly reduced amounts of medication being inhaled. Overall errors were any non-critical error in inhaler use. Actions constituting an error were outlined per a similar study [4], but with the addition of ‘did not rinse mouth out with water’ (overall error) for the ELLIPTA inhaler, and ‘failed to open inhaler’ (critical error), and ‘did not close the inhaler and cap’ (overall error), for BREEZHALER. The overall error, ‘blocked air inlet during inhalation maneuver’, was not included for either inhaler in this study as it is not listed as an error to collect within the PIL for the BREEZHALER inhaler and no patients made this type of error using the ELLIPTA inhaler.

Patients read the relevant instruction section of the PIL provided by the HCP, before attempting inhaler use for the first time (Attempt 1). If the patient made any errors (critical or overall), the HCP provided the first instruction to show correct inhaler technique, and the patient then tried to use the inhaler again (Attempt 2). If the patient continued to make errors, the HCP would provide a second instruction, and the patient made another attempt to use the inhaler (Attempt 3). Following further errors in inhaler use, the HCP provided a final instruction to show correct use and allowed the patient to make a final attempt to demonstrate correct use of the inhaler (Attempt 4). The time taken for patients to demonstrate correct inhaler use was recorded by the HCP. The events that were timed included: T0 (time taken to read the relevant section of the PIL); T1 (time taken for Attempt 1 by the patient after reading the PIL); and T2 (time taken from the beginning of HCP instruction one, until the patient demonstrated correct inhaler technique [up to three HCP instructions]; this included the time used by the HCP to give the instruction[s]), and T1+T2 (time taken from the patient starting Attempt 1 until correct use was demonstrated, with up to four attempts allowed). After the error assessment, patients completed the ease-of-use
questionnaire for that inhaler. The questionnaire covered factors such as ease of seeing how many doses were left, learning how to use the inhaler, ease of handling, ease of preparing the inhaler for use, and ease of holding the device while using it. Patients were asked how willing they were to continue using that inhaler, measured on a visual analogue scale scoring between 0 (not willing) and 100 (definitely willing). Patients were given up to 30 minutes’ break between completing assessment of the first inhaler and beginning assessment for the second inhaler. This process was repeated in the same manner for both inhalers. Finally, after assessments and ease-of-use questionnaires for both inhalers were completed, patients filled out the preference questionnaire (Version 1 or 2, depending on randomization). Preference for factors such as the number of steps needed to use the inhaler, the amount of time needed, the ease of use, ease of opening the inhaler, size of the inhaler, and comfort of the mouthpiece were assessed. Two versions of the questionnaire were used to minimize any potential bias introduced by the order in which the inhalers were listed in the questions.
Fig. 2. Summary of error assessment steps.

Key
- Attempt
- Errors
- No errors

If DPI is not used correctly, HCP will provide 1st instruction to correct errors
If DPI is not used correctly, HCP will provide 2nd instruction to correct errors
If DPI is not used correctly, HCP will provide 3rd instruction to correct errors
If used incorrectly, no further assessments made

Patient reads PIL for the current DPI to be tested

Attempt 1
- Patient demonstrates DPI use, HCP records errors

Attempt 2
- Patient demonstrates DPI use, HCP records errors

Attempt 3
- Patient demonstrates DPI use, HCP records errors

Attempt 4
- Patient demonstrates DPI use, HCP records errors

If DPI is used correctly, this is recorded and no further assessment is required

DPI, dry powder inhaler; HCP, healthcare professional; PIL, patient information leaflet.
Endpoints

The primary endpoint was the number of patients who made ≥1 critical error at Attempt 1 after reading the PIL. Key secondary endpoints were the number of patients who still made ≥1 critical error after receiving each of the three instructions from the HCP, the number of patients who made ≥1 overall error after reading the PIL, the total amount of time taken to demonstrate inhaler use (T1+T2), and overall inhaler preference from the questionnaire (ELLIPTA, BREEZHALER, or no preference). Further secondary endpoints were the number of patients who still made ≥1 overall error after receiving each of the three HCP instructions, the total number of errors made with that inhaler, the number of patients who required any further instruction from the HCP, T1, T2, ease-of-use, willingness to continue using that inhaler, and safety, including assessment of adverse device events, serious adverse device events, and serious adverse events arising from the use of the inhaler.

Statistics

Continuous data were summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum, maximum, and interquartile range [IQR]). Categorical data were summarized as the number and percentage of patients in each category. The primary endpoint was analyzed using an exact conditional logistic regression model with patients included as fixed strata, and the respective inhalers and period between error assessments were included as fixed effects. The primary estimand was the odds ratio (OR) between the ELLIPTA inhaler and BREEZHALER in patients with mild to moderate asthma who made ≥1 critical error in use of either inhaler after reading the respective PIL, based on patients who were able to demonstrate use of both inhalers. The intercurrent event (patients who did not attempt demonstration of inhaler use for either inhaler) was addressed in the population attribute using a principal stratum strategy. The same summary measure (OR) was used for the number of patients who still made ≥1 critical error after each HCP instruction, the number of patients who still made ≥1 overall error after reading the PIL, and the number of patients who made ≥1 overall error after each HCP instruction as for the primary estimand. Learning
time was summarized using the median time to reach correct inhaler use for each inhaler. T0 was separated from other time measurements, as a longer T0 could be due to a longer PIL and was not reflective of the time taken to demonstrate inhaler use; therefore, T0 was not included in the analysis.

The superiority of one inhaler over the other was declared based on significance at the two-sided 5% level. A one-sided 2.5% level of significance was used where the number of patients making errors was too small for the lower bound of the two-sided 95% confidence interval (CI) to be estimated; in these cases, a one-sided 97.5% CI is presented.

Patient preferences for either inhaler were compared using Prescott’s test, inhaler ease-of-use was compared (easy [very easy or easy] versus difficult [neutral, difficult or very difficult]) using McNemar’s test, and willingness to continue using either inhaler was compared using a paired t-test at the 5% significance level. Median times to learn correct inhaler use technique were estimated using Kaplan-Meier analyses, where time was censored for patients who failed to demonstrate correct use.

The target sample size of 114 patients was based on evidence from similar studies [4, 6], and was required to provide 90% power to the study, based on a two-sided type I error rate of 5%. A consensus was reached that 6% of patients were expected to make ≥1 critical error with the ELLIPTA inhaler and not BREEZHALER, and that 20% of patients were expected to make ≥1 critical error when using the BREEZHALER and not the ELLIPTA inhaler. No withdrawals were expected.

**Ethics**

The study protocol, any amendments, informed consent, and other information that required pre-approval were reviewed and approved by the Medical Research Ethics Committees United. Written informed consent was obtained from each subject prior to the performance of any study-specific procedures.
Data availability

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com

Results

Patients

Overall, 114 patients were randomized, and all patients demonstrated use of both inhalers. Patient demographics are presented in Table 1; most patients were White (97%) and female (57%), and the mean age was 55.3 (SD 16.2) years.
Table 1

Patient demographics.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Total (N = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in Years&lt;sup&gt;a&lt;/sup&gt;, mean (SD)</td>
<td>55.3 (16.21)</td>
</tr>
<tr>
<td>Age Group&lt;sup&gt;a&lt;/sup&gt;, (years), n (%)</td>
<td></td>
</tr>
<tr>
<td>≤18</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>19-64</td>
<td>74 (65)</td>
</tr>
<tr>
<td>≥65</td>
<td>39 (34)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>65 (57)</td>
</tr>
<tr>
<td>Male</td>
<td>49 (43)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>114 (100)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>Asian- South-East Asian Heritage</td>
<td>2 (2)</td>
</tr>
<tr>
<td>White</td>
<td>111 (97)</td>
</tr>
<tr>
<td>White – Arabic/North African Heritage</td>
<td>2 (2)</td>
</tr>
<tr>
<td>White – White/Caucasian/European Heritage</td>
<td>109 (96)</td>
</tr>
<tr>
<td>Mixed Race</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Age was approximate and derived from year of birth.

SD = standard deviation.
Inhaler use error assessment

For the primary endpoint, seven (6%) patients made ≥1 critical error using the ELLIPTA inhaler after reading the PIL, compared with 30 (26%) when using BREEZHALER (OR: 0.11, 95% CI: 0.01–0.40; p < 0.001).

After reading the PIL (Attempt 1), 31 (27%) patients made ≥1 overall error with the ELLIPTA inhaler, compared with 47 (41%) for BREEZHALER (OR: 0.25, 95% CI 0.03–0.74; p = 0.005). After receiving the first HCP instruction (Attempt 2), one (<1%) patient made ≥1 critical error with the ELLIPTA inhaler versus five (4%) with BREEZHALER (OR: 0.71, 97.5% CI: 4.42; one-sided p = 0.33). For both inhalers, no critical errors were made after second or third instructions (Attempt 3, Attempt 4). For overall errors after the first HCP instruction (Attempt 2), three (3%) patients made ≥1 overall error with the ELLIPTA inhaler compared with 10 (9%) using BREEZHALER (OR: 0.34, 97.5% CI: 1.20; one-sided p = 0.048 [not significant]). After a subsequent HCP instruction (Attempt 3), no patients made overall errors with the ELLIPTA inhaler, and one (1%) made ≥1 overall error with BREEZHALER (Tables 2 and 3).
Table 2

Number of Errors with the ELLIPTA inhaler.

<table>
<thead>
<tr>
<th>Error Description</th>
<th>After reading the PIL (N = 114)</th>
<th>After first instruction from HCP (n = 31)</th>
<th>After second instruction from HCP</th>
<th>After third instruction from HCP (n = 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of Critical Errors, n</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total number of Overall Errors, n</td>
<td>44</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Number of Patients with errors, n (%)</td>
<td>31 (27)</td>
<td>3 (10)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Failed to open cover until click was hearda, n (%)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intentionally shook the inhaler after dose preparationa, n (%)</td>
<td>2 (6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No exhalation before an inhalation, n (%)</td>
<td>20 (65)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Exhaled directly into mouthpiecea, n (%)</td>
<td>3 (10)</td>
<td>1 (33)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No seal created by lips around the mouthpiece during the inhalationa, n (%)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inhalation maneuver was NOT: - long - steady – deep, n (%)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Did not hold breath, n (%)</td>
<td>4 (13)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Error Description</td>
<td>n (%)</td>
<td>Read PIL</td>
<td>Required Instruction</td>
<td>Water Use</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>-------</td>
<td>----------</td>
<td>----------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Did not close the inhaler</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Did not rinse mouth out with water</td>
<td>11 (35)</td>
<td>2 (67)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*a Indicates a Critical Error.

*b This was an error but one which did not affect the medication that was inhaled.

Note: Percentages of number of patients with errors based on number of patients who read the PIL or required further instruction. Percentages of type of errors were calculated based on the number of patients with errors.

HCP, healthcare professional; PIL, patient information leaflet.
### Table 3

**Number of Errors with BREEZHALER inhaler.**

<table>
<thead>
<tr>
<th></th>
<th>After reading the PIL (n = 114)</th>
<th>After first instruction from HCP (n = 47)</th>
<th>After second instruction from HCP (n = 10)</th>
<th>After third instruction from HCP (n = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of Critical Errors, n</strong></td>
<td>47</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total number of Overall Errors, n</strong></td>
<td>121</td>
<td>18</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Number of Patients with any errors, n (%)</strong></td>
<td>47 (41)</td>
<td>10 (21)</td>
<td>1 (10)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Failed to open inhaler</strong>, n (%)</td>
<td>2 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Failed to remove capsule from blister pack</strong>, n (%)</td>
<td>4 (9)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Failed to insert capsule into the chamber</strong>, n (%)</td>
<td>2 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Failed to close the inhaler (heard ‘click’ when satisfactory)</strong>, n (%)</td>
<td>2 (4)</td>
<td>1 (10)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Failed to pierce capsule and failed to release the piercing buttons</strong>, n (%)</td>
<td>11 (23)</td>
<td>3 (30)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Intentionally shook the inhaler after dose preparation</strong>, n (%)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>No exhalation before inhalation</strong>, n (%)</td>
<td>19 (40)</td>
<td>3 (30)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Exhaled directly into mouthpiece</strong>, n (%)</td>
<td>2 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
No seal created by lips around the mouthpiece during the inhalation.  

Pressed the side buttons while inhaling through the mouthpiece\(^a\), \(n\ (%\)  

<table>
<thead>
<tr>
<th>Error Description</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation maneuver was NOT: - rapid - deep, (n\ (%)</td>
<td>4 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Capsule did not whirr(^a), (n\ (%)</td>
<td>22 (47)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Failed to hold breath, (n\ (%)</td>
<td>10 (21)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Did not check the capsule chamber, (n\ (%)</td>
<td>16 (34)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Failed to repeat inhalation when powder remained in the capsule, (n\ (%)</td>
<td>20 (43)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Did not close the inhaler and close the cap, (n\ (%)</td>
<td>4 (9)</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)Indicates a Critical Error.

Note: Percentages of number of patients with errors based on number of patients who read the PIL or required further instruction. Percentages of type of errors were calculated based on the number of patients with errors.

HCP, healthcare professional; PIL, patient information leaflet.
With the ELLIPTA inhaler, 28 (25%) patients required one HCP instruction, and three (3%) required a second HCP instruction before demonstrating correct inhaler use. For BREEZHALER, 37 (32%) patients required one HCP instruction, nine (8%) required a second HCP instruction, and one patient (<1%) required a third HCP instruction before demonstrating correct inhaler technique. After reading the PIL, the most common critical errors for the ELLIPTA inhaler were exhaling directly into the mouthpiece (three critical errors), and intentionally shaking the inhaler after dose preparation (two critical errors). For BREEZHALER, the most common critical errors were that the capsule did not whirr (22 critical errors), failing to pierce the capsule and failing to release the piercing buttons (11 critical errors), and failing to remove the capsule from the blister pack (four critical errors). The most common overall errors for the ELLIPTA inhaler were no exhalation before an inhalation (20 errors), and for BREEZHALER failure to repeat inhalation when powder remained in the capsule (20 errors), and no exhalation before an inhalation (19 errors). Further types of critical and overall errors made by patients at each attempt to use the ELLIPTA and BREEZHALER inhalers are shown in Tables 2 and 3, respectively.

Time to correct inhaler use

The median amount of time taken to demonstrate correct inhaler use with the ELLIPTA inhaler after reading the PIL (T1) was 1.0 minute (IQR, 0.0–2.0) versus 2.0 minutes (IQR, 2.0–4.0) for BREEZHALER. The median time taken to demonstrate correct inhaler use from when the HCP began to give the first instruction (T2) was 0 minutes (IQR, 0.00–0.00) for the ELLIPTA inhaler, and 0 minutes (IQR, 0.00–2.00) for BREEZHALER. The median amount of time taken to demonstrate correct inhaler use (T1+T2) was 1.0 minute (IQR, 0.0–1.0) for the ELLIPTA inhaler, and 2.0 minutes (IQR, 2.0–4.0) for BREEZHALER. Specific results for T1 and T2 are reported in Supplementary Table S1.

Inhaler ease-of-use

On the ease-of-use questionnaire, 64 (56%) patients rated the ELLIPTA inhaler as ‘very easy’ to use versus 18 (16%) for BREEZHALER; 107 (94%) patients rated the ELLIPTA
inhaler as ‘easy or very easy’ to use compared with 59 (52%) for BREEZHALER.

Significantly more patients rated the ELLIPTA inhaler as ‘easy’ compared with the BREEZHALER; this was consistent across various attributes of the inhalers relevant to learning the correct inhaler use technique (Table 4).
Table 4

Patient ratings of the ease-of-use of the ELLIPTA inhaler and BREEZHALER.

<table>
<thead>
<tr>
<th></th>
<th>ELLIPTA (N = 114)</th>
<th>BREEZHALER (N = 114)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall ease-of-use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easy</td>
<td>107 (94)</td>
<td>59 (52)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Difficult</td>
<td>7 (6)</td>
<td>55 (48)</td>
<td></td>
</tr>
<tr>
<td>Seeing how many doses were left in the inhaler, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easy</td>
<td>112 (98)</td>
<td>82 (72)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Difficult</td>
<td>2 (2)</td>
<td>32 (28)</td>
<td></td>
</tr>
<tr>
<td>Ease of learning how to use the inhaler, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easy</td>
<td>110 (96)</td>
<td>69 (61)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Difficult</td>
<td>4 (4)</td>
<td>45 (39)</td>
<td></td>
</tr>
<tr>
<td>Ease of handling the inhaler, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easy</td>
<td>109 (96)</td>
<td>68 (60)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Difficult</td>
<td>5 (4)</td>
<td>46 (40)</td>
<td></td>
</tr>
<tr>
<td>Ease of preparing the inhaler for use, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easy</td>
<td>112 (98)</td>
<td>64 (56)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Difficult</td>
<td>2 (2)</td>
<td>50 (44)</td>
<td></td>
</tr>
<tr>
<td>Ease of holding the inhaler while using it, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easy</td>
<td>103 (90)</td>
<td>84 (74)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Difficult</td>
<td>11 (10)</td>
<td>30 (26)</td>
<td></td>
</tr>
</tbody>
</table>

‘Very Easy’ or ‘Easy’ responses were grouped as ‘Easy’ and ‘Neutral’, ‘Difficult’ or ‘Very Difficult’ were grouped as ‘Difficult’. The p-value was calculated using McNemar’s test.
Willingness to continue use and inhaler preference

On a visual analogue scale of 0 (not willing) to 100 (definitely willing), patients were more willing to continue using the ELLIPTA inhaler than BREEZHALER (mean [SD] 79.9 [24.3] and 52.3 [30.9], respectively; mean difference: 27.6, 95% CI: 21.3–34.0; p < 0.001). Patient preferences for either inhaler based on various attributes are presented in Fig. 3. Overall, 85 (75%) patients preferred the ELLIPTA inhaler, 19 (17%) preferred BREEZHALER, and 10 (9%) had no preference (p < 0.001). Across most attributes, including the number of steps needed to take the medication, the amount of time needed to take the medication, the ease-of-use of the inhaler, and the ease of opening the inhaler, more patients preferred the ELLIPTA inhaler than the BREEZHALER (p < 0.001). However, there were no significant differences between patient preferences regarding the size of the device and the comfort of the mouthpiece (p = 0.053, p = 0.250, respectively). Further details are presented in Supplementary Table S2.
Fig. 3. Patient inhaler preference.

Details of the number of patients expressing ‘no preference’ for each attribute are presented in Supplementary Table 2.

*Indicates statistically significant differences in patient preference (p < 0.001).
There were no adverse events reported during this study.

Discussion

This study assessed how easy it was for patients with asthma who were naïve to ELLIPTA and BREEZHALER DPIs to achieve good inhaler technique after reading the PIL and after receiving additional HCP instructions if required. The proportion of patients who made ≥1 critical error or ≥1 overall error was significantly lower with the ELLIPTA inhaler than with BREEZHALER. Furthermore, patients found it easier to use the ELLIPTA inhaler across all criteria assessed, were more willing to continue using the ELLIPTA inhaler, and more patients preferred the ELLIPTA inhaler compared with BREEZHALER over most inhaler attributes assessed.

These results demonstrate fewer critical and overall errors were made with the ELLIPTA inhaler, and suggest that most patients found it easier to use than BREEZHALER; this may be due to factors such as having fewer steps to demonstrate correct inhaler technique and a more comprehensive PIL [3, 7]. These factors may also be pertinent in the consideration of some critical errors, such as whether the sound of the inhaler capsule whirring could be heard, as this may not be easy to distinguish if the patient was not aware of its importance in correct BREEZHALER use. Features of an inhaler considered most important to patients include overall ease-of-use, ease of reading the dose counter, and the ease of learning correct inhaler use [8, 9]. In our study, a greater proportion of patients rated the ELLIPTA inhaler as ‘easy’ compared with BREEZHALER for all three of these features. Previous studies in patients with asthma or COPD have also shown that patients find the ELLIPTA inhaler easier to use than other inhalers [4, 10]. Such factors likely contributed to patients generally preferring the ELLIPTA inhaler over BREEZHALER. Preference for an inhaler device may be associated with increased patient satisfaction and improved adherence to the
treatment regimen [11]; this is likely to have a positive effect on asthma management outcomes [12].

In the current study, however, a minority of patients did make errors (critical and overall) when using the ELLIPTA inhaler after reading the PIL; a finding consistent with a similar study comparing ELLIPTA and BREEZHALER in patients with COPD [4]. The reduction, and eventual elimination of critical errors after HCP instruction confirm the value of face-to-face instruction, particularly a practical demonstration of correct inhaler use, with a trained professional when using a new device. This is additionally supported by the significant associations between a lack of inhaler technique review and making ≥1 critical error [13], and between a lack of instruction from HCPs and inhaler misuse [14-16]. Given that inhaler misuse frequency can range from 14% to 90%, and could reduce lung deposition of drugs from 20% to 7% [17], the GINA recommendations for patients with asthma emphasize the importance of ensuring correct inhaler technique by patients through practical demonstration and regular review at routine check-ups. However, this is often not done to an adequate standard in clinical practice due to tight time constraints on HCP schedules [18].

This is the first clinical study to compare the ELLIPTA and BREEZHALER inhalers in patients with asthma. A strength of the study design was that while all patients included were receiving treatment for asthma, all were naïve to both inhalers used, which improved the validity of the results. The crossover design and use of two preference questionnaires also reduced the likelihood of bias and meant that each patient acted as their own control, supporting the strength of the study design. Rates were similar for errors common to both devices, such as no exhalation before an inhalation (20 vs 19 errors for the ELLIPTA inhaler vs BREEZHALER), or exhalation directly into mouthpiece (3 vs 2 errors for the ELLIPTA inhaler vs BREEZHALER), further highlight the validity of the results. Finally, all center staff were trained in the assessment of critical and overall errors in inhaler technique, and clear criteria for errors were outlined prior to the study. This reduced the impact of subjectivity on the results and made the study more reproducible.
There were also limitations to the study design. While a single-visit design was more convenient for patients, the validity of the results might have been further strengthened by including a follow-up period to allow patients more time with the inhalers while unsupervised, and in a more realistic setting. This would better reflect the true experiences of the large proportion of patients who do not have their inhaler technique reviewed and rely on reading the PIL to learn and maintain correct inhaler technique when collecting a new inhaler from their pharmacy [19]. Similarly, patients tried both inhalers at the same time, with up to a 30-minute break in between, rather than having an extended period to try each inhaler separately and develop a more informed opinion of the inhalers. All patients were naïve to the study inhalers, however information regarding previous experience using other inhalers was not assessed. Patients who had previously used inhalers similar to one of the two inhalers assessed in this study may have been more confident with its use. Finally, whilst there was a trend suggesting that correctly using the ELLIPTA inhaler took less time than the BREEZHALER, this was not formally tested for.

**Conclusions**

After reading the PIL, fewer patients with asthma made critical and overall errors with the ELLIPTA inhaler compared with BREEZHALER. Patients found the ELLIPTA inhaler easier to use than BREEZHALER for most factors that were considered. Similarly, the ELLIPTA inhaler was preferred by most patients, and more were willing to continue using the ELLIPTA inhaler than BREEZHALER.

**Author contributions**

JvdP contributed to the conception and/or design of the study.

DS contributed to the conception and/or design of the study and the acquisition of data.

SR contributed to the conception and/or design of the study data analysis and interpretation.
MP contributed to data analysis and interpretation.

MV contributed to data analysis and interpretation.

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Competing interests
JvdP has no conflicts to report.

DS is an employee of and holds shares in GSK

SR is an employee of GSK

MP is an employee of and holds shares in GSK

MV is an employee of and holds shares in GSK

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References


Highlights

- We assessed errors by asthma patients using placebo ELLIPTA or BREEZHALER inhalers
- Our crossover study included adults naive to the tested inhalers
- Inhaler use was assessed after patients read the patient information leaflet (PIL)
- Fewer patients made ≥1 overall/critical error with ELLIPTA vs BREEZHALER post PIL
- Fewer patients required further instruction post PIL with ELLIPTA vs BREEZHALER
Competing interests

Job van der Palen has no conflicts to report.

David Slade is an employee of and holds shares in GSK.

Sunita Rehal is an employee of GSK.

Maximilian Plank is an employee of and holds shares in GSK.

Manish Verma is an employee of and holds shares in GSK.