Supplementary Data

Additional Methods

Inclusion Criteria

Additional inclusion criteria included a post-albuterol sulfate (salbutamol sulphate) forced expiratory volume in 1 second (FEV_1)/forced vital capacity ratio of < 0.70 and FEV_1 of ≤ 70% predicted, both obtained within the 2 years prior to randomization; receipt of maintenance therapy for COPD for ≥ 4 weeks prior to randomization; and the ability to remain on prescribed maintenance treatment for the duration of the study.

Patient checklists

Patient checklists were developed through review of the IFU in the approved prescribing information for each inhaler and of the available literature, with further review of the checklists by external inhaler experts.(1) The correct use checklist for each inhaler comprised both critical and overall errors. Critical errors, defined as errors leading to no or significantly reduced medication being inhaled,(2) were recorded; examples included, but were not limited to, 'participant does not shake the inhaler after the click is heard upon opening cover' for ELLIPTA, 'participant did not tilt or shake the device after dose preparation' for DISKUS, and 'participant placed the capsule in the center chamber of the inhaler' for HandiHaler. All other errors were considered overall errors. Correct use was assessed twice for each inhaler regimen (ELLIPTA or DISKUS plus HandiHaler), once at baseline (Day 1 for Period 1; Day 28 for Period 2) and once on returning to the clinic after 28 days of use in each of the 2 treatment periods (Day 28 for Period 1; Day 56 for Period 2).

Exploratory Endpoints and Safety

Exploratory endpoints in this study that are not described in the main text were: 'comparison of participants demonstrating correct inhaler use after reading the instructions for use (IFU) at the start of each treatment period', 'comparison of correct inhaler use as defined by the

percentage of patients with zero errors after 28 days of use, including the number of prescribed maintenance inhalers as a covariate', and 'inhaler preference based on ease of use, dosing regimen, and number of steps required to take the medication'.

In safety assessments, serious adverse events (SAEs) were defined as any AE that led to death; was life threatening or required hospitalization or prolongation of existing hospitalization; or which led to persistent disability or incapacity.

Statistical Analyses and Study Estimands

The error rates for DISKUS and HandiHaler were calculated using 10,000 simulations, in which a total of 216 participants (54 participants per randomized treatment/questionnaire sequence) was estimated to provide ≥ 90% power to show a statistically significant difference at the 5% level between the overall error rate with ELLIPTA versus DISKUS plus HandiHaler.

An estimand was employed in this study, referred to as the primary estimand. Estimands allow the precise predefinition of questions of interest with regards to the population and endpoint involved, and the impact of intercurrent events (events occurring after treatment initiation that either preclude observation of an endpoint or affect its interpretation) occurring post-randomization.(3) Possible intercurrent events were study withdrawal; a change in regular maintenance treatment to one delivered via ELLIPTA, DISKUS or HandiHaler; and failure to bring an inhaler to a study visit. The primary hypothetical estimand estimated the treatment effect in participants of the ITT population who completed assessment of both inhaler regimens with no intercurrent events.

Statistical analysis of the primary endpoint (comparison of correct inhaler use after 28 days) used exact conditional regression; participants were included as fixed strata, treatment option was included in the exact statement, and period was included as a fixed effect. Sensitivity analysis of the primary endpoint was performed on discordant cases (participants

with correct use of 1 inhaler regimen and errors with the other) using the CMH test, a stratified approximation of the Mainland–Gart test that accounts for period effects.

Exploratory Endpoint Results

Participants Demonstrating Correct Use After Reading the IFU on Day 1

After reading the IFU on Day 1, 208 participants (96%) demonstrated correct use of ELLIPTA compared with 170 participants (78%) using DISKUS plus HandiHaler. Of the participants making errors with 1 regimen but not the other, 40 (95%) made at least 1 error with DISKUS plus HandiHaler and 0 errors with ELLIPTA. The odds of demonstrating correct use with ELLIPTA were 13.13 times higher (95% CI: 5.43–∞) than the odds of making 0 critical errors on DISKUS plus HandiHaler ($p < 0.001$).

Correct Use After 28 Days of Use, Including the Number of Prescribed Maintenance Inhalers as a Covariate

There was no evidence of a potential interaction between the percentage of participants demonstrating correct use with an inhaler and the number of prescribed maintenance inhalers ($p = 1.0$). After 28 days of use, 96% of participants demonstrated correct use with the ELLIPTA inhaler versus 87% of participants with DISKUS plus HandiHaler, when including the number of prescribed maintenance inhalers as a covariate.

Table S1. Error Rates used in Sample Size Calculations to Achieve ≥ 90% Power to Show a Statistically Significant Difference

ELLIPTA error rate[a]	**DISKUS plus HandiHaler error rate**[b]
33%	≥ 50%
30%	≥ 47%
20%	≥ 35%
10%	≥ 23%
5%	≥ 15%

[a]Based on the results of van der Palen et al (2016)(1)

[b]Calculated from 10,000 simulations using conditional logistic regression, to achieve ≥ 90% power to show a statistically significant difference

References

1. van der Palen J, Thomas M, Chrystyn H, et al. A randomised open-label cross-over study of inhaler errors, preference and time to achieve correct inhaler use in patients with COPD or asthma: comparison of ELLIPTA with other inhaler devices. NPJ primary care respiratory medicine. 2016;26:16079. Epub 2016/11/25. doi: 10.1038/npjpcrm.2016.79. PubMed PMID: 27883002.

2. Usmani OS, Lavorini F, Marshall J, et al. Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. Respiratory research. 2018;19(1):10. Epub 2018/01/18. doi: 10.1186/s12931-017-0710-y. PubMed PMID: 29338792; PubMed Central PMCID: PMCPMC5771074.

3. Leuchs AK, Brandt A, Zinserling J, et al. Disentangling estimands and the intention-to-treat principle. Pharmaceutical statistics. 2017;16(1):12–9. Epub 2016/12/03. doi: 10.1002/pst.1791. PubMed PMID: 27910217.