Effect of the connected inhaler system on medication adherence in uncontrolled asthmatic patients

ONLINE DATA SUPPLEMENT

Methods

Inclusion criteria

1. Participants aged 18 years or older, at the time of signing the informed consent.

2. Participants with documented physician diagnosis of asthma as their primary respiratory disease.

3. Asthma Control Test (ACT) score <20 at screening visit

4. Non-smokers (never smoked or not smoking for >6 months with <10 pack years history (Pack years = [cigarettes per day smoked/20] x number of years smoked)

5. Male or Female participants:

A female participant was eligible to participate if she was not pregnant, not breastfeeding, and at least one of the following conditions applied:

(i) Not a woman of childbearing potential (WOCBP)

OR

(ii) A WOCBP who agreed to take adequate contraceptive precautions during the treatment period and for at least 5 days after the last dose of study treatment.

6. Capable of giving signed informed consent which included compliance with the requirements and restrictions listed in the consent form and in this protocol.

7. Participant understood and was willing, able, and likely to comply with study procedures and restrictions.

8. Participant must have been able to read in a language supported by the smart phone app in their region.

9. Participant must have been on maintenance therapy (fixed dose combination ICS/LABA) for 3 months, could not have changed dose in the month prior to

screening and was able to change to an equivalent dose of Relvar/Breo for the duration of the study. Other background asthma medication such as anti-leukotrienes and oral corticosteroids were permitted provided the dose had been stable for 1 month prior to screening.

10. Participant must have been able to change to salbutamol/albuterol MDI rescue for the duration of the study and was judged capable of withholding albuterol/salbutamol for at least 6 hours prior to study visits.

11. Participant must have had their own Android or IOS smart phone and a data package suitable for the installation and running of the App and sending and receiving data. Data used by the CIS is approximately 1MB per month as a maximum; this is less data than a 1-minute video streamed from YouTube (2MB).

12. Participants must have been willing and able to download the app on to their personal smart phone and keep it turned on for the duration of the study. This also required Bluetooth to be turned on for the duration of the study. Participants also had to turn on mobile data for the app for the duration of study (unless travelling and when extra data roaming costs could be incurred).

Inclusion criteria for randomization

1. Asthma Control Test (ACT) score <20 at randomization visit (V2, 3, or 4)

Exclusion criteria

1. Participants with known or suspected alcohol or drug abuse which in the opinion of the investigator could interfere with the participant's proper completion of the protocol requirements.

2. History of life-threatening asthma, defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures within the last 6 months

3. A lower respiratory tract infection within 7 days of the screening visit.

4. Concurrent diagnosis of COPD or other respiratory disorders including active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases.

5. History of hypersensitivity/intolerance to any components of the study inhalers (e.g., lactose, magnesium stearate). In addition, participants with a history of severe milk protein allergy that, in the opinion of the study physician, contraindicated participation were also excluded.

6. Historical or current evidence of clinically significant or rapidly progressing or unstable cardiovascular, neurological, cardiovascular, neurological, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or haematological abnormalities that were uncontrolled. Significant was defined as any disease that, in the opinion of the investigator, would have put the safety of the participant at risk through participation, or which would have affected the analysis if the disease/condition exacerbated during the study.

7. Patients who had ever received treatment with biological based therapy (e.g. omalizumab, mepolizumab) for asthma.

8. Participants who had received an investigational drug and/or medical device within 30 days of entry into the study (screening), or within five drug half-lives of the investigational drug, whichever was longer.

9. A participant was not eligible for this study if he/she was an immediate family member of the participating investigator, sub-investigator, study coordinator, employee of the participating investigator, or any family member of a Propeller Health employee.

Study design

Screening and the start of run-in could occur at the same visit or were required to be within 7 days of each other. The study used a flexible run-in period which could last for 1, 2 or 3 months (1 month was equivalent to 28 days). At the end of each month, ACT was re-assessed at the clinical centre. If at the first monthly visit of the flexible run-in the participant's ACT was <20 (uncontrolled) then the participant was randomised to study treatment and subsequent run-in visits were not required. Participants with an ACT of ≥20 after month 1 or 2 of the run-in period could repeat the 1-month run-in. Participants who had an ACT ≥20 at all 3 visits during the flexible run-in were not randomised and were classified as a run-in failure.

All participants received once daily fluticasone furoate/vilanterol ELLIPTA, either at their already prescribed dose or at a dose equivalent to their current ICS/LABA maintenance therapy if switched onto fluticasone furoate/vilanterol ELLIPTA. Salbutamol MDI rescue medication was prescribed to participants to use as needed throughout the study for relief of asthma symptoms as per usual practice.

Participants were assigned to one of five CIS study arms:

1. Data on Maintenance use supplied to Participant (app) and HCP (dashboard)
2. Data on Maintenance use supplied to Participant (app)
3. Data on Maintenance and Rescue use supplied to Participant (app) and HCP (dashboard)
4. Data on Maintenance and Rescue use supplied to Participant (app)
5. No data supplied to Participant or HCP

Following randomization, participants in Arms 1, 2, 3 and 4 received training on how to download and use the smart phone app, including how to connect and register the sensors via Bluetooth to their smart phone and to the app. Participants in Arm 5 who

received no data were provided with a home hub so that their data could be uploaded during the study; neither they or their HCP could see this data.

For Arms 1 and 3, the HCP reviewed a participant's sensor data with respect to maintenance therapy via the dashboard at least every 4 weeks, or more often as needed. The HCP could, at their own discretion, use the data to discuss adherence with these participants, and if needed, the importance of taking their maintenance medication as prescribed. In reviewing the data, the HCP was instructed to have considered how they would respond if these data were available as part of normal standard of care. For Arm 3 the HCP also reviewed the participant's rescue medication use and again was instructed to consider how they would respond if these data were available as part of normal standard of care.

Both the fluticasone furoate/vilanterol ELLIPTA and salbutamol MDI medication used by all participants included in the study had a sensor fitted that was switched on at the clinic visit. During the run-in period, adherence data capture relied on the manual syncing of inhalers at the site and no feedback information was provided to the participants or HCPs on their adherence to maintenance or rescue medication. By comparison, during randomised treatment, the inhalers were synced daily to the app (study Arms 1 to 4) or to a home hub (study Arm 5) and transferred data were checked weekly to ensure no loss of data.

Study Outcomes

Adherence

Daily adherence was defined as the participant taking one dose of Relvar/Breo ELLIPTA, within a 24-hour period, starting at 12.00am each day of the run-in and treatment period. For the analysis months, the following types of days were recorded:

- D1 = Adherence recorded (as defined above)
- D2 = A device incident (due to a technical malfunction of the device/sensor)
- D3 = Post discontinuation of the maintenance sensor
- D4 = Non-adherent.
- D5 = D1 + D2 + D3 + D4, i.e. The total number of days within the Analysis Month; the total number of days between Beginning Timepoint and Ending Timepoint

For each analysis month, the observed adherence for that month was calculated as:

$$Monthly\ observed\ maintenance\ adherence\ (\%) = \left(\frac{D1}{D5 - D2 - D3}\right) \times 100$$

For further information on the estimand strategy for intercurrent events, please refer to the Statistical Analysis Plan (Section 10.5.3.1.) on ClinicalTrials.gov.

Rescue Free Days

Rescue free days was defined as the participant not taking an actuation of Salbutamol MDI, within a 24-hour period, starting at 12:00am each day of the run-in and treatment period. In the same way to adherence above, an estimand strategy for intercurrent events was implemented for rescue free days with similar definitions for the types of Days. Refer to the Statistical Analysis Plan (Section 10.5.3.2.) on ClinicalTrials.gov for further information.

Asthma Control Test (ACT)

The ACT is a validated, self-administered, 5-item questionnaire which assesses asthma control during the past 4 weeks (1). The total score, calculated as the sum of the scores from all 5 questions, has a total score range of 5 to 25 with higher scores indicating better control. An ACT score of 5 to 19 suggests that the participant's asthma is unlikely to be well controlled; a score of 20 to 25 suggests that the

participant's asthma is likely to be well controlled (2). The minimal clinically important difference (MCID) for the ACT is 3 (3).

Fractional exhaled nitric oxide (FeNO) in breath

FeNO was measured using the NIOX VERO® portable system (Circassia, Oxford, UK). Measurements were obtained in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide (4).

Peak expiratory flow (PEF)

PEF was measured using a Mini Wright Peak Flow Meter provided by GSK. At visits where PEF was measured, participants were asked to withhold salbutamol/albuterol for 6 hours before the visit and ICS/LABA for approximately 24 hours prior to assessment.

Safety

Safety was assessed by incidence of serious adverse events (SAE), adverse events (AEs) leading to withdrawal and adverse drug reactions. Serious exacerbations of asthma were recorded, defined as deterioration of asthma requiring the use/additional use of systemic corticosteroids or antibiotics, an inpatient hospitalisation, or emergency department visit due to asthma that required systemic corticosteroids or antibiotics

Statistical analysis

The fixed sample size calculation was based on the primary endpoint, percentage of ELLIPTA doses taken (daily adherence) between Months 4 and 6 as determined by the maintenance sensor and had approximately 90% power to detect an absolute difference of 15% in the primary comparison with significance declared at the two-

sided 5% level. A conservative SD of 28% was chosen based on the control arm from the Charles et al. paper (27%) (5), and due to the technological uncertainty of variability of this type of data.

It was planned to randomise approximately 432 participants to obtain at least 380 participants (i.e. 76 participants per arm) with available data over the last three months of the treatment period, in anticipation of a 12% drop-out within the first three months. A difference of 15% was selected based on clinical expert opinion, sought during the design of the study, and deemed a clinically meaningful improvement equating to approximately one extra dose per week of a once daily product.

Using the above assumptions, the smallest observed effect predicted to result in a statistically significant difference between study arm groups was 9% (minimum detectable difference).

The intent-to-treat population was used for all primary and secondary analyses, defined as all participants who had been randomised to treatment.

The primary analysis estimated the treatment effect of 6 months use of the ELLIPTA maintenance therapy with CIS when both the participant and the HCP were supplied with data from the maintenance sensor versus no data supplied to the participant and HCP (Arm 1 vs Arm 5) for the percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor. The analysis was conducted using an Analysis of Covariance (ANCOVA) model with randomised treatment (study arm) entered as a five-level categorical predictor and adjusting for baseline adherence, number of run-in visits, country, sex, and age (years). The pre-specified treatment arm comparisons (1 vs 5, 2 vs 5, 3 vs 5 and 4 vs 5) were extracted from the full model. Baseline adherence was the percentage ELLIPTA doses taken (daily adherence) during the

last 28 days of the run-in period prior to randomization. For participants with missing intermittent adherence data, data was imputed as non-adherent i.e. assumed to have not taken their treatment within the 24-hour time period/window, where there was no evidence of a medical device incident having occurred. Participants who prematurely discontinued the study had their post-withdrawal daily adherence data imputed using data from the control arm, based on a de-facto treatment policy estimand which reflects the anticipated behaviour that participants would continue to take an asthma combination therapy without the CIS intervention.

Missing data due to a medical device incident such as device failure, technical failure of the e-sensor, or data transmission failure were assumed to be missing at random (MAR). For each participant the percentage adherence measure was calculated under the assumption that any missing data due to a medical device incident was MAR, from the proportion of the number of days a participant was adherent divided by the number of days data provided within each month of the treatment period.

Due to an oversight at some sites to perform the required manual syncing of inhalers at the end of the run-in period, 101 participants who did not record any actuations of the maintenance inhalers during run-in, suggesting zero adherence, actually represented missing data. For the statistical analyses the baseline data were imputed via the Fully Conditional Specification (FCS) regression method, adjusting for country, age, gender, number of run-in (visits), baseline and all post baseline adherence measurements. This issue did not impact recordings during randomised treatment as the inhalers were automatically synced daily to the app or home hub. Similarly, 102 participants who did not record any actuations of the rescue inhalers during run-in represented missing data due to omittance of syncing the sensors at the randomization visit. The baseline rescue medication data was imputed via the

same method, adjusting for baseline and all post baseline rescue use measurements instead of maintenance adherence.

The adjusted means for each study arm and the estimated difference for the primary study comparison of Arm 1 versus Arm 5 were presented together with a 95% confidence interval for the difference and corresponding p-value. Summary statistics (mean, standard deviation, median, minimum, maximum) of the primary endpoint were provided.

The same analysis method was performed for each of the following secondary endpoints:

- Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 4 and the end of month 6 as determined by the maintenance sensor for
    - Maintenance data only supplied to participants versus no data supplied to the participant (Arm 2 vs Arm 5)
    - Rescue and Maintenance data supplied to participant and HCP versus no data supplied to the participant and HCP (Arm 3 vs Arm 5)
    - Rescue and Maintenance data only supplied to participant versus no data supplied to the participant (Arm 4 vs Arm 5)
- Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 1 and the end of month 3
- Percentage of ELLIPTA doses taken (daily adherence) between the beginning of month 1 and the end of month 6
- Percentage of rescue-free days measured between the beginning of month 4 and the end of month 6 as determined by the rescue sensor records of date, time, and number of inhaler actuations.

For the change from baseline ACT endpoint, the analysis was conducted using mixed model repeated measures (MMRM) adjusted for randomised treatment (study arm), visit, baseline ACT total score, gender, age, country, randomised treatment (study arm)-by-visit interaction, baseline ACT total score-by-visit interaction, and participant fitted as a random factor. The model utilized the restricted maximum likelihood (REML) estimation approach and the default unstructured covariance matrix structure. Whilst missing data were not implicitly imputed in this analysis, there was an underlying assumption that the data were MAR. All non-missing data for a participant was used within the analysis and, via modelling of the within-participant correlation structure, the derived differences were adjusted to take into account missing data.

Responder analyses at month 6 (ACT ≥ 20, increase from baseline ≥ 3, and composite endpoint) were analysed using a logistic regression model adjusted for randomised treatment (study arm), baseline ACT total score, country, gender and age. Only the month 6 (visit 10) data was included in the model. Month 1 (visit 5) data was not implemented as by this timepoint participants may not have reverted to steady medicating behaviour. Participants with missing data or who discontinued study treatment or withdrew from the study before month 6 were imputed as non-responders.

References

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3. Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. J Allergy Clin Immunol 2009;124:719-23.
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Results

Table E1: Summary of observed mean monthly adherence

	Arm 1 Maintenance to participants and HCPs (N=87)	Arm 2 Maintenance to participants (N=88)	Arm 3 Maintenance and rescue to participants and HCPs (N=88)	Arm 4 Maintenance and rescue to participants (N=88)	Arm 5 No feedback (control) (N=86)
Baseline					
n (observed)	63	69	66	65	72
Mean (SD), %	76.5 (24.4)	73.7 (28.6)	69.7 (33.8)	73.1 (27.4)	73.2 (30.2)
Month 1					
n (observed)	86	87	88	88	86
Mean (SD), %	87.9 (15.4)	87.9 (13.3)	83.1 (20.3)	83.2 (22.8)	75.2 (28.9)
n ((CFB)	62	68	66	65	72
Mean CFB (SD), %	11.2 (24.4)	13.8 (28.4)	12.9 (35.3)	10.4 (22.1)	6.8 (26.9)
Month 2					
n (observed)	85	85	86	85	86
Mean (SD), %	86.3 (13.7)	85.0 (18.3)	82.8 (20.1)	80.5 (26.6)	76.0 (25.0)
n (CFB)	61	66	64	62	72
Mean CFB (SD), %	8.9 (24.0)	11.5 (32.1)	13.7 (35.3)	7.5 (23.3)	4.4 (31.2)
Month 3					
n (observed)	84	84	85	81	85
Mean (SD), %	84.2 (16.9)	82.5 (20.4)	80.6 (24.2)	80.3 (26.3)	75.0 (25.7)
n (CFB)	60	65	63	59	72
Mean CFB (SD), %	7.7 (25.6)	8.6 (31.8)	12.4 (36.5)	7.4 (24.5)	1.7 (32.7)
Month 4					
n (observed)	83	84	83	81	85
Mean (SD), %	83.0 (17.4)	81.5 (20.9)	80.9 (23.3)	79.9 (27.8)	74.8 (25.4)

n (CFB)	59	65	61	59	72
Mean CFB (SD), %	5.9 (26.7)	9.5 (31.4)	11.1 (35.1)	8.4 (24.1)	1.7 (34.5)
Month 5					
n (observed)	83	84	84	80	83
Mean (SD), %	82.8 (19.1)	76.7 (27.8)	80.3 (23.1)	80.5 (25.5)	71.5 (30.2)
n (CFB)	59	65	62	59	70
Mean CFB (SD), %	4.8 (28.0)	4.5 (35.1)	11.1 (36.7)	8.7 (28.0)	-0.5 (38.6)
Month 6					
n (observed)	82	83	81	79	83
Mean (SD), %	81.0 (20.2)	75.7 (27.4)	78.2 (23.4)	77.5 (25.9)	67.1 (31.6)
n (CFB)	58	65	59	58	70
Mean CFB (SD), %	5.2 (27.3)	3.8 (37.4)	9.7 (37.2)	6.7 (29.7)	-3.8 (40.7)
Average Month 1-3					
n (observed)	86	87	88	88	86
Mean (SD), %	86.2 (13.1)	85.6 (14.0)	81.7 (20.6)	81.0 (23.9)	75.2 (21.9)
n (CFB)	62	68	66	65	72
Mean CFB (SD), %	9.2 (23.3)	11.6 (28.3)	12.1 (34.7)	8.7 (21.5)	4.3 (27.4)
Average Month 4-6					
n (observed)	83	84	84	81	85
Mean (SD), %	82.2 (16.6)	77.9 (23.5)	79.7 (22.0)	78.7 (26.0)	70.8 (27.3)
n (CFB)	59	65	62	59	72
Mean CFB (SD), %	5.2 (26.0)	5.9 (33.2)	11.0 (35.6)	7.9 (25.8)	-1.2 (36.3)

HCP: healthcare professional; SD: Standard deviation; CFB: Change from Baseline

Table E2: Daily adherence to maintenance therapy during months 4 to 6: difference in Arms 1 to 4 versus Arm 5 - Sensitivity analysis

Month 4 to Month 6	Arm 1 Maintenance to participants and HCPs (N=87)	Arm 2 Maintenance to participants (N=88)	Arm 3 Maintenance and rescue to participants and HCPs (N=88)	Arm 4 Maintenance and rescue to participants (N=88)	Arm 5 No feedback (control) (N=86)
n (observed and imputed)	59	65	62	60	73
LS Mean (SE), %*	81.5 (3.63)	77.7 (3.43)	78.1 (3.54)	79.8 (3.63)	68.8 (3.46)
CIS Arm vs Arm 5					
Difference, %	12.7	8.9	9.3	11.0	
95% CI, %	(5.4, 20.1)	(1.9, 15.9)	(2.1, 16.5)	(3.8, 18.3)	
p-value	<0.001	0.013	0.011	0.003	

*Adjusted for effects due to randomised treatment (study arm), baseline adherence, number of run-in visits, country, sex, and age (years)
n is the number of participants between beginning of month 4 and end of month 6 who have completely observed adherence or partially observed adherence with intermittent missing data imputed and no missing baseline adherence apart from 2 participants; one participant (arm 4) had no observed adherence for this time period and had all of their adherence data imputed; one participant (arm 5) was not provided a sensor during the run-in period and had their baseline adherence imputed as 0%.
CI: Confidence interval; HCP: healthcare professional; LS: Least squares; SE: Standard error

Table E3: Daily adherence to maintenance therapy during months 1 to 3: difference in Arms 1 to 4 versus Arm 5

	Arm 1 Maintenance to participants and HCPs (N=87)	Arm 2 Maintenance to participants (N=88)	Arm 3 Maintenance and rescue to participants and HCPs (N=88)	Arm 4 Maintenance and rescue to participants (N=88)	Arm 5 No feedback (control) (N=86)
Baseline					
n (observed)	63	69	66	65	72
Mean (SD), %	76.5 (24.4)	73.7 (28.6)	69.7 (33.8)	73.1 (27.4)	73.2 (30.2)
Month 1 to Month 3					
n (observed with baseline)	62	68	66	65	72
n (observed and imputed)	86	87	88	88	86
LS Mean (SE), %*	85.7 (2.82)	84.2 (2.66)	82.0 (2.74)	79.2 (2.78)	76.4 (2.82)
CIS Arm vs Arm 5					
Difference, %	9.3	7.7	5.5	2.8	
95% CI, %	(3.2, 15.3)	(1.8, 13.7)	(-0.4, 11.4)	(-3.1, 8.7)	
p-value	0.003	0.011	0.066	0.359	

*Adjusted for effects due to randomised treatment (study arm), baseline adherence, number of run-in visits, country, sex, and age (years)
n (observed with baseline) is the number of participants between beginning of month 1 and end of month 3 who have completely observed adherence or partially observed adherence with intermittent missing data imputed and no missing baseline adherence; n (observed and imputed) additionally includes participants who have missing baseline adherence imputed due to a device transmission failure of human error, or who have no observed adherence for this time period and had all of their adherence data imputed.
CI: Confidence interval; HCP: healthcare professional; LS: Least squares; SE: Standard error

Table E4: Summary of HCP actions following data feedback (study Arms 1 and 3) during 6-month treatment period

Actions taken post review of HCP Dashboard*	Arm 1 Maintenance to participants and HCPs (N=87)	Arm 3 Maintenance and rescue to participants and HCPs (N=88)
Feedback		
Maintenance to HCP	X	X
Maintenance to participant	X	X
Rescue to HCP		X
Rescue to participant		X
n	85	86
No action taken†	**33 (39%)**	**28 (33%)**
Action: phone call, e mail, text†	**52 (61%)**	**58 (67%)**
Discuss adherence	38 (45%)	43 (50%)
Discuss rescue medication	10 (12%)	31 (36%)
Other	20 (24%)	27 (31%)
Action: bring participant in for a visit‡	**10 (12%)**	**20 (23%)**
Discuss adherence	4 (5%)	8 (9%)
Discuss rescue medication	2 (2%)	10 (12%)
Other	5 (6%)	12 (14%)

*More than one action could be performed per participant; †Counts were calculated post-hoc; ‡Participants called in for an unscheduled clinic visit were a subset of participants who were contacted by the HCP via phone call, e-mail or text, post-review of HCP dashboard
HCP: healthcare professional

Table E5; Summary of observed mean monthly rescue-free days

	Arm 1 Maintenance to participants and HCPs (N=87)	Arm 2 Maintenance to participants (N=88)	Arm 3 Maintenance and rescue to participants and HCPs (N=88)	Arm 4 Maintenance and rescue to participants (N=88)	Arm 5 No feedback (control) (N=86)
Baseline*					
n (observed)	61	68	63	69	73
Mean (SD), %	70.1 (28.5)	75.7 (26.1)	66.7 (32.9)	70.8 (31.1)	74.5 (27.2)
Month 1					
n (observed)	87	88	88	88	86
Mean (SD), %	66.6 (30.8)	70.0 (30.9)	71.3 (30.2)	75.0 (27.6)	76.8 (29.1)
Month 2					
n (observed)	85	87	87	87	86
Mean (SD), %	74.9 (29.6)	77.3 (29.3)	80.3 (24.7)	80.9 (24.6)	80.5 (27.6)
Month 3					
n (observed)	84	84	86	83	85
Mean (SD), %	79.8 (27.0)	81.6 (25.9)	83.1 (24.8)	84.4 (23.7)	79.5 (27.9)
Month 4					
n (observed)	83	84	85	81	85
Mean (SD), %	78.1 (28.5)	84.4 (23.8)	85.5 (22.1)	86.5 (21.3)	80.4 (25.2)
Month 5					
n (observed)	83	84	84	80	83
Mean (SD), %	80.2 (26.5)	84.3 (23.0)	84.4 (21.9)	84.8 (24.4)	80.8 (27.4)
Month 6					
n (observed)	82	83	82	78	83
Mean (SD), %	81.1 (25.7)	83.6 (24.0)	86.0 (21.6)	85.8 (21.3)	80.4 (27.2)

*****Baseline rescue use is calculated using up to the last 28 days of daily adherence data during the run-in period
HCP: healthcare professional; SD: Standard deviation

Table E6: Mean total rescue medication use at baseline and during months 4 to 6

	Arm 1 Maintenance to participants and HCPs (N=87)	Arm 2 Maintenance to participants (N=88)	Arm 3 Maintenance and rescue to participants and HCPs (N=88)	Arm 4 Maintenance and rescue to participants (N=88)	Arm 5 No feedback (control) (N=86)
Baseline*					
n	61	69	63	69	73
Mean (SD)	20.3 (31.9)	20.9 (32.5)	35.5 (54.8)	24.3 (33.1)	19.5 (29.5)
Months 4 to 6 (scaled)†					
n	83	84	85	82	85
Mean (SD)	18.4 (35.9)	13.5 (30.5)	9.8 (18.1)	9.0 (15.1)	18.6 (52.8)

*****Baseline total rescue medication use is calculated using up to the last 28 days of daily rescue medication use data during the run-in period

†These values were scaled from a combined monthly total to a one-month total, for easier comparison with baseline and subsequent months. For participants who completed the study, the combined months total rescue value was calculated by adding the monthly total rescue use values and dividing by the number of months in the period. For participants who did not complete the study, the combined months total rescue values were weighted according to the observed time the participant was in the monthly periods.

HCP: healthcare professional; SD: Standard deviation

Table E7: Mean monthly percentage of rescue-free days at baseline and during months 4 to 6

	Arm 1 Maintenance to participants and HCPs (N=87)	Arm 2 Maintenance to participants (N=88)	Arm 3 Maintenance and rescue to participants and HCPs (N=88)	Arm 4 Maintenance and rescue to participants (N=88)	Arm 5 No feedback (control) (N=86)
Baseline*, observed					
n	61	68	63	69	73
Mean (SD), %	70.1 (28.5)	75.7 (26.1)	66.7 (32.9)	70.8 (31.1)	74.5 (27.2)
Months 4 to 6, observed					
n	83	84	85	81	85
Mean (SD), %	79.8 (25.3)	83.7 (22.5)	85.2 (20.4)	85.9 (21.2)	80.6 (24.3)
Statistical analysis Month 4 to 6					
n (observed with baseline)	58	64	60	62	72
n (observed and imputed)	87	88	88	88	85
LS Mean (SE), %†	81.1 (2.82)	81.2 (2.66)	85.6 (2.76)	83.7 (2.80)	76.4 (2.82)
CIS Arm vs Arm 5					
Difference, %	4.8	4.8	9.2	7.3	
95% CI, %	(-1.2, 10.8)	(-1.0, 10.7)	(3.3, 15.1)	(1.5, 13.2)	
p-value	0.118	0.105	0.002	0.015	

*****Baseline rescue use is calculated using up to the last 28 days of daily rescue use data during the run-in period; †Adjusted for effects due to randomised treatment (study arm), baseline rescue use, number of run-in visits, country, sex, and age (years)
n (observed with baseline) is the number of participants between beginning of month 4 and end of month 6 who have completely observed rescue use data or partially observed with intermittent missing data imputed and no missing baseline rescue data; n (observed and imputed) additionally includes participants who have missing baseline rescue use data imputed due to a device transmission failure of human error, or who have no observed rescue data for this time period and had all of their rescue data imputed.
CI: Confidence interval; HCP: healthcare professional; LS: Least squares; SD: Standard deviation; SE: Standard error

Table E8: Summary of observed mean ACT score

	Arm 1 Maintenance to participants and HCPs (N=87)	Arm 2 Maintenance to participants (N=88)	Arm 3 Maintenance and rescue to participants and HCPs (N=88)	Arm 4 Maintenance and rescue to participants (N=88)	Arm 5 No feedback (control) (N=86)
Baseline					
n (observed)	87	88	88	88	86
Mean (SD), %	16.1 (2.5)	15.9 (2.9)	15.0 (3.1)	16.0 (3.0)	15.7 (2.7)
Month 1					
n (observed)	84	86	86	82	86
Mean (SD), %	17.8 (3.6)	18.6 (3.8)	17.8 (3.4)	18.5 (3.6)	18.3 (3.7)
Mean CFB (SD), %	1.6 (3.4)	2.8 (2.9)	2.7 (3.4)	2.6 (3.1)	2.6 (3.8)
Month 6					
n (observed)	82	82	78	78	82
Mean (SD), %	19.1 (4.0)	20.3 (3.9)	20.2 (3.8)	20.1 (3.7)	19.9 (4.0)
Mean CFB (SD), %	3.0 (4.1)	4.4 (3.9)	4.9 (4.0)	4.1 (3.6)	4.2 (4.1)

HCP: healthcare professional; SD: Standard deviation; CFB: Change from Baseline

Figures legend

Figure E1: Connected inhaler system

HCP: healthcare professional

Figure E2: Participant flow through the study

HCP: healthcare professional

Figure E3: Mean daily adherence over months 1 to 3 and months 4 to 6 (observed data)

Arm 1: Maintenance to participants and HCPs; Arm 2: Maintenance to participants; Arm 3: Maintenance and rescue to participants and HCPs; Arm 4: Maintenance and rescue to participants; Arm 5: No feedback (control)

On the box plot, the box denotes the interquartile range (IQR) with lines for the 25th percentile, median and 75th percentile, the upper and lower whiskers denote 1.5IQR above the 75th percentile and below the 25th percentile respectively. The symbol within the whiskers denotes the mean and the symbols outside the whiskers denotes outliers.

Figure E4: Mean percentage of rescue-free days during treatment over months 1 to 3 and months 4 to 6

Arm 1: Maintenance to participants and HCPs; Arm 2: Maintenance to participants; Arm 3: Maintenance and rescue to participants and HCPs; Arm 4: Maintenance and rescue to participants; Arm 5: No feedback (control)

On the box plot, the box denotes the interquartile range (IQR) with lines for the 25th percentile, median and 75th percentile, the upper and lower whiskers denote 1.5IQR above the 75th percentile and below the 25th percentile respectively. The symbol within the whiskers denotes the mean and the symbols outside the whiskers denotes outliers.

Figure E5: Mean FeNO at screening and during the 6-month study period

Arm 1: Maintenance to participants and HCPs; Arm 2: Maintenance to participants; Arm 3: Maintenance and rescue to participants and HCPs; Arm 4: Maintenance and rescue to participants; Arm 5: No feedback (control)

NB: Study arms were assigned at randomization visit. FeNO: fractional exhaled nitric oxide

Figure E6: Mean PEF at screening and during the 6-month study period

Arm 1: Maintenance to participants and HCPs; Arm 2: Maintenance to participants; Arm 3: Maintenance and rescue to participants and HCPs; Arm 4: Maintenance and rescue to participants; Arm 5: No feedback (control)

NB: Study arms were assigned at randomization visit. PEF: peak expiratory flow

Figure E1: Connected inhaler system

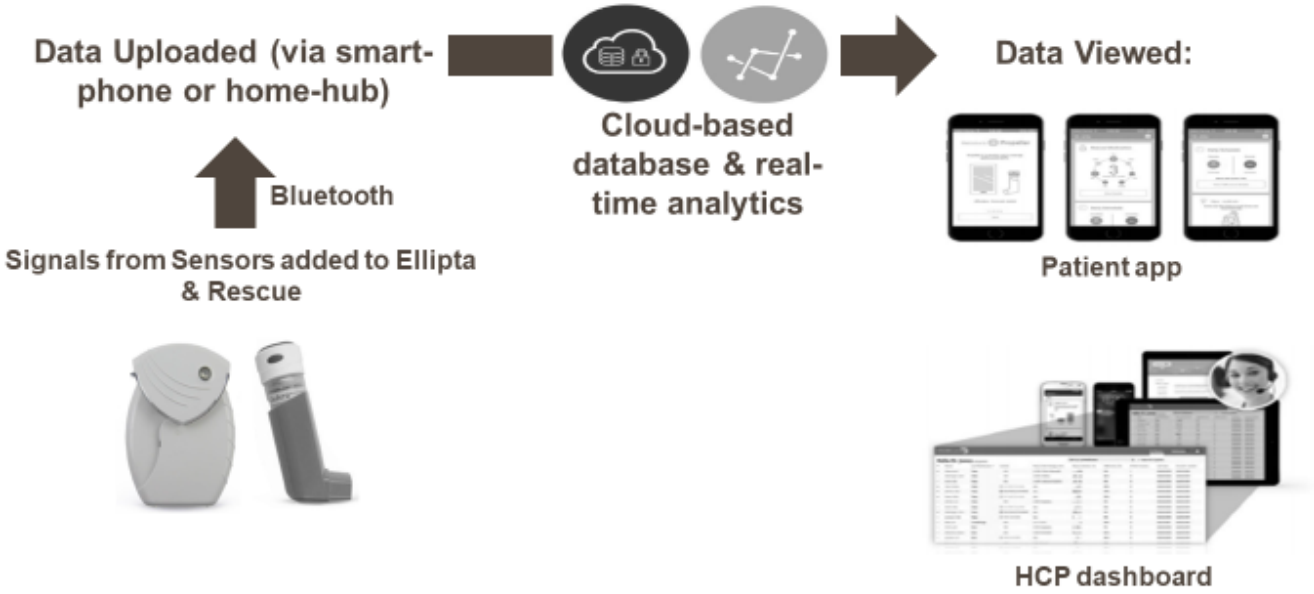

Figure E2: Participant flow through the study

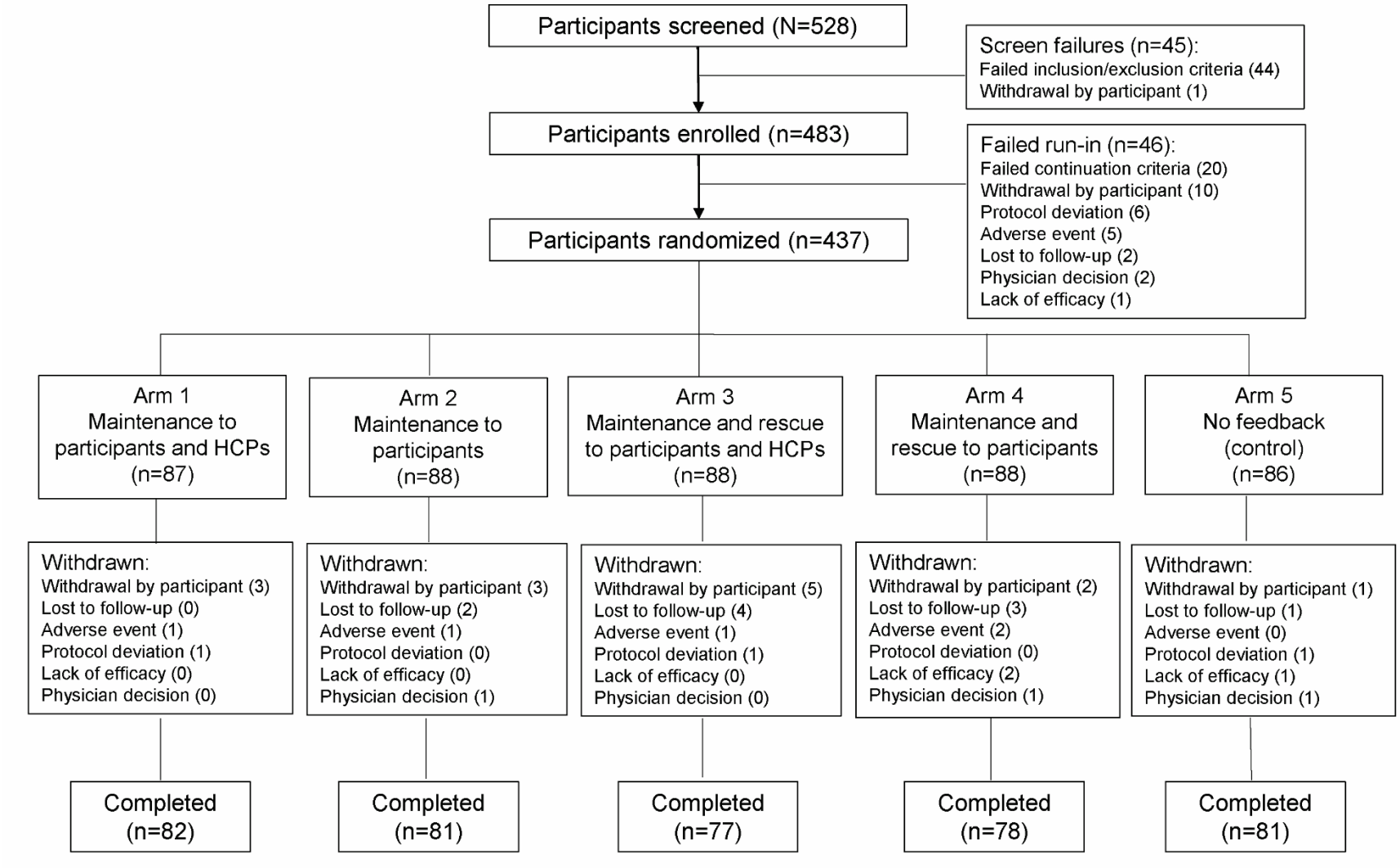

Figure E3: Mean daily adherence over months 1 to 3 and months 4 to 6 (observed data)

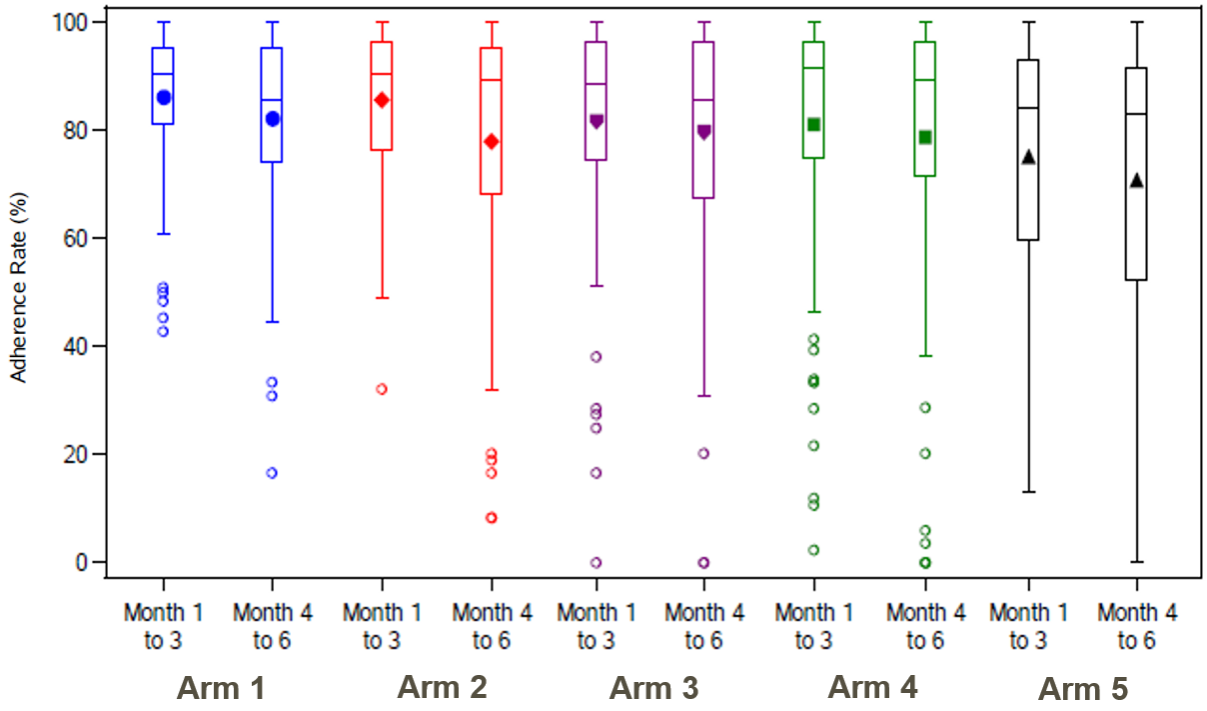

Figure E4: Mean percentage of rescue-free days during treatment over months 1 to 3 and months 4 to 6

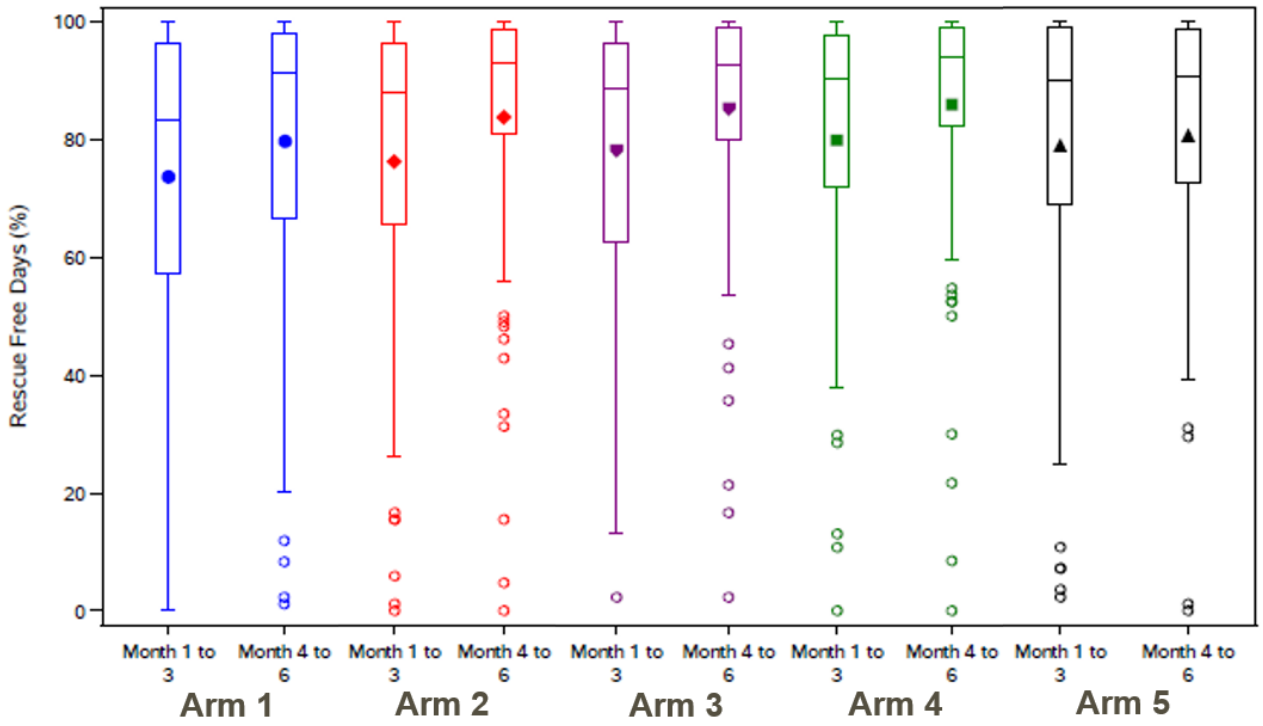

Figure E5: Mean FeNO at screening and during the 6-month study period

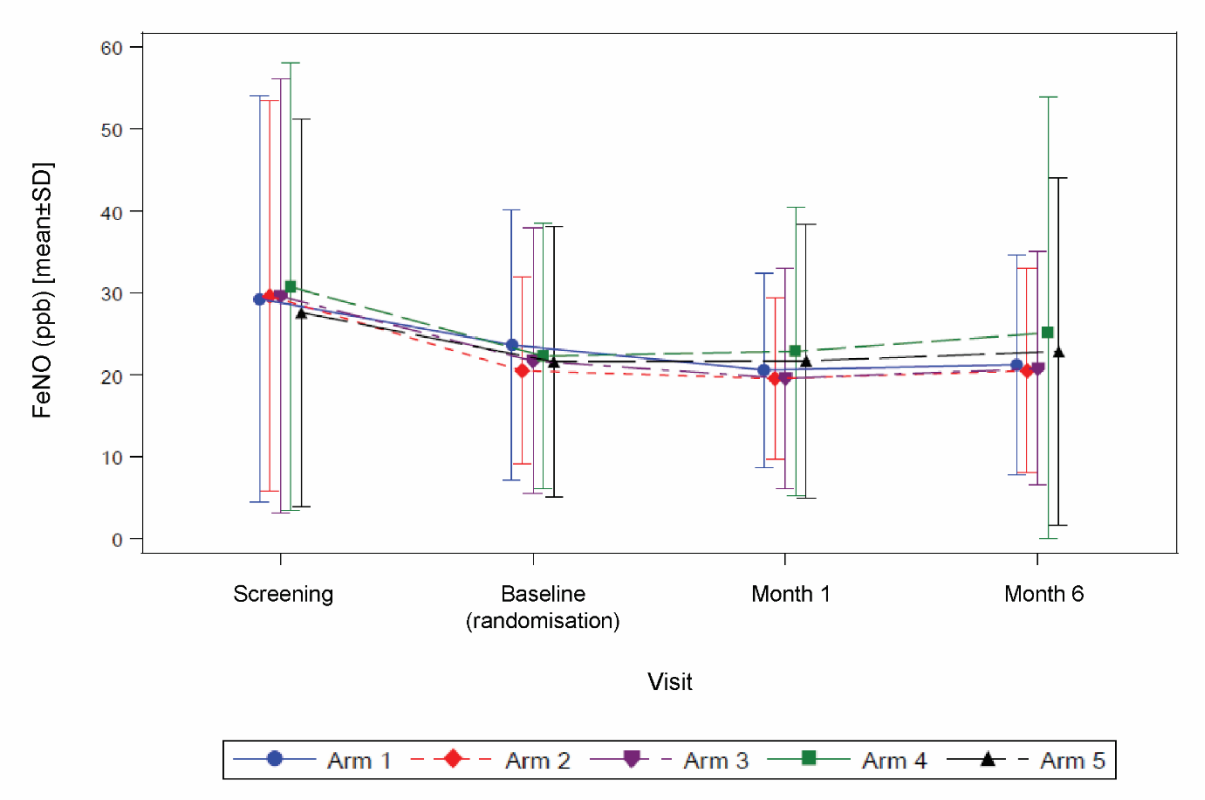

Figure E6: Mean PEF at screening and during the 6-month study period