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CLINICAL TRIAL REPORT

Albuterol Digihaler in COPD Disease Management: A Real-World Study to Assess Digihaler Inhalation Parameters, Thresholds and Their Use to Identify Deterioration in Clinical Practice

Gary T Ferguson[1], Amanda Boe[2], Tanisha D Hill[2], Daisy Yu[2], Meena Krishnamony[1]

[1]Pulmonary Research Institute of Southeast Michigan, Farmington Hills, MI, USA; [2]Teva Branded Pharmaceutical Products R&D, Inc., Parsippany, NJ, USA

Correspondence: Gary T Ferguson, Pulmonary Research institute of Southeast Michigan, Farmington Hills, MI, USA, Email garytferguson@msn.com

Purpose: Despite increasing awareness, chronic obstructive pulmonary disease (COPD) exacerbations are often unrecognized, not reported or not treated. Assisting patients and caregivers to better identify deteriorations in COPD can help improve care. This study was designed to collect usage and inhalation parameters from albuterol Digihaler devices and its associated Digihaler dashboard, to identify potential inhalation parameters and alerts that might predict worsening COPD.

Patients and Methods: Real-time rescue albuterol Digihaler (albuterol sulfate) results for peak inspiratory flow (PIF), rescue inhaler usage and inhalation volume (InV) were assessed in 20 COPD patients over 6 months. Alert thresholds from device measurements were analyzed for 14 days prior to all COPD deteriorations defined by a COPD exacerbation or an acute worsening in COPD assessment test (CAT) score.

Results: Eleven subjects experienced 22 COPD exacerbations, and 16 subjects experienced 40 CAT score worsening over 6 months' time. No demographic or physiologic differences were identified comparing patients with or without exacerbations or CAT score worsening. Falls in PIF and increases in rescue inhaler usage were weak predictors of impending exacerbations, while a higher percentage (36%) of subjects had a fall in InV prior to an exacerbation. No notable changes in inhaler parameters were associated with deteriorating CAT scores, and no changes in lung function were observed over the study. A combination of 3 alert thresholds was present in 59% of patients within the 2 weeks prior to a COPD exacerbation.

Conclusion: Our study suggests that alert thresholds based on Digihaler device-measured physiologic parameters may have value in a predictive model for clinical deterioration in COPD.

Keywords: COPD exacerbation, prediction alerts, peak inspiratory flow, rescue inhaler use, inhalation volume

Introduction

Despite increasing awareness of problems and needs of chronic obstructive pulmonary disease (COPD) patients, COPD remains the 3rd leading cause of death in the world.[1,2] COPD exacerbations are often unrecognized, not reported or not treated, with many COPD patients deprioritizing their worsening symptoms and indications of an impending COPD exacerbation.[3–7] The consequences of COPD exacerbations are well known, with negative impacts on lung function, symptoms, quality of life, future exacerbations and increased mortality.[8–13] Finding a way to assist patients and caregivers to better identify deterioration in their COPD status and improve disease management is essential to overcoming these continued limitations in COPD care.[14] The use of remote digital/electronic inhaler monitoring devices has been suggested as a potential tool to assist in COPD care, with results to date suggesting that tracking inhaler use/abuse with such devices may improve patient outcomes.[15–17]

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The albuterol Digihaler (albuterol sulfate) inhaler is a handheld albuterol dry powder inhalation device that provides real-time feedback to a patient as to whether each inhalation effort with the device was performed properly. The Digihaler device can provide time-stamped recording of inhaler dosing and certain physiologic measurements with each device inhalation, including peak inspiratory flow (PIF) and inhalation volume (InV). Information recorded during inhaler usage can be transmitted to a patient via a smartphone application and to healthcare providers (HCP) via a web-based dashboard displaying inhaler data, allowing for remote monitoring of device usage, technique, PIF and InV for each inhalation effort.[18–22] Information from the Digihaler device and dashboard could be used to identify inhalation changes in COPD patients and, with appropriate monitoring, could provide HCPs and patients with information to help identify earlier disease deterioration and allow for more timely management of COPD exacerbations.

This study was designed to follow a small sample of patients with COPD, collect usage and inhalation parameters from the Digihaler device and then, by monitoring the Digihaler dashboard, identify potential inhalation parameters and thresholds or alerts that might be associated with worsening COPD. This information could then be used to develop studies to determine the clinical validity of using such a tool in the management of patients with COPD in clinical practice.

Materials and Methods

Study Objectives

The primary objective of this study was to identify trends in PIF that may be associated with 1) disease deterioration with a worsening of symptoms and 2) reduced lung function during the study. Disease deterioration was defined as a) any acute COPD exacerbation or b) any acute worsening in COPD Assessment Test (CAT)[23] score. PIF trends were assessed based on baseline PIF measurements and the presence of acute PIF deterioration alerts in the 14 days prior to any identified clinical deterioration event. For lung function evaluation, pre and post bronchodilator spirometry with forced expiratory volume in 1 second (FEV_1) and inspiratory capacity (IC)[24,25] was performed and compared between subjects with and without a PIF alert during the preceding 3-month window. Secondary objectives were to 1) identify trends in short-acting beta-agonist (SABA) use and InV that may be associated with disease deterioration and 2) evaluate if varying alert thresholds for PIF, SABA use and InV may provide alerts associated with any acute disease deterioration.

Study Design

This was a Phase 4, unblinded, open-label, single-center, 6-month pragmatic/exploratory study of 20 patients meeting GOLD diagnostic criteria for COPD requiring intermittent SABA rescue inhaler usage while on routine COPD maintenance therapies as a part of their disease management. Subjects with a current diagnosis of asthma were excluded. The trial was designed by the principal investigator in collaboration with Teva Pharmaceuticals. The study was conducted at the Pulmonary Research Institute of Southeast Michigan between May 10, 2021, and June 21, 2022 (ClinicalTrials.gov protocol - NCT04821869). All subjects were recruited from the known subjects with COPD in the principal investigators clinical practice and research center.

Inclusion/exclusion criteria are listed in Table 1. After obtaining informed consent, a run-in period of 2–3 weeks was performed prior to study enrollment. Subjects were recruited from the principal investigators practice and research center and allowed to participate irrespective of prior hospitalizations or exacerbations and maintenance therapy. All subjects continued on their concurrent medications, other than their rescue albuterol inhalers. Patients were provided an albuterol Digihaler (117 ug), instructed in proper Digihaler usage and the Digihaler devices were linked to the web-based dashboard via an application added to their cell phone. All usage was recorded and electronically transmitted to, monitored at, and downloaded from the dashboard by the research center on at least every other business day (Monday, Wednesday, and Friday). Participants were required to use a minimum of 8 inhalations of their rescue medication and have a stable clinical status during the run-in before being enrolled in the study.

Data collected from the Digihaler device during run-in was used to establish baseline inhalation parameters for each participant. Measured parameters, including Peak Inspiratory Flow (PIF), Rescue Inhaler Usage (SABA Use) and Inhalation Volume (InV), and their baseline values are defined in Table 2. In the event that a study participant did not meet run-in criteria due to inadequate or inconsistent Digihaler device use, additional device training was provided and an additional 2–3 weeks of run-in allowed to establish a baseline. If, at the end of the extended run-in period, patients

Table 1 Study Inclusion and Exclusion Criteria

Inclusion Criteria
Documented history of COPD by ATS/GOLD criteria
Age > 45 years
Patient willing and able to: a. Participate in the study, including all scheduled visits b. The ability to use the albuterol Digihaler, including transfer of Digihaler data via Bluetooth® to a smart device c. Perform all required testing, including spirometry and walk tests d. Complete all home questionnaires and participate in all telephone contacts e. Switch current rescue inhaler/device to albuterol Digihaler
Baseline spirometry consistent with COPD (post bronchodilator FEV_1 < 80% predicted, FEV_1/FVC <70%)
Use of albuterol inhaler as primary device for administration of rescue therapy
Reported use of rescue inhaler at least twice (4 inhalations) a week in the previous 6 months
Access to smartphone with Bluetooth® and cellular/internet access
Exclusion Criteria
Allergy, contraindication or inability to use albuterol sulfate
Frequent use of a nebulizer as rescue therapy (>1 time per day)
Current diagnosis of asthma
Medical condition that could prevent the completion of the research trial
Pregnancy, planning to become pregnant or breast feeding
Failure to use rescue inhaler during Run-in period (minimum of at least 8 rescue inhaler inhalations over the 2 weeks)
Exacerbations that require discontinuation from study (during run-in period)

Abbreviations: ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 2 Digihaler Measurement Definitions, Baseline Values and Low and High Threshold Alert Criteria

Peak Inspiratory Flow (PIF): maximal inspiratory flow was measured by the Digihaler device during each inhalation effort, expressed in Liters/minute (L/min). An average daily PIF was derived for each day of inhaler use from all individual inhalations for that given day	**Baseline PIF** - the mean value of the average daily PIF measurements for a subject collected during run-in
	Low Threshold PIF Alert - a 20% or more decline in average daily PIF compared to a subject's baseline PIF for 2 or more consecutive days
	High Threshold PIF Alert - a 30% or more decline in average daily PIF compared to a subject's baseline PIF for 2 or more consecutive days
Rescue Inhaler Usage (SABA Use): SABA Use - each inhaler use was recorded by the Digihaler device and usage was expressed as the number of inhalations used per day (Inh/day)	**Baseline SABA Use** - the total number of inhalations inhaled during run-in divided by the total number of days during the run-in
	Low Threshold SABA Use Alert - an increase in daily rescue inhalations by 2 puffs/day or more above a subject's baseline daily SABA use for 2 or more consecutive days
	High Threshold SABA Use Alert - an increase in daily rescue inhalations by 4 puffs/day or more above a subject's baseline daily SABA use for 2 or more consecutive days

(*Continued*)

Table 2 (Continued).

Inhalation Volume (InV): the total volume of air inhaled during a rescue inhalation effort measured by the Digihaler device, expressed in Liters (L). An average daily InV was derived for each day of inhaler usage from all individual inhalations for that given day	**Baseline InV** - the mean value of the average daily InV measurements for a subject collected during run-in.
	Low Threshold InV Alert - a 20% or more decline in average daily InV compared to a subject's baseline InV for 2 or more consecutive days
	High Threshold InV Alert - a 30% or more decline in average daily InV compared to a subject's baseline InV for 2 or more consecutive days

Abbreviations: Inh/day, inhalations per day; InV, inhalation volume; L, liters; L/min, liters per minute; SABA, short acting beta agonist; PIF, peak inspiratory flow.

were unable to effectively use the device or the patient continued to have inadequate or inconsistent readings, the patient was discontinued from the study.

Once run-in was completed and enrollment criteria established, participants returned to the study site for baseline testing (Table 3). Patients were re-instructed in proper Digihaler usage and research center monitoring of each subject's rescue albuterol Digihaler usage was initiated using the Digihaler Dashboard. Defined alert criteria for acute changes from baseline in individual subject PIF, SABA use or InV levels (Table 2) were used to assess for the onset of any new low or high threshold alerts throughout the study. The presence of an alert from any of the 3 individual alert parameters (PIF, SABA use or InV) was considered a nonspecific Digihaler alert and any new onset Digihaler alert triggered the research center to contact that patient to assess for any changes in clinical status and/or health care utilization.

Throughout the study, subjects completed and submitted monthly patient reported outcome questionnaires, including CAT,[23] modified medical research council (mMRC)[26] dyspnea score and Anthonisen exacerbation criteria (AEC)[27] plus a health care utilization questionnaire (HCRU) assessing changes in health history/medications, any healthcare contacts/visits and any safety issues. When changes in PROs or HCRU were identified, subjects were contacted to obtain as much detail as possible about the related event. COPD exacerbations identified as a part of HCRU were defined using Global Initiative for Chronic Obstructive Lung Disease (GOLD), recommendations[2] and classified as mild, moderate, or severe. Acute deteriorations by CAT score were defined as an increase in CAT score from baseline of ≥2 points. In the event CAT scores post-event did not return to baseline, a new CAT baseline was established for future events using the average of the next two CAT measurements post-event. Future acute CAT events were then based on the updated baseline.

When a COPD exacerbation or worsening CAT score occurred, Digihaler parameters for the 14 days prior to the start of the event were examined. In addition to raw data, categorical alert thresholds were defined for Digihaler Alert analysis. Low and high alert thresholds are defined in Table 2. In-person visits were conducted at months 3 and 6 (end-of-study), at

Table 3 Baseline Measurements

Direct Measurements	**Derived Baseline Measurements**
Complete history and physical exam	Body mass index (BMI)
Vital signs, height, weight	GOLD stage
Pre and post bronchodilator spirometry with forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) plus inspiratory capacity (IC)	GOLD group
	BODE stage
6-minute walk distance	
Patient reported outcome health questionnaires	
a. COPD Assessment Test (CAT)	
b. Modified Medical Research Council Dyspnea Scale (mMRC)	
c. Anthonisen Exacerbation Criteria (AEC)].	

Abbreviations: AEC, Anthonisen exacerbation criteria; BMI, Body mass index; BODE, Body-mass index, Obstruction, Dyspnea and Exercise scale; CAT, COPD assessment test; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IC, inspiratory capacity; mMRC, modified medical research council dyspnea scale.

which time PROs and HCRU were obtained, prior reports reviewed and vital signs and pre and post bronchodilator spirometry were performed. A final safety telephone call was made 2 weeks after the end-of-study visit.

Statistical Analysis

Given the exploratory nature of the study, all endpoints were analyzed using descriptive statistics. This study did not have pre-specified power calculations or expected predicative probabilities. The number of subjects and duration of study were chosen, without statistical powering, based on empiric projections of likely COPD events and budget limitations.

Ethics

The study was performed in accordance with Good Clinical Practice, including the Declaration of Helsinki, and applicable regulatory requirements.[28] The clinical study protocol and informed consent form were approved by an independent institutional review board (Advarra ICF Pro00050600). All patients gave informed consent before performing any study procedures. Subjects were nominally compensated for study participation.

Results

Baseline demographics for enrolled subjects are shown in Table 4. 27 participants were screened and consented, with 7 participants failing run-in. 4 patients failed due to a COPD exacerbation during run-in, 1 subject did not meet FEV_1 entry

Table 4 Baseline Demographics

	All (20)	**Any Exacerbations (11)**	***P* value**
Age (years)- mean(range)	67 (57–78)	66 (57–74)	0.375
Gender (Female) – n (%)	12(60)	9 (82)	0.028
Post BD FEV_1 – % predicted (SEM)	53 (6)	53 (11)	0.889
Post BD FEV_1 - L (SEM)	1.23 (0.16)	1.16 (0.23)	0.319
BMI	30 (4)	31 (7)	0.617
CAT	18 (3)	18 (4)	0.838
mMRC – n (%)			0.279
1	2 (10)	0 (0)	
2	6 (30)	4 (36)	
3	9 (45)	6 (55)	
4	3 (15)	1 (9)	
GOLD Stage - n (%)			0.343
2	11(55)	5 (45)	
3	9 (45)	6 (55)	
GOLD Group - n (%)			0.089
A	2 (10)	0 (0)	
C	15 (76)	8 (73)	
D	3 (15)	3 (27)	
6 minute Walk - ft (SEM)	922 (127)	916 (161)	0.920

(*Continued*)

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Table 4 (Continued).

	All (20)	Any Exacerbations (11)	*P* value
BODE Quartile – n (%)			0.142
1	3 (15)	0 (0)	
2	8 (40)	6 (55)	
3	7 (35)	5 (45)	
4	2 (10)	0 (0)	

Abbreviations: BD, bronchodilator; BMI, body mass index; BODE, Body-mass index, Obstruction, Dyspnea and Exercise scale; CAT, COPD assessment test; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified medical research council dyspnea scale; n, number; SEM, standard error of the mean.

criteria after run-in and 2 subjects withdrew during run-in unrelated to study participation (Figure 1). All 20 participants enrolled in the study completed the study and were included in all analyses. Thirty percent (6/20) of enrolled study participants required an extra 1–3 weeks of run-in to meet inhaler use requirements and ensure appropriate device technique and reproducible device usage. There were no differences in FEV_1 in those subjects needing/not needing extra run-in training.

PIF Alerts and Exacerbations

Eleven subjects experienced 22 COPD exacerbations during the 6-month study. Comparison of subjects with and without exacerbations revealed no differences in any baseline demographics or need for extra device training during run-in.

Table 5 shows PIF in the 2 weeks prior to an exacerbation compared to baseline. Although a significant PIF decline was identified, the relative change was very small (−4 ± 1 L/min, −3 ± 1%: mean ± SEM). Evaluation of low and high threshold PIF alerts in the 2 weeks prior to an acute exacerbation are shown in Table 6 and Figure 2. Fourteen percent of patients had a low threshold PIF alert and 9% of patients had a high threshold PIF alert proceeding an exacerbation.

PIF Alerts and CAT Scores

Acute worsening in CAT score occurred 40 times in 16 subjects throughout the study. Changes in low and high threshold PIF alerts in the 2 weeks prior to an acute CAT worsening are shown in Table 7. Three (8%) low threshold PIF alerts and no high threshold PIF alerts occurred in the 2 weeks prior to a deterioration in patient CAT score.

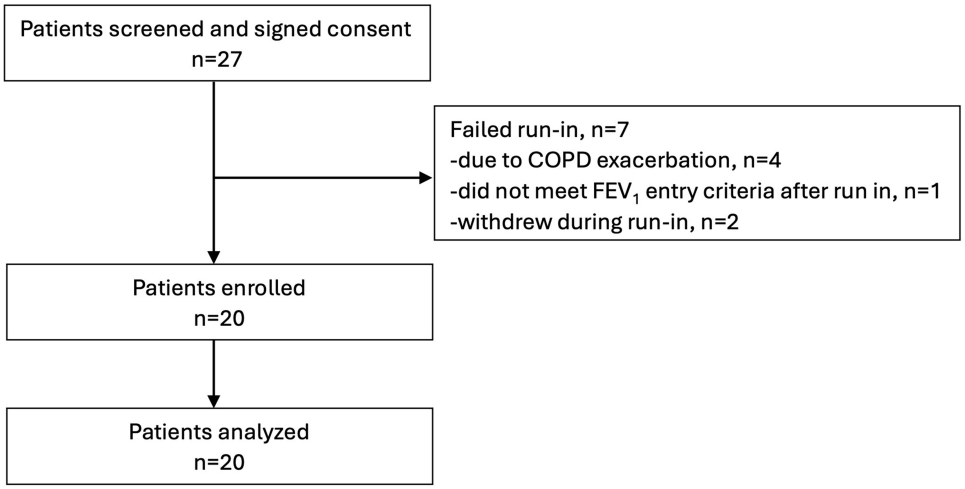

Figure 1 Patient disposition.

Table 5 PIF/InV Values During the 14 days Prior to a COPD Exacerbation vs Baseline

	Patients With COPD Exacerbations (n=11)		Patients Without COPD Exacerbations (n=9)	
	PIF (L/min)	**InV (mL)**	**PIF (L/min)**	**InV (mL)**
Baseline				
Mean	73.58	1514.98	66.19	1336.50
SD	23.18	644.48	18.30	679.77
Median	62.83	1272.22	65.38	1051.60
Min, Max	50.31, 128.58	662.83, 2762.61	38.24, 110.30	662.68, 3463.08
Change from baseline				
Mean	−4.34	−190.80	2.94	−27.68
SD	16.40	501.18	12.30	357.44
SE	1.11	33.87	–	–
Median	−3.60	−162.69	2.97	12.04
Min, Max	−65.08, 47.85	−1890.11, 2149.56	−42.55, 55.70	−1717.08, 2372.67
P value	<0.0001	<0.0001	–	<0.0001
% Change from baseline				
Mean	−2.98%	−4.77%	7.54%	4.39%
SD	20.18%	44.01%	20.49%	24.18%
SE	1.36%	2.97%	–	–
Median	−4.69%	−12.72%	4.45%	1.36%
Min, Max	−50.61%, 74.37%	−68.42%, 300.66%	−39.92%, 107.65%	−57.07%, 111.66%
P value	<0.0001	<0.0001	<0.0001	<0.0001

Abbreviations: COPD, chronic obstructive pulmonary disease; InV, inhalation volume; L/min, liters per minute; max, maximum; mL, milliliters; min, minimum; n, number; PIF, peak inspiratory flow; SD, standard deviation; SE, standard error.

Table 6 Digihaler Alerts Preceding COPD Exacerbations

COPD Exacerbations (n=22)	Digihaler Alert within 14 days Prior to Exacerbation	No Digihaler Alert within 14 days Prior to Exacerbation
High Alert Threshold (any high alert)	6 (27%)	16 (73%)
InV	4 (18%)	18 (82%)
SABA Use	0	22 (100%)
PIF	2 (9%)	20 (91%)

(*Continued*)

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Table 6 (Continued).

COPD Exacerbations (n=22)	Digihaler Alert within 14 days Prior to Exacerbation	No Digihaler Alert within 14 days Prior to Exacerbation
Low Alert Threshold (any low alert)	13 (59%)	9 (41%)
InV	8 (36%)	14 (64%)
SABA Use	2 (9%)	20 (91%)
PIF	3 (14%)	19 (85%)

Abbreviations: COPD, chronic obstructive pulmonary disease; InV, inhaled volume; PIF, peak inspiratory flow; SABA, short acting beta agonist.

Spirometry

FEV_1, force vital capacity (FVC) and IC collected at baseline and months 3 and 6 were evaluated for changes in the 3-month windows preceding an event in subjects with/without exacerbations, with/without worsening CAT score and with/without low and high threshold PIF alerts. FEV_1, FVC and IC changed very little over the course of the study, with no significant spirometry changes found between any of the comparison groups.

SABA Use, InV Alerts and Exacerbations

The average number of extra rescue SABA inhalations used above the daily baseline in the 2-week period prior to a COPD exacerbation were minimal. Table 6 and Figure 2 show extra SABA use above baseline based on low (≥2 extra

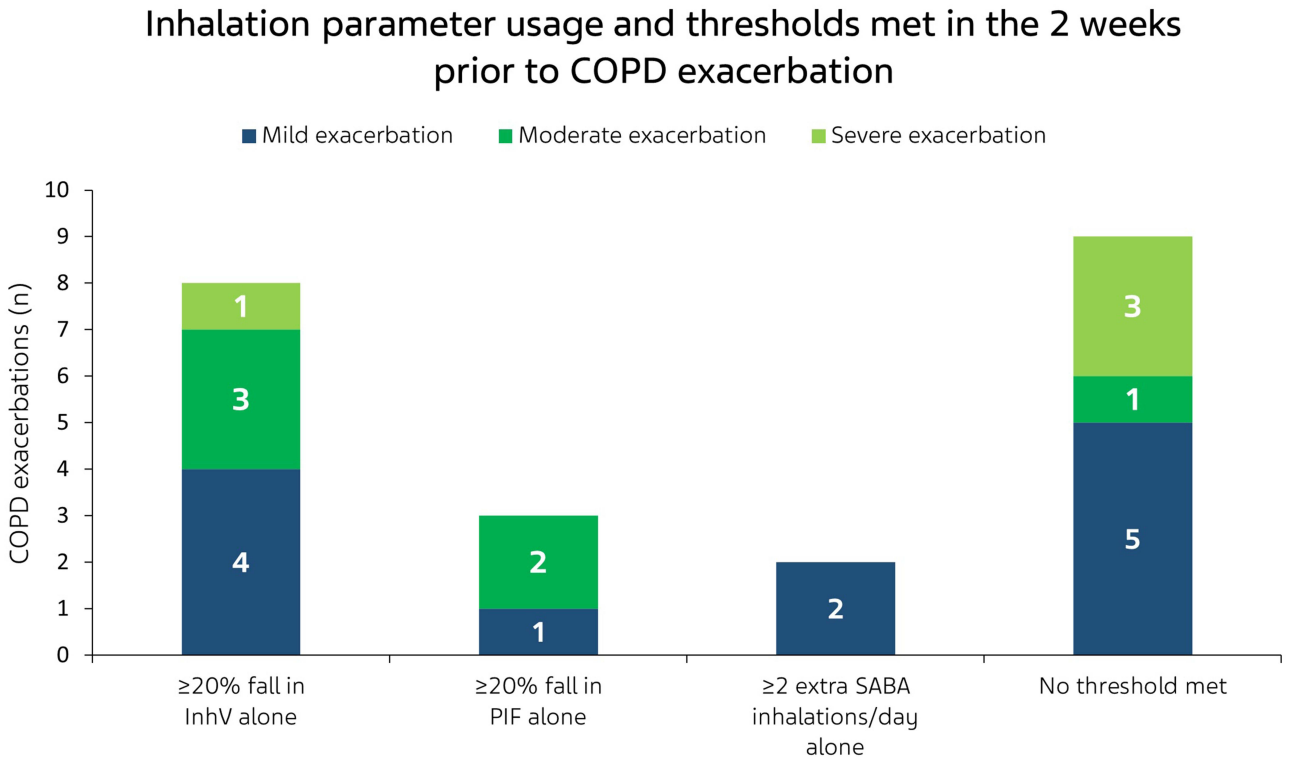

Figure 2 Inhalation parameter usage and thresholds met in the two weeks prior to COPD exacerbation.
Abbreviations: COPD, chronic obstructive pulmonary disease; InhV, inhalation volume; PIF, peak inspiratory flow; SABA, short-acting beta agonist.

Table 7 Digihaler PIF, SABA Use, and InV Threshold Alerts Preceding CAT Events (Increase in CAT ≥2)

CAT Events (n=40)	Digihaler Alert within 14 days Prior to CAT Event	No Digihaler Alert Within 14 Days Prior to CAT Event
High Alert Threshold (any high alert)	4 (10%)	36 (90%)
InV	2 (5%)	38 (95%)
SABA Use	2 (5%)	38 (95%)
PIF	0 (0%)	40 (100%)
Low Alert Threshold (any low alert)	16 (40%)	24 (60%)
InV	8 (20%)	32 (80%)
SABA Use	5 (13%)	35 (87%)
PIF	3 (8%)	37 (92%)

Abbreviations: CAT, COPD assessment test; InV, inhalation volume; PIF, peak inspiratory flow; SABA, short acting beta agonist.

inhalations/day) and high (≥4 extra inhalations/day) threshold alerts. Nine percent of patients had a low threshold SABA Use alert, and no patient had a high threshold SABA Use alert in the 2 weeks preceding an exacerbation.

InV declined significantly compared to baseline in the 2 weeks prior to an exacerbation (Table 5), with the relative fall in InV being modest (−191 ± 34 mL, −5 ± 3% change: mean ± SEM). Low (≥20% decline) and high (≥30% decline) threshold InV alerts in the 2 weeks prior to an acute exacerbation are shown in Table 6 and Figure 2. Thirty-six percent of patients had a low threshold InV alert and 18% of patients had a high threshold InV alert preceding an exacerbation.

SABA Use, InV and CAT Scores

High and low threshold alerts for daily SABA use above baseline and declines in InV in the 2 weeks before an acute change in CAT score is shown in Table 7. The number of SABA Use alerts were low (13% low and 5% high threshold alerts). On the other hand, 20% of clinical deteriorations in CAT score had a low threshold InV alert in the 2 weeks before a CAT event, with 5% having a high threshold InV alert.

Combined PIF, SABA and InV Alerts and Exacerbations

High and low alert thresholds for PIF, SABA Use, and InV prior to an exacerbation are described above, in Table 6 and Figure 2. Combining individual alerts into a composite alert if any one of the 3 individual alerts occurred in the 2 weeks prior to an exacerbation increased the likelihood of an alert occurring prior to an exacerbation. Indeed, 59% of patients with an exacerbation had a low threshold alert and 27% of patients had a high threshold alert in the 2 weeks preceding their exacerbation.

Safety Data

Six serious adverse events (SAEs) occurred during the study, all COPD exacerbations requiring hospitalization, with 4 occurring during the study and 2 occurring during run-in. Two subjects had moderate exacerbations during run-in. During the study, there were a total of 22 COPD exacerbations (12 mild, 6 moderate and 4 severe), none leading to study withdrawal. There were 12 non-COPD adverse events (AEs) and no non-COPD SAEs. None of the non-COPD AEs were related to use of study medication and none led to study withdrawal.

Discussion

This pilot study was designed to evaluate whether real-time digital technology information obtained from the albuterol Digihaler inhaler device and dashboard could help HCPs and patients identify clinical deterioration in COPD patients. We examined whether COPD patients were able to use the Digihaler inhaler device technology as their rescue inhaler and whether specific rescue inhaler usage patterns, changes in inspiratory physiologic parameters and "alerts" from the albuterol Digihaler device preceded acute COPD deteriorations. Our study suggests that patients, including older subjects over the age of 65, are

able to use the Digihaler device and its related technology. During the study run-in, a subset of patients did demonstrate initial variability in device usage and PIF measurements. However, with additional training, all of these subjects were subsequently able to demonstrate consistent device use and appropriate inhalation technique throughout the 6 months of the study. This suggests that with adequate training, inspiratory flows for effective DPI medication delivery and device usage can be met, irrespective of baseline lung function. Indeed, the subset of patients who did not move beyond the study run-in were prevented from continuing due to a lack of rescue inhaler need/use, and not due to inhaler technique issues.

Our study also suggests that alert thresholds based on predefined changes in Digihaler device-measured physiologic parameters may be of value in predicting clinical deterioration in COPD. A 20% decline in InV from baseline was the alert most often associated with a subsequent COPD exacerbation. A decline in InV as the most frequent alert prior to an exacerbation was somewhat surprising. Indeed, our original hypothesis was that a fall in PIF would be the best warning for COPD deterioration. Although alerts from a fall in PIF or increase in daily SABA use prior to a COPD exacerbation did occur in some subjects, these were much less likely to be found than the fall in InV. The fall in InV prior to an exacerbation could be related to reduced inspiratory effort or an inability to fully exhale prior to inhalation due to increasing dyspnea or to other processes, such as unrecognized air trapping and hyperinflation. The mechanism for how/why a fall in InV relates to an impending exacerbation needs to be investigated further.

Our results on SABA use prior to an exacerbation differ from other studies. An increase in rescue SABA use has been suggested as a possible marker associated with COPD exacerbations,[15–17,29–31] offering hope that this simple measure could be used in clinical practice as a tool similar to asthma. However, most of this information comes from by large studies doing post hoc analyses on mean data for large cohorts of COPD patients, with none analyzing individual patients and none of the results obtained prospectively or in real-time.[29,30] It is possible that the lack of SABA use alerts in our study was due to subjects using rescue inhalers other than their study Digihaler device or even using nebulized medications in place of the study inhaler, leading to an undercount of rescue inhaler usage. However, our subjects were queried about rescue medication usage around the time of any exacerbation and patients denied use of alternative rescue therapies. One study of 35 COPD patients over 12 weeks noted a 14% increase (<1 puff/day) in rescue puffs overall prior to an exacerbation.[31] However, if baseline rescue inhaler use doubled, an increased risk of exacerbation was likely. Ultimately, our exploratory findings suggest that digital rescue inhaler usage could be a marker for COPD disease deterioration and support other studies in asthma where inhaler use data has been used to predict impending exacerbations. Alternate thresholds need to be considered, and further investigations made before any clear inferences can be made about patient use of rescue inhalers predicting COPD patient deterioration in clinical practice.

Interestingly, Digihaler alerts (PIF, SABA Use and InV) appeared to be minimally associated with acute clinical changes in COPD based on CAT scores. It is possible that the weak association could be related to a timing issue, with patient perceptions of their symptoms and function initially delayed or ignored by patients, even when prompted by a PRO. In addition, CAT was only measured once a month or following an acute exacerbation in this study, and the 2-week alert window could have passed before a CAT change was identified. Although a Digihaler alert triggered a telephone call to a patient and an acute CAT score was recorded at that time, it still may not have been obtained in a sufficiently timely fashion. It is possible that an alternative health status measurement designed to be used on a daily basis to assess patient status, such as the Evaluating Respiratory Symptoms™ in COPD (E-RS:COPD) questionnaire, might have better detected a relationship between the Digihaler alerts and acute changes in patient quality of life. Whether digital inhaler data may be a more objective marker of COPD disease deterioration compared to more subjective measures requires further investigation.

Finally, the combination of 3 alert measures in our study did result in a greater likelihood of an alert being present prior to a COPD exacerbation as compared to any single measure. It is possible that with additional evaluation and refining of alert threshold levels, a composite alert might be derived for the Digihaler better identifying when a patient has a strong likelihood of disease worsening and COPD exacerbation.

Limitations

Our study was not designed for or intended to statistically evaluate the use the Digihaler for predicting future clinical events in COPD patients. Rather, it was a small, non-powered, exploratory pilot study designed to provide preliminary

information and insights that might serve as the basis for future studies to assess whether the use of rescue albuterol in a digital inhaler device might be used as a predictive tool. With this in mind, we made no attempt to prospectively analyze any Digihaler alerts, with and without subsequent deterioration events, or to determine false positive and negative alert rates, positive and negative predictive values or to perform regression analysis related to specific Digihaler variables. Such statistical analysis is needed, but requires a study with a larger cohort of subjects and a greater number of COPD events to provide meaningful statistical outcomes.

Conclusion

Our study suggests that alert thresholds based on Digihaler device-measured physiologic parameters may have value in a predictive model for clinical deterioration in COPD. These results may hopefully be used to help define future predictive measures and alerts that might be used in a study to achieve the predictive results needed for COPD care. Ultimately, this device could help patients with their self-care and help healthcare providers by providing for early identification and treatment of COPD exacerbations.

Data Sharing Statement

The data sets used and/or analyzed for the study described in this manuscript are available upon reasonable request. Qualified researchers may request access to patient-level data and related study documents including the study protocol and the statistical analysis plan. Patient-level data will be de-identified, and study documents will be redacted to protect the privacy of trial participants and to protect commercially confidential information. Please visit www.clinicalstudydatarequest.com to make your request.

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Author Contributions

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

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Disclosure

GF has served as a consultant for Teva, Boehringer Ingelheim, AstraZeneca, DevPro, Galderma/Syneos/PPD, GlaxoSmithKline, Teva, Verona, Orpheris, AER Therapeutics, Altesa, Syndax. He has served as a speaker for GlaxoSmithKline and has performed research with Teva, AstraZeneca, Chiesi, GlaxoSmithKline, Novartis, Verona. AB, TH, DY are employees of Teva Pharmaceuticals. MK reports no conflicts of interest in this work.

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