CONNected Electronic Inhalers Asthma Control Trial 3 (*CONNECT 3*), a 24-Week Treatment, Multicenter, Open Label, Randomized, Parallel Group Comparison Study of Standard of Care Treatment Versus the Budesonide/Formoterol Digihaler Digital System, to Optimize Outcomes in Adult Patients with Asthma

Published: 01-12-2022
Last updated: 08-04-2024

The primary objective of this study is to demonstrate the effectiveness of the DS compared to the SoC group. The secondary objectives:(#1) is to describe the asthma management actions by HCPs for all patients in both groups. (#2) is to evaluate...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Respiratory disorders NEC
Study type	Interventional

Summary

ID

NL-OMON53851

Source
ToetsingOnline

Brief title
CONNECT 3

Condition

- Respiratory disorders NEC

Synonym
Asthma

Research involving
Human

Sponsors and support

Primary sponsor: PRA Group BV
Source(s) of monetary or material Support: Teva Branded Pharmaceutical Products;R&D;Inc.

Intervention

Keyword: Asthma, Budesonide/Formoterol, Digihaler Digital System

Outcome measures

Primary outcome

The primary endpoint is the proportion of patients for the DS and SoC groups achieving well-controlled asthma as defined by an ACT score of greater than or equal to 20, or a clinically important improvement in asthma control as defined by an increase of at least 3 ACT units from baseline at the end of the 24-week treatment period.

Secondary outcome

(#1)

This secondary endpoint is the frequency of clinically driven assessments and types of interventions done to improve asthma control including:

• number of discussions regarding inhaler technique

• number of discussions regarding adherence

• number of adjustments of therapy including:

- changes to current inhaler therapy (stepping up and stepping down)

- change to different inhaled medication

- additional inhaled medication

- addition of a systemic corticosteroid medication for asthma or another controller, including LAMA or biologics

• frequency of intervention to manage comorbid conditions associated with poor asthma control (gastroesophageal reflux disease, sinusitis, etc.)

(#2)

This secondary endpoint is the change from baseline in adherence to the BF Digihaler DS when prescribed as maintenance treatment, defined as the proportion of actual inhalation doses taken out of the total number of inhalation doses prescribed over the 24-week treatment period.

(#3)

This secondary endpoint is the change from baseline measured by the WPAI questionnaire, completed by patients in both groups, at baseline and at the end of the 24-week treatment period.

(#4)

This secondary endpoint is the assessment of the DS (BF Digihaler, App, DHP [Cloud solution], and HCP-facing dashboard) acceptability and usability, utilizing the SUS completed by the patients in the DS group and the investigational center personnel at the End of treatment visit.

(#5)

This secondary endpoint is the reporting of adverse events related to BF

Digihaler DS at participating investigational centers.

The safety endpoints for this study include the following for all patients in

both groups:

• adverse event data

• adverse device effect data

Study description

Background summary

1. INTRODUCTION AND BACKGROUND INFORMATION
1.1. Introduction
Asthma is a heterogeneous disease usually characterized by chronic airway inflammation and defined by the history of respiratory symptoms that vary over time and in intensity (Global Initiative for Asthma [GINA] 2021). These asthma symptoms may be associated with suboptimal treatment or aging, may lead to chronic changes in airway structure and function, increasing the morbidity and mortality of those affected (Global Initiative for Asthma [GINA] 2021).
GINA includes maintenance and reliever therapy (MART) with low-dose ICS formoterol as the preferred treatment for asthma that remains uncontrolled despite good adherence and inhaler technique, based on evidence of reduced exacerbations compared with the same dose ICS-long acting beta2 agonist (LABA) or higher dose ICS used as maintenance and a SABA as rescue.
Budesonide is a potent synthetic glucocorticosteroid with potent anti inflammatory activity. Inflammation is an important component in the pathophysiology of asthma, and corticosteroids have been shown to inhibit multiple inflammatory cells and mediators involved in the pathophysiology of asthma. Formoterol is a potent, selective LABA producing relaxation of bronchial smooth muscle in patients with reversible airway obstruction. The pharmacologic effects of beta2 adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase that leads to increased levels of cyclic 3*,5* adenosine monophosphate (cyclic AMP), which causes relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.
Teva Branded Pharmaceutical Products R&D, Inc. (Teva) has developed a budesonide/formoterol fumarate dihydrate (BF) multidose dry powder inhaler with an integrated electronic module as a next-generation inhaler solution for

patients with asthma and chronic obstructive pulmonary disease (COPD). The investigational product, BF Digihaler, delivers a dose of BF equivalent to DUORESP SPIROMAX® and adds electronic capabilities ultimately intended to provide patients with feedback to potentially improve inhalation technique, disease understanding, management, and outcomes.
In this study, BF will be delivered via a Digihaler. The system is an inhaler with integrated data logger capable of storing and transmitting timestamped data. The information from the BF Digihaler will be transmitted wirelessly (Bluetooth Low Energy) to the mobile phone App. From the App, with the patient*s informed consent, data may be transmitted to the Digital Health Platform (DHP; Cloud solution) and then to a Healthcare professional (HCP)-facing dashboard. The DHP is used to provide patient-specific data to the patient*s healthcare professional (HCP) via the dashboard, a secure web interface. The following devices will be evaluated in this study:
• Budesonide/formoterol (BF) Digihaler Digital System (DS) with 4 component devices:
- Device 1: BF Digihaler used as both MART
- Device 2: Patient-facing mobile phone application (App)
- Device 3: DHP (Cloud solution)
- Device 4: HCP-facing dashboard
The purpose of the study is to evaluate whether outcomes for patients using the BF Digihaler DS as MART can be optimized better than a Standard of Care (SoC) group who will be treated with their current treatment prescribed by the investigational center based on asthma guidelines and clinician judgement and will not use the DS during the treatment period. The study will also assess adherence patterns to maintenance treatment (BF Digihaler) in the BF Digihaler DS group and the asthma management actions of HCPs using the dashboard as part of the DS and will collect information from patients and investigational center personnel questionnaires on system usability, quality of life, and work productivity.
1.2. Findings from Nonclinical and Clinical Studies
The pharmacology and safety profile of BF Digihaler have been well established. Refer to the DUORESP SPIROMAX summary of product characteristics (SmPC) for relevant BF Digihaler (budesonide and formoterol) inhalation powder nonclinical safety information.
Teva*s BF SPIROMAX has been evaluated in 15 completed clinical studies in over 2141 subjects (720 healthy adult volunteers, 605 asthmatic adolescents and adults, 739 asthmatic adults, and 77 pediatric subjects). The results from these studies evaluating the doses of 160/4.5 mcg and 320/9 mcg are included in the DUORESP SPIROMAX SmPC.
1.3. Known and Potential Benefits and Risks to Patients
The investigational product, BF Digihaler, delivers a dose of BF equivalent to DUORESP SPIROMAX and adds electronic capabilities intended to provide patients with feedback to potentially improve inhalation technique, disease understanding, management, and outcomes. The addition of the integrated electronic module has no impact on the pharmaceutical performance of the BF Digihaler relative to BF SPIROMAX, and it does not affect the user steps

required to take a dose (performance and functional testing on file at Teva). Additional information regarding benefits and risks of BF Digihaler to patients may be found in the Investigator*s Brochure (IB).

Study objective

The primary objective of this study is to demonstrate the effectiveness of the DS compared to the SoC group.
The secondary objectives:
(#1) is to describe the asthma management actions by HCPs for all patients in both groups.
(#2) is to evaluate adherence patterns to maintenance treatment (BF Digihaler) in the DS group.
(#3) is to evaluate work productivity and activity impairment in asthma patients in both groups.
(#4) is to assess the usability and acceptability of the DS by patients in the DS group and the investigational center personnel.
(#5) is to evaluate the safety of BF Digihaler DS.

Study design

3. STUDY DESIGN
3.1. General Study Design and Study Schematic Diagram
This is a 24-week treatment, multicenter, open-label, randomized, parallel group comparison study of SoC treatment versus the BF Digihaler DS, including inhaler, App, DHP (Cloud solution), and HCP-facing dashboard, to optimize outcomes in adult patients with asthma.
The study will consist of a screening/baseline visit (Visit 1), a 24-week, open-label treatment period with Visit 2 at week 12, Visit 3 at week 24, and a follow up telephone call (2 weeks after treatment completion).
Patients with suboptimal asthma control will be enrolled in the study and randomly assigned to 1 of 2 parallel groups (Table 4), stratified by investigational center. The randomization will be done by the IRT system with a randomization blocks assigned to a study site when the site is ready to randomize patients. The IRT system manages this process automatically. The BF Digihaler DS group patients will use the BF Digihaler with the App and DHP (Cloud solution). The SoC group patients will be treated with their current treatment prescribed by the investigational center to the patient based on asthma guidelines and clinician judgement. The SoC group patients will not use the DS during the treatment period. Similar data will be collected regarding outcomes for both groups, which are as follows: ACT, Mini AQLQ and WPAI questionnaire responses, and the frequency of CAEs.
Table 4: Description of Treatment Groups

BF Digihaler DS group Standard of Care group

BF Digihaler* (as MART) + App Current rescue medication, ICS/LABA and any additional controller medication for asthma
DHP (Cloud solution) Not applicable
HCP-facing dashboard Not applicable

App=mobile phone application; BF Digihaler=budesonide/formoterol electronic multidose dry powder inhaler; DHP=Digital Health Platform; DS=Digital System; HCP=healthcare professional; ICS=inhaled corticosteroid; LABA=long-acting beta2 agonist; MART=maintenance and reliever therapy.
* If needed, the HCP can add another controller medication other than an ICS with LABA, including a biologic, to the DS and SoC patient*s treatment.

All patients will have a screening/baseline visit, at which they will be asked if they own a mobile phone (with iOS or Android) and use different applications on their mobile phone. A baseline ACT score and Mini AQLQ and WPAI questionnaire responses for all patients will be collected. At Visit 1, patients in the BF Digihaler DS group will be trained on the use of the BF Digihaler (including instructions on how to use the inhaler and the App), and patients in the SoC group will be re trained on the use of their current inhalers. Upon demonstrating competency, patients in the BF Digihaler DS group will have their maintenance ICS with LABA and rescue medication or ICS/formoterol MART switched to the BF Digihaler given as MART (at a dose of BF comparable to their most recent current ICS dose). All other asthma maintenance medications, except for ICS with LABA, may be continued. If needed, the HCP can add another controller medication other than an ICS with LABA, including a biologic, to the DS and SoC patient*s treatment. Patients in the SoC group will receive reimbursement for their maintenance ICS with LABA and rescue medications according to their specific country*s policy.

Investigational centers will receive similar instruction regarding features of the App, as well as features of the associated dashboard, which mirrors the digital information obtained from the BF Digihaler and the App, including frequency and times of inhaler use and associated inspiratory flow parameters measured by the BF Digihaler with each inhalation (peak inhalation flow and inhaled volume).

At the baseline visit (Visit 1), the following information from the patient*s EMR will be collected, if available: blood eosinophils, FeNO, IgE (total), and lung function (FEV1, FVC, FEV1/FVC).

Patients in both the BF Digihaler DS and the SoC groups will be followed for their asthma according to the clinical judgement of the investigator; the asthma of patients in both groups will be managed in a manner consistent with the clinical judgement of the investigator and based on local practices, routines, and asthma management guidelines (eg, Global Initiative for Asthma [GINA]). In addition, the BF Digihaler DS group patients will be followed by the investigational centers with the addition of objective information on BF

Digihaler usage being available to both patients and investigational centers through the App and the dashboard, respectively. The HCPs will check the dashboard at least once a week per patient and use this information, along with any other additional information about the patient, as per their clinical judgement, to modify patients* asthma management. The investigator may, if indicated, modify the patient*s regime, including adding asthma controllers or biologics as otherwise clinically indicated in the judgement of the investigator. Clinically Driven Assessments for both groups, if necessary, should be arranged per the clinical judgement of the HCP managing the patient and can be via a video call, a telephone call, or an on-site visit.

For all patients, at Visit 2, Visit 3, and any Clinically Driven Assessment, the HCP will record answers to Asthma Management questions, including discussions regarding adherence, or inhaler technique, treatment adjustments, or additions of new treatments, including biologic medication usage. Additionally, in the case of a Clinically Driven Assessment, the HCP will be asked whether or not the contact with the patient was originated from the HCP interaction with the dashboard.

The ACT and Mini AQLQ will be completed on Visit 2.

At the end of the treatment period (24 weeks, Visit 3), final assessments of the DS and SoC groups will be completed, as specified in the study procedures and assessments schedule (Table 5), and the rest of the inhalers that were dispensed to the BF Digihaler DS group patients will be returned to the investigational center. Two weeks after the return of the inhalers, the investigational center will perform a follow-up telephone call for all patients, and will confirm that the BF Digihaler DS group patients have returned to their previous asthma treatments.

It should also be noted that no specific clinical decisions are being mandated. One secondary objective of this study is to describe how clinicians actually use the information provided by the DS to manage their patients.

Intervention

Budesonide/formoterol 160/4.5 mcg powder for oral inhalation
1-2 inhalations, twice daily; 1 additional inhalation as needed in response to symptoms. Not more than 6 inhalations should be taken on any single occasion. A total daily dose of more than 8 inhalations is not normally needed; however, a total daily dose of up to 12 inhalations could be used for a limited period. Patients using more than 8 inhalations daily should be strongly recommended to seek medical advice.

Study burden and risks

1.3. Known and Potential Benefits and Risks to Patients
The investigational product, BF Digihaler, delivers a dose of BF equivalent to DUORESP SPIROMAX and adds electronic capabilities intended to provide patients with feedback to potentially improve inhalation technique, disease understanding, management, and outcomes. The addition of the integrated electronic module has no impact on the pharmaceutical performance of the BF Digihaler relative to BF SPIROMAX, and it does not affect the user steps required to take a dose (performance and functional testing on file at Teva). Additional information regarding benefits and risks of BF Digihaler to patients may be found in the Investigator*s Brochure (IB).

Contacts

Public
PRA Group BV

Van Swietenlaan 6
Groningen 9728NZ
NL
Scientific
PRA Group BV

Van Swietenlaan 6
Groningen 9728NZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion Criteria: Patients may be included in the study only if they meet all of the following criteria:
a. The patient is 18 years or older at the time of screening.
b. The patient has a documented diagnosis of asthma established at the investigational center at the time of informed consent or the investigator confirms a diagnosis of asthma.
c. The patient is currently on treatment with a moderate- to high-dose ICS with LABA.
d. The patient has an ACT score of less than 19 at the screening/baseline visit.
e. The patient is willing to discontinue all other maintenance ICS with LABA medications and rescue medications and replace them with the study-provided BF Digihaler as MART for the duration of the trial, if randomized to the BF Digihaler DS group. All other asthma maintenance medications, except for ICS with LABA, may be continued.
f. The patient can read fluently and communicate in United Kingdom English, Dutch, or German, as applicable, and is familiar with and is willing to use his/her own mobile phone that meets the minimum App requirements and download and use the App.
g. The patient is able to provide written informed consent.
h. The patient must be willing and able to comply with study requirements and restrictions and to remain at the investigational center for the required duration during the study period, and willing to return to the investigational center for the follow up procedures and assessments as specified in this protocol.

Exclusion criteria

Exclusion Criteria: Patients will be excluded from participating in this study if they meet any of the following criteria:
a. The patient has any clinically significant uncontrolled medical condition (treated or untreated) other than asthma, which in the view of the investigator would preclude participation.
b. The patient has any medical or psychiatric condition that, in the opinion of the investigator, could jeopardize or would compromise the patient*s ability to participate in this study.
c. The patient is currently using or has used, in the 12 months prior to enrollment, a digital inhaler system designed to monitor inhaler usage such as, but not limited to, the Propeller Health, Adherium, or Amiko systems.
d. The patient has a diagnosis of chronic obstructive pulmonary disease (COPD) or asthma-COPD overlap (ACO).
e. The patient is a current smoker or has a greater than 10 pack-year history of smoking.

f. The patient was treated for asthma exacerbation, including hospitalization or emergency visits, in the last 30 days.
g. The patient is currently being treated with systemic corticosteroids (oral, intramuscular, or intravenous) or has been treated within the last 30 days.
h. The patient has any treatment with biologics for asthma (eg, omalizumab, anti interleukin (IL)5, anti-IL5R, anti-IL4R), or has had such treatment within the last 90 days.
i. The patient has a known hypersensitivity to any components of the IMPs stated in this protocol.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	95
Type:	Anticipated

Medical products/devices used

Generic name:	BF Digihaler DS
Registration:	No
Product type:	Medicine
Brand name:	Budesonide Formoterol
Generic name:	Budesonide Formoterol
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-12-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-05-2023
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-06-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-003951-41-NL
CCMO	NL82348.100.23