# Novartis Clinical Trial Results Template

## Sponsor

Novartis

## Generic Drug Name

Devices; Concept2 inhaler plus patient application to use in combination with the Concept2 inhaler

## Trial Indication(s)

Improvement of treatment adherence in subjects with Chronic Obstructive Pulmonary Disease (COPD), receiving reminder notification and motivational/adaptive messages

## Protocol Number

CIDD001D2402

## Protocol Title

A 24-week randomized, controlled, multicenter, open-label study to evaluate the effect of reminder notifications and motivational/adaptive messaging on treatment adherence of COPD subjects receiving Ultibro® Breezhaler® treatment using the Concept2 inhaler for dose administration and tracking

## Clinical Trial Phase

Phase III

**Phase of Drug Development**

Not Applicable

**Study Start/End Dates**

Study Start Date: 11-Jul-2018
Study Completion Date: 22-Jan-2019 (last subject last visit)
Study Termination Date: 24-Jan-2019

**Reason for Termination (If applicable)**

Novartis terminated the study due to technical issues with the investigational Concept2 inhalers.

**Study Design/Methodology**

Study CIDD001D2402 was a multicenter, 1:1 randomized, controlled, parallel-group open label study to investigate whether COPD subjects on Ultibro Breezhaler 110/50 micrograms (µg) clinical trial formulation once daily dosing regimen using a subject application in conjunction with the Concept2 inhaler have improved treatment adherence compared to subjects using the Concept2 inhaler alone. This study recruited subjects who had been prescribed treatment with Ultibro Breezhaler 110/50 µg for at least 3 months prior to Visit 1.

**Centers**

9 centers in 2 countries Germany (5), Netherlands (4).

**Objectives:**

**Primary objective(s)**

This study considered two primary endpoints:

- the effect of the intervention on the on-time treatment adherence of the subjects

- the effect of the intervention on the total treatment adherence of the subjects

These objectives were planned to evaluate the effect of reminder notifications and motivational/adaptive messages sent by the patient application over 24 weeks on:

- the subject's on-time treatment adherence, and
- the subject's total treatment adherence

On-time adherence was defined as percentage of days on which the subject inhaled at least one dose within (±) 2 hours of the agreed preferred daily inhalation time (PIT). The preferred daily inhalation time was defined by the subject at study start (Visit 1). Total adherence was defined as percentage of days on which the subject inhaled at least one dose and represents the sum of on-time adherence and off-time adherence. Off-time adherence was defined as percentage of days on which the subject inhaled a dose of medication, but did not do so within the target window (±) 2 hours of the agreed PIT.

**Secondary objective(s)**

To evaluate the effect of reminder notifications and motivational/adaptive messages sent by the patient application over 24 weeks for the subject's:

- On-time adherence over the last four weeks of the Interventional period compared to baseline
- Total adherence over the last four weeks of the Interventional period compared to baseline

**Test Product (Devices), Dose(s), and Mode(s) of Administration**

The intervention in this study consisted solely in the use of an investigational digital system, composed by the patient application and the Concept2 inhaler. The digital system was used in half of the subjects while the other group (control) was only receiving Usual Care delivered by the Concept2 inhaler, with no patient application. The drug treatment in this trial was not under investigation. The clinical trial formulation of Ultibro® Breezhaler® medicinal product was required to be inhaled with the Concept2 inhaler instead of the commercial available Concept inhaler (Breezhaler).

**Telehealth Group**: Subjects in this group receive Ultibro Breezhaler 110/50 µg clinical trial formulation once daily for 24 weeks via the Concept2 inhaler, able to track inhaler use, and dose reminder notifications and motivational/adaptive messages from the patient application aimed at encouraging treatment adherence

**Usual Care Group**: Subjects in this group receive Ultibro Breezhaler 110/50 µg clinical trial formulation once daily for 24 weeks via the Concept2 inhaler able to track subject's inhaler use

## Statistical Methods

The study was terminated early, due to technical issues observed with the investigational Concept2 inhalers. Only 7 subjects were randomized in the study and most of these subjects completed only a few weeks in the interventional period. Due to the early termination of the study, no summary statistics or inferential analyses as specified in the study protocol were performed. The limited data collected in the study were presented mainly by listings. Due to limited and inaccurate data, efficacy endpoints with respect to change in on-time and total treatment adherence were not evaluated.

## Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Male and female adults  18 years and older
- A historical diagnosis of COPD confirmed by a post-bronchodilator Forced expiratory volume in 1 second/Forced Vital Capacity (FEV1/FVC) less than(<) 0.70 in the past and a pre-bronchodilator or post-bronchodilator FEV1 > or = 30 percent (%) and less than (<) 80% of the predicted normal value within the last year
- Had been taking 143 µg of indacaterol maleate equivalent to 110 µg of indacaterol and 63 µg of glycopyrronium bromide equivalent to 50 µg of glycopyrronium for at least 3 months prior to Visit 1 (in accordance with the local product label)
- Had a total adherence of more than 10% but less than or equal to 70% during Screening period. Total adherence was defined as percentage of days on which the subject inhaled a dose of Ultibro Breezhaler 110/50 µg
- Had been in the Screening period > or = 35 days

Exclusion criteria

- Subjects contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof: anticholinergic agents, long and short acting beta-2 agonists and sympathomimetic amines
- Subjects contraindicated for having a history of reactions/ hypersensitivity to lactose or any of the other excipients of trial medication
- Subjects who have had a COPD exacerbation that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalization in 6 weeks prior to Visit 1
- Subjects who develop a COPD exacerbation between screening (Visit 1) and prior to intervention (Visit 110) will not be eligible but will be permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation
- Use of investigational drugs or other investigational devices at the time of enrollment, or within 30 days or 5 half-lives of Visit 1, whichever is longer
- Subjects with a preferred inhalation time between 10.00 pm and 2.00 am
- Subjects taken off treatment by the investigator during the Screening period for more than 7 days
- Subjects not returning all Concept2 inhalers, received during the Screening period, for the calculation of total adherence at Visit 110
- Subjects who have demonstrated inability or unwillingness to use the digital adherence system or to fill in questionnaires
- Subjects with a current diagnosis of asthma
- Subjects with concomitant pulmonary disease (e.g. lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, and pulmonary tuberculosis)

**Subject Flow Table**

Subject disposition for each treatment group (Randomized Population):

| | **Telehealth Group** | **Usual Care Group** |
|---|---|---|
| Started | 1 | 6 |
| Completed | 0 | 0 |
| Not Completed | 1 | 6 |
| Reason for non completion* | 1 | 6 |

*Technical issues with the Concept2 leading to limited and inaccurate data, for the efficacy endpoints

**Baseline Characteristics**

Demographics and characteristics by treatment group (Randomized Population):

| | | **Telehealth Group N=1** | **Usual Care Group N=6** | **Total N=7** |
|---|---|---|---|---|
| Age group (n) | <=18 years | 0 | 0 | 0 |
| | Between 18 and 65 years | 1 | 2 | 3 |
| | ≥ 65 years | 0 | 4 | 4 |
| Sex (n) | Male | 1 | 2 | 3 |
| | Female | 0 | 4 | 4 |
| Race (n) | White | 1 | 6 | 7 |
| Ethnicity (NIH/OMB) (n) | Not Hispanic or Latino | 1 | 6 | 7 |

**Primary Outcome Result(s)**

1. Change in Subject's On-Time Adherence over 24 Weeks of intervention compared to baseline
2. Change in Subject's Total Adherence over 24 Weeks of intervention compared to baseline

The primary objectives were to determine whether the use of dose tracking by the Concept2 inhaler in conjunction with reminder notifications and motivational/adaptive messages sent by the patient application could improve subject's on-time adherence or total adherence over 24 weeks of intervention.

Due to technical issues the actual time and day of inhaler use could not be evaluated. Therefore data for the primary outcome results were not estimable.

**Secondary Outcome Result(s)**

3. Change from subject's 6 weeks baseline On-Time Adherence to the subject's on-time adherence over the last four weeks of intervention
4. Change from subject's 6 weeks baseline Total Adherence to the subject's total adherence over the last four weeks of intervention

Due to the early discontinuation of the study, only very few subjects were randomized (7) and no subject completed the last 4 weeks of intervention, required for the evaluation of the secondary efficacy outcome results. Therefore data for the secondary outcome results was not evaluated.

**Safety Results**

**Frequency Threshold for Reporting Other Adverse Events: 0%**

**Subjects with frequent Adverse Events (AEs) by system organ class (Enrolled Population)**

| | Telehealth Group (N=1) (n) | Usual Care Group (N=6) (n) | Overall (N=7) (n) |
|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | 0 | 2 | 2 |

**Subjects with frequent AEs by preferred term (Enrolled Population)**

| | Telehealth Group (N=1) (n) | Usual Care Group (N=6) (n) | Overall (N=7) (n) |
|---|---|---|---|
| Cough | 0 | 2 | 2 |
| Respiratory Tract Infection | 0 | 1 | 1 |

**Serious Adverse Events (SAEs) and Deaths**

| | Telehealth Group (N=1) | Usual Care Group (N=6) |
|---|---|---|
| No. (%) of subjects studied | 1 | 6 |
| Death | 0 (0%) | 0 (0.0) |
| SAE(s) | 0 (0%) | 0 (0%) |
| Discontinued due to SAE(s) | 0 (0%) | 0 (0%) |

**Other Relevant Findings**

During the trial 52 device deficiencies were reported. All were related to the Concept2 inhaler, none was related to the patient application. None of the reported device deficiency led to an AE or SAE. Most frequently reported device deficiency was single or multiple reset of Real Time Clock (RTC) resulting in decoding instability of the system for the inhaler use time data. 29 of the 51 enrolled subjects (56%) had at least one inhaler with a device deficiency and 17 subjects (33.3%) had at least one inhaler with at least one RCT reset event. The device deficiencies "Single or multiple reset of Real Time Clock" were considered to fulfill the definition of a reportable device deficiency and were reported to the relevant Health Authority.

**Conclusion:**

The study was prematurely terminated due to technical issues with the investigational Concept2 inhalers. With the limited and inaccurate data captured by the Concept2 inhalers, it was not justified to assess any efficacy results with respect to inhaler use data and adherence behavior.

**Date of Clinical Trial Report:**

16-Jul-2019