NOVARTIS

Clinical Development

IDD001D Electronic Remote Patient Monitoring

CIDD001D2402 / NCT03379233

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

Statistical Analysis Plan (SAP)

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Document type:	SAP Documentation
Document status:	Draft
Release date:	18-March-2018
Number of pages:	12

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
Mar-18 2019	Prior to Database Lock		Final 2.0	Not applicable

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1 Introduction

The purpose of this document is to provide the scope of the statistical analysis that will be performed to report the data from the Phase III study CIDD001D2402 (prematurely terminated).

The study was designed to evaluate the effect of dose tracking in conjunction with reminder notifications and motivational/adaptive messages over 24 weeks on treatment adherence behavior in subjects with Chronic Obstructive Pulmonary Disease (COPD). Because of technical issues with the investigational Concept2 inhalers, the study was formally terminated prematurely on January 24, 2019, after 7 months from the First Patient First Visit, FPFV (11 July, 2018); the last Patient Last Visit, LPLV, was on January 22, 2019. Only 7 subjects were randomized. Of these 7 randomized subjects, 5 subjects discontinued after 4 weeks in intervention, 1 subject after 8 weeks in intervention and 1 subject after 12 weeks in intervention. None of them reached 24 weeks

This statistical analysis plan is an abbreviated approach of presenting the limited data collected in the study and does not reflect the full analysis scope described in Section 12 of the study protocol (Version 01, Amendment 1 to original protocol released on 10Nov2017).

1.1 Study design

This is a 24 weeks multicenter, randomized, controlled, open label parallel-group study.

It was planned to randomize 146 COPD subjects in to two groups (Interventions vs. Usual care) in 1:1 ratio, with the projection of 124 subjects completing the study. Sample size calculation considerations are detailed in Section 12.8 of the protocol (Section 3 in this document).

Randomization was stratified by COPD severity (moderate vs. Severe) and baseline total adherence group (less than 50% vs. $\geq$ 50%; inclusion criterion: 10% - 70%).

Figure 1-1   Study design
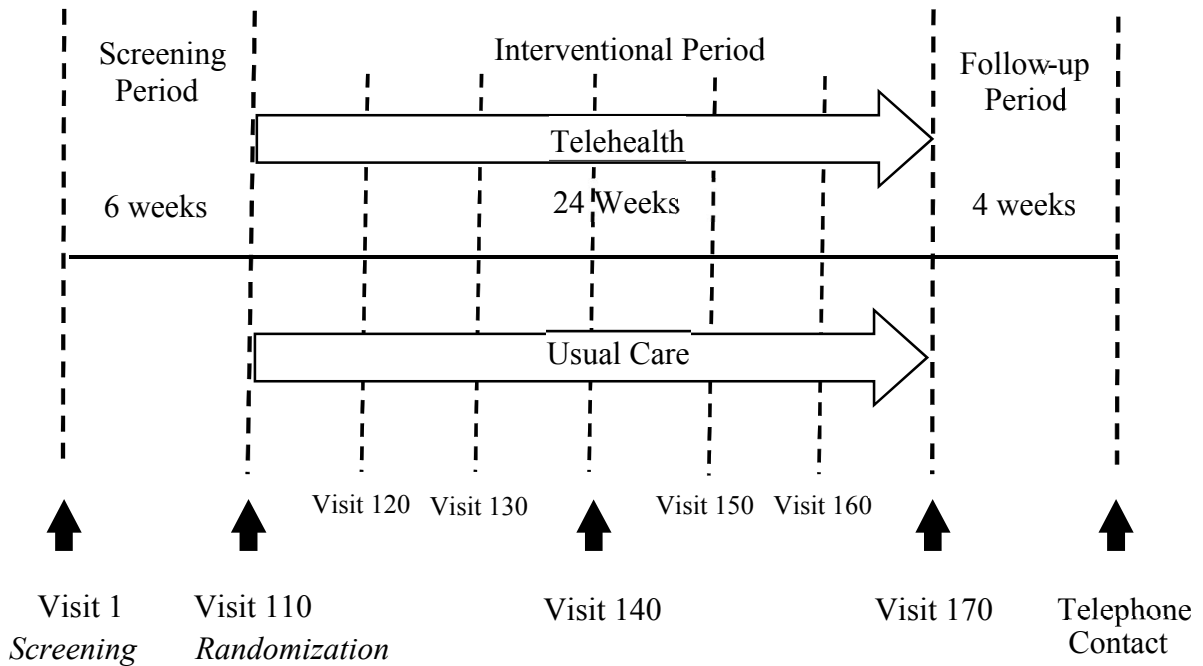
## 1.2   Study objectives and endpoints

1.3   Primary objectives

This study considers two primary endpoints:

(1) the effect of the intervention on the on-time treatment adherence of the subjects

(2) the effect of the intervention on the total treatment adherence of the subjects

1.4   Secondary objectives

To evaluate the effect of dose tracking in conjunction with reminder notifications and motivational/adaptive messages sent by the patient application over 24 weeks on the subject's

• On-time adherence over the last four weeks of the Interventional period

• Total adherence over the last four weeks of the Interventional period
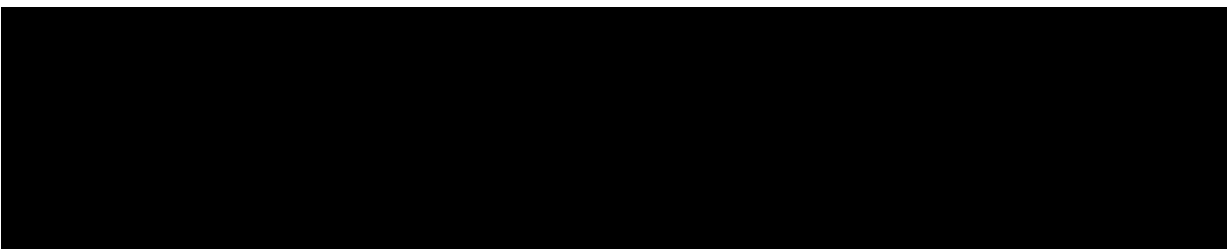
2 Statistical methods

2.1 Data analysis general information

The study was early terminated due to technical issues observed with the investigational Concept2 inhalers (see Section 2.3.2). Only 7 subjects were randomized in the study and most of these subjects had complete only a few weeks in the interventional period. Out of 52 enrolled subjects, 45 were screening failures.

As the study was early terminated, no summary statistics or inferential analyses that are outlined in the protocol (Section 12) will be performed.

A selected number of data listings (Appendix 1, Section5) will be presented, which will be used to furnish an abbreviated clinical study report (CSR).

2.1.1 General definitions

2.1.1.1 Intervention group

The two groups in the study were defined as

(1) Telehealth group: Concept2 inhaler plus patient application pre-installed on a tablet to encourage treatment adherence

The patient application in this trial was considered the intervention, and included functionalities such as an instructional video on Concept2 inhaler use, dose-reminder notifications, feedback to the subjects about their Concept2 inhaler use during the trial and motivational/adaptive messages, to encourage the treatment adherence of the subject.

(2) Usual Care group: Concept2 inhaler only.

 All subjects in the trial received the same treatment, which was prescribed by their physicians prior to their enrollment in the study - Ultibro® Breezhaler® (QVA149), a fixed combination of LABA and LAMA (a long acting β2-agonist Indacaterol maleate (QAB149) and a long acting

muscarinic antagonist Glycopyrronium bromide (NVA237)), but differ in terms of receiving a patient application (Telehealth group) vs. no patient application (Usual care group).

2.1.1.2 Study day

Study day is defined as the number of days since the date of first visit (Day 1) in the screening period. Study day is calculated as-

Study day = Assessment date – Date of visit 1 in screening (Day1) + 1;

2.2   Analysis sets

Enrolled subjects- All subjects who signed informed consent and had some assessment done in screening period. The enrolled subjects set will be used to list the study data.

Randomized subjects- All subjects who were randomized to one of the interventions (Telehealth group or Usual Care group).

2.3   Subject disposition, demographics and other baseline characteristics

2.3.1   Subject disposition

All enrolled subjects were discontinued either in the screening period or in the interventional period. Separate listings will be prepared to list the randomized subjects and enrolled subjects who discontinued in screening, specifying primary reason for discontinuation.

2.3.2   Subject demographics and baseline characteristics

Listings will be provided for demographic variables and baseline characteristics including type or pattern of non-adherence (questionnaire), as well as for medical history and current medical conditions.

2.4   Treatments (study treatment, rescue medication, concomitant therapies)

Study groups/ treatments are outlined in Section 2.1.1.1

2.4.1   Prior, concomitant and post therapies

Prior and concomitant medications and significant non-drug therapies will be presented in listings by study period and by interventional groups for enrolled subjects. Listings by interventional groups will be furnished for the interventional period only.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary objectives are 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 can improve on-time adherence or total adherence over 24 weeks of intervention.

The primary endpoints are:

(1) On-time adherence: defined as the percentage of days on which the subject inhaled at least one dose within (±) 2 hours of the agreed preferred daily inhalation time. The daily preferred inhalation time (PIT) must be defined by the subject at the start of the study and can only be modified at scheduled study visits by the study investigator at the request of the subject. The on-time adherence is calculated as-

On-time adherence=

$$\frac{\textit{Number of days with at least one dose/inhaler use recorded via the Concept2 Inhaler within (\pm) 2 hours of planned PIT}}{\textit{Number of days the subject had the Concept2 inhaler over 24 weeks}}$$

(2) Total adherence: defined as the percentage of days on which the subject inhaled at least one dose and is calculated as the sum of on-time adherence and off-time adherence. Off-time adherence is defined as percentage of days on which the subject did not inhale the daily dose within the (±) 2 hours of the PIT, but outside. The off-time adherence is calculated as-

Off-time adherence=

$$\frac{\textit{number of days the subject did not inhale the daily dose within the (\pm) 2 hours of the predefined PIT, but outside}}{\textit{Number of days the subject had the Concept2 inhaler over 24 weeks}}$$

The total adherence is calculated as-

Total adherence= on-time adherence + off-time adherence

2.5.2 Technical Issue with the Concept2 inhalers and consequence on estimation of endpoints

The clock inside the electronics in the base of the Concept2 inhaler, that records (or stamps a time point) whenever the blue buttons are pressed (with or without an inhalation) was supposed to be in a chronological order in reference to the first time the Concept2 inhaler was used (first time the blue buttons were pressed). During blinded data review, the clinical team identified erroneous time stamps in the inhalation records. The root cause of the erroneous

time stamps was identified as residing in an abnormally high rate of internal real-time clock resets. The precise time of occurrence of each internal real-time clock reset event is unknown. As a result, the calculated total adherence levels of subject at the end of the screening period, calculated by the investigator application, based on the recorded inhalations, were inaccurate, resulting in subjects being randomized into the intervention period of the study even if they did not meet the eligibility criteria for enrollment (total adherence). This invalidated the adherence data during the screening period such that the adherence rates, screening failure rates and randomization rates cannot be considered correct anymore.

Because of this resetting of the internal real time clock of the Concept2 inhalers, it was not possible to determine the actual time and day of inhalation from the point of resetting, especially if multiple resetting happened. Therefore, in these instances it was not possible to assess if an inhalation actually happened within ($\pm$) 2 hours of planned PIT, leading to the inability of determining the number of days with at least one dose/ Concept2 inhaler used within the PIT window, and as such the co-primary endpoint 'on-time adherence' was not estimable. The observed issues with data quality and data integrity regarding inhaler use was also leading to the inability of determining the number of days subjects actually did not inhale, and as such the co-primary endpoint 'total adherence' was not estimable (as off-time adherence was not estimable)

During the trial halt the company has investigated whether a technical solution can be identified to solve the observed Concept2 deficiencies. As a robust solution not requiring multiple assumptions could not be identified, the sponsor determined that the study, if resumed, could no longer offer sufficiently robust data to support the protocol objectives. The study was prematurely terminated, having 7 subjects being randomized (as outlined in Section 1). With the limited and inaccurate data, it was not justified to assess any efficacy endpoint with respect to inhalation data and adherence behavior.

2.6 Analysis of secondary efficacy objective(s)

2.6.1 Secondary endpoints

The secondary objectives are to evaluate the effect of dose tracking in conjunction with reminder notifications and motivational/adaptive messages sent by the patient application over 24 weeks on the subject's

- On-time adherence over the last four weeks of the Interventional period

- Total adherence over the last four weeks of the Interventional period

As mentioned in Section 2.3.2, no endpoint is assessed with respect to adherence (on-time and total).

2.7   Safety analyses

2.7.1   Adverse events (AEs)

For all enrolled subjects, all device deficiencies, reportable device deficiencies, device related ADE/SADE and non-device related AE/SAE will be listed by study period (screening and interventional periods) and by interventional group (for interventional period only).

2.7.1.1   Vital signs

Vital signs (Sitting systolic and diastolic blood pressure, pulse rate) will be listed by study period (screening and interventional periods) and by interventional group (for interventional period only)
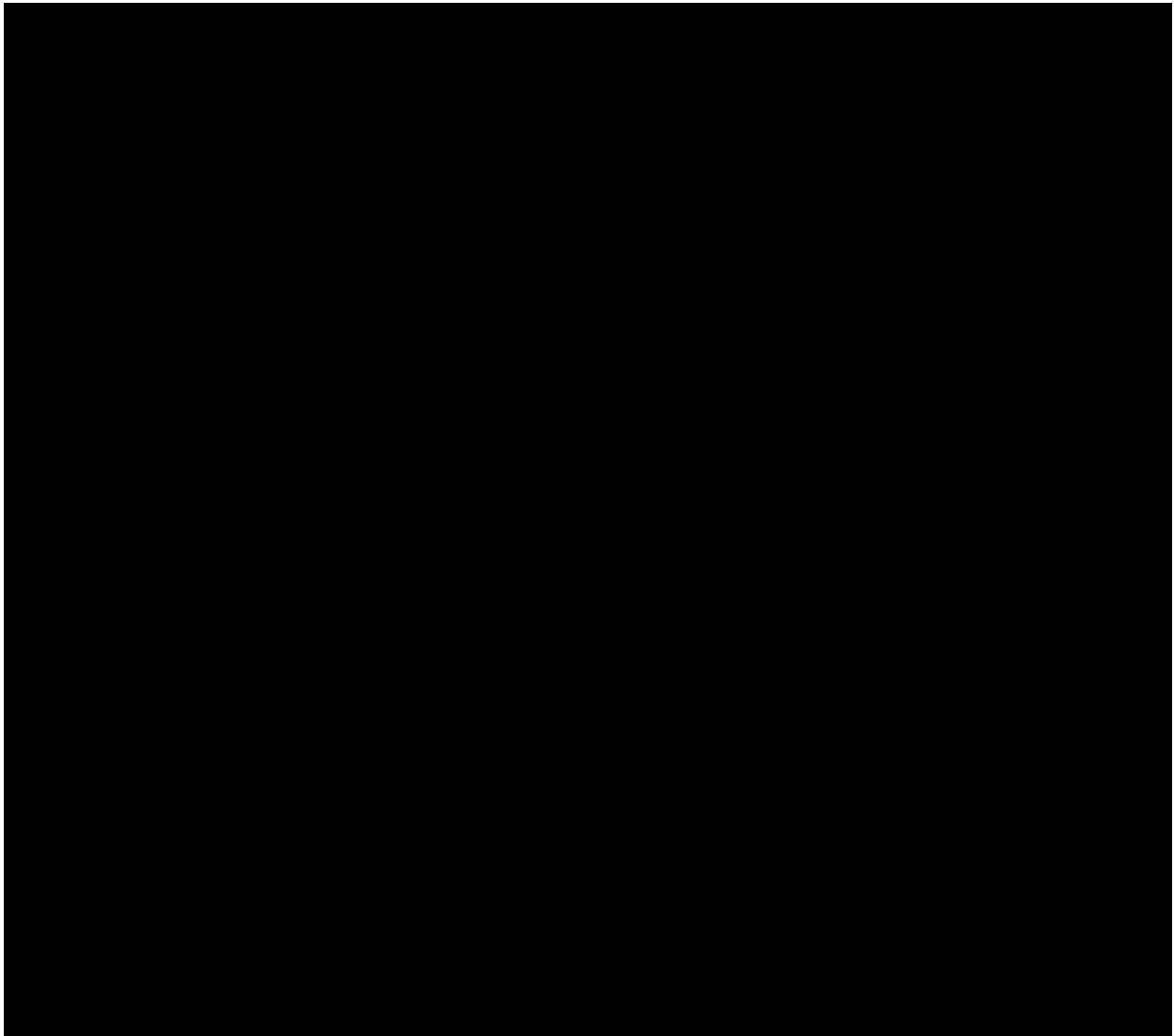
3   Sample size calculation

Sample size calculation takes into account the following considerations:

1. To achieve 90% power (with multiplicity adjustment) for primary endpoint on-time adherence with a group difference of 15% between intervention group vs. Usual Care group (i.e. change from baseline in mean on-time adherence in intervention group – (minus) change from baseline in mean on-time adherence in Usual Care group), assuming a common standard deviation of 25%, based on reference below.

2. To achieve 90% power (with multiplicity adjustment) for primary endpoint total adherence with a group difference of 15% between intervention group vs. Usual Care group (i.e. change from baseline in mean total adherence in intervention group – (minus) change from baseline in mean total adherence in Usual Care group), assuming a common standard deviation of 25%, based on reference below.

In absence of any available assessment of the correlation between the two primary endpoints, a relatively conservative measurement (of 0.8) has been chosen for the simulation. Considering a 15% dropout, the simulation (under the testing scheme in Section 12.4.4 of the protocol) shows that the sample size of 146 (73 per arm) will provide 90% power for on-time adherence and 90% power for total adherence, with multiplicity adjustment. With zero (0) correlation the power for on-time adherence will be above 90% and the power for total adherence will be above 90%.

The sample size and power calculations are performed in R 3.3.0.

(Reference: Charles et al (2007) an audiovisual reminder function (AVRF) study reported a difference in median adherence between the two groups (AVRF group vs. control group) as 18% (95% CI, 10% to 26%, P<0.0001); Strandbygaard et al (2009), a daily SMS reminder study reported a difference in change from baseline in mean adherence between two groups, one received daily SMS and one did not, as 17.8%, 95% CI (3.2 – 32.3%), p=0.019; common standard deviation for mean changes in adherence = 19%, (calculated)).

4   Change to protocol specified analyses

Because of the early termination of the study and the few subjects randomized (7 subjects) no planned analysis as specified in the protocol will be performed; however, listings presenting the assessed data, are listed in Appendix 1 (Section 5).

5   References

Charles T, Quinn D, Weatherall M et al (2007), An audiovisual reminder function improves adherence with inhaled corticosteroid therapy in asthma. J Allergy Clin Immunol; 119(4):811‑816.

Strandbygaard U, Thomsen SF, Backer V (2009), Daily SMS reminders for asthma treatment adherence: A three month follow up study. Respiratory medicine; 104:166-171.

6   Appendix 1

6.1   List of listings