



## Clinical trial results:

**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**

### Summary

EudraCT number	2017-001593-42
Trial protocol	AT BE NL
Global end of trial date	24 January 2019

### Results information

Result version number	v1 (current)
This version publication date	01 February 2020
First version publication date	01 February 2020

### Trial information

#### Trial identification

Sponsor protocol code	CIDD001D2402
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03379233
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Forum 1, Novartis Campus, Basel, Switzerland, 4056
Public contact	Clinical Trial Information Desk, Novartis Pharma AG, +41 61 324 1111, clinicaltrial.enquiries@novartis.com
Scientific contact	Clinical Trial Information Desk, Novartis Pharma AG, +41 61 324 1111, clinicaltrial.enquiries@novartis.com

Notes:

### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 January 2019
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

This study considered 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

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) E6 and Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 July 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Netherlands: 3
Worldwide total number of subjects	7
EEA total number of subjects	7

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	3
From 65 to 84 years	4

85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at Netherlands and Germany between 11 July 2018 (first subject first visit) and 22 January 2019 (last subject last visit).

### Pre-assignment

Screening details:

A total of 7 subjects were randomized in the study.

### Period 1

Period 1 title	Intervention Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Telehealth Group

Arm description:

Subjects inhaled Ultibro Breezhaler 110/50 micrograms (mcg) clinical formulation once daily via Concept2 inhaler with an electronic connectivity to a patient application pre-installed on a tablet device for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Concept2 Inhaler with patient application
Investigational medicinal product code	
Other name	Ultibro Breezhaler
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Subjects inhaled 110 mcg of indacaterol and 50 mcg of glycopyrronium capsule once daily via Concept2 inhaler with an electronic connectivity to a patient application pre-installed on a tablet device. The drug products were not under the investigation in this study.

<b>Arm title</b>	Usual Care Group
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Arm description:

Subjects inhaled Ultibro Breezhaler 110/50 mcg capsule once daily via Concept2 inhaler for 24 weeks.

Arm type	Active comparator
Investigational medicinal product name	Concept 2 inhaler
Investigational medicinal product code	
Other name	Ultibro Breezhaler
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Subjects inhaled 110 mcg of indacaterol and 50 mcg of glycopyrronium capsule once daily via Concept2 inhaler. The drug products were not under investigation in this study.

<b>Number of subjects in period 1</b>	Telehealth Group	Usual Care Group
Started	1	6
Completed	0	0
Not completed	1	6
Technical issues with the Concept 2 inhalers	1	6

## Baseline characteristics

### Reporting groups

Reporting group title	Telehealth Group
Reporting group description:	
Subjects inhaled Ultibro Breezhaler 110/50 micrograms (mcg) clinical formulation once daily via Concept2 inhaler with an electronic connectivity to a patient application pre-installed on a tablet device for 24 weeks.	
Reporting group title	Usual Care Group
Reporting group description:	
Subjects inhaled Ultibro Breezhaler 110/50 mcg capsule once daily via Concept2 inhaler for 24 weeks.	

Reporting group values	Telehealth Group	Usual Care Group	Total
Number of subjects	1	6	7
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1	2	3
From 65-84 years	0	4	4
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	1	2	3
Male	0	4	4
Race (NIH/OMB)			
Units: Subjects			
White	1	6	7
Ethnicity (NIH/ OMB)			
Units: Subjects			
Not Hispanic or Latino	1	6	7

## End points

### End points reporting groups

Reporting group title	Telehealth Group
Reporting group description: Subjects inhaled Ultibro Breezhaler 110/50 micrograms (mcg) clinical formulation once daily via Concept2 inhaler with an electronic connectivity to a patient application pre-installed on a tablet device for 24 weeks.	
Reporting group title	Usual Care Group
Reporting group description: Subjects inhaled Ultibro Breezhaler 110/50 mcg capsule once daily via Concept2 inhaler for 24 weeks.	

### Primary: Change in Subject's On-time Adherence Over 24 Weeks of Intervention Compared to Baseline

End point title	Change in Subject's On-time Adherence Over 24 Weeks of Intervention Compared to Baseline <sup>[1]</sup>
End point description: On-time treatment adherence was defined as percentage of days on which the subject inhaled at least one dose on-time. Dose inhaled on-time was a dose inhaled within (+ or -) 2 hours of the agreed predefined preferred daily inhalation time (PIT). PIT was defined by the subject at study start. Due to technical issues, the actual time and day of inhaler use could not be evaluated. Therefore data for this endpoint was not collected and reported.	
End point type	Primary
End point timeframe: Baseline 6 weeks, intervention over 24 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the early termination of the study, no summary statistics or inferential analyses were performed.

End point values	Telehealth Group	Usual Care Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[2]</sup>	0 <sup>[3]</sup>		
Units: Number of subjects				
arithmetic mean (standard deviation)	( )	( )		

Notes:

[2] - Due to technical issues actual time and day of inhaler use was not evaluated.

[3] - Due to technical issues actual time and day of inhaler use was not evaluated.

### Statistical analyses

No statistical analyses for this end point

### Primary: Change in Subject's Total Adherence Over 24 Weeks of Intervention Compared to Baseline

End point title	Change in Subject's Total Adherence Over 24 Weeks of Intervention Compared to Baseline <sup>[4]</sup>
End point description: Total adherence was defined as percentage of days on which the subject inhaled at least one dose and represented the sum of on-time adherence and off-time adherence. Off-time adherence was defined as percentage of days on which the subject did not inhale the daily dose within the (+ or -) 2 hours of the	

predefined PIT, but outside. The number of doses not inhaled on-time was recorded by the Concept2 inhaler. Due to technical issues, the actual time and day of inhaler use could not be evaluated. Therefore data for this endpoint was not collected and reported.

End point type	Primary
End point timeframe:	
Baseline 6 weeks, intervention over 24 weeks	

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the early termination of the study, no summary statistics or inferential analyses were performed.

End point values	Telehealth Group	Usual Care Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[5]</sup>	0 <sup>[6]</sup>		
Units: Number of subjects				
arithmetic mean (standard deviation)	()	()		

Notes:

[5] - Due to technical issues actual time and day of inhaler use was not evaluated.

[6] - Due to technical issues actual time and day of inhaler use was not evaluated.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Subject's 6 Weeks Baseline On-time Adherence to the Subject's On-time Adherence Over the Last Four Weeks of Intervention

End point title	Change from Subject's 6 Weeks Baseline On-time Adherence to the Subject's On-time Adherence Over the Last Four Weeks of Intervention
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End point description:

On-time treatment adherence was defined as percentage of days on which the subject inhaled at least one dose on-time. Dose inhaled on-time was a dose inhaled within (+ or -) 2 hours of the agreed PIT. PIT was defined by the subject at study start. 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 endpoints. Therefore data for this endpoint was not collected and reported.

End point type	Secondary
End point timeframe:	
Baseline, Week 21 - 24	

End point values	Telehealth Group	Usual Care Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[7]</sup>	0 <sup>[8]</sup>		
Units: Number of subjects				
arithmetic mean (standard deviation)	()	()		

Notes:

[7] - Due to the early discontinuation of the study no subject completed the last 4 weeks of intervention.

[8] - Due to the early discontinuation of the study no subject completed the last 4 weeks of intervention.



## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Subject's 6 Weeks Baseline Total Adherence to the Subject's Total Adherence Over the Last Four Weeks of Intervention

End point title	Change from Subject's 6 Weeks Baseline Total Adherence to the Subject's Total Adherence Over the Last Four Weeks of Intervention
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End point description:

Total adherence was defined as percentage of days on which the subject inhaled at least one dose and represented the sum of on-time adherence and off-time adherence. Off-time adherence was defined as percentage of days on which the subject did not inhale the daily dose within the (+ or -) 2 hours of the predefined PIT, but outside. The number of doses not inhaled on-time was recorded by the Concept2 inhaler. 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 endpoint. Therefore data for this endpoint was not collected and reported.

End point type	Secondary
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End point timeframe:

Baseline, Week 21 - 24

End point values	Telehealth Group	Usual Care Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[9]</sup>	0 <sup>[10]</sup>		
Units: Number of subjects				
arithmetic mean (standard deviation)	()	()		

Notes:

[9] - Due to the early discontinuation of the study no subject completed the last 4 weeks of intervention.

[10] - Due to the early discontinuation of the study no subject completed the last 4 weeks of intervention.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events were reported from start of treatment up to follow up (34 weeks)

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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### Reporting groups

Reporting group title	Telehealth Group
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Reporting group description:

Subjects inhaled Ultibro Breezhaler 110/50 micrograms (mcg) clinical formulation once daily via Concept2 inhaler with an electronic connectivity to a patient application pre-installed on a tablet device for 24 weeks

Reporting group title	Usual Care Group
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Reporting group description:

Subjects inhaled Ultibro Breezhaler 110/50 mcg capsule once daily via Concept2 inhaler for 24 weeks.

Serious adverse events	Telehealth Group	Usual Care Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 6 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Telehealth Group	Usual Care Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	2 / 6 (33.33%)	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 1 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 May 2018	<ul style="list-style-type: none"><li>-The classification of this study has been changed to 'an open label controlled trial' instead of 'single blind' to match with the study procedures already planned for the trial.</li><li>-The trial phase has been changed from Proof of Concept to Phase III since the Investigational Medicinal Product is a registered/ approved product being investigated in this trial with unapproved Concept2 inhaler and the trial is intended to support registration of the Concept2 inhaler with the DAS with potential inclusion in Summary of Product Characteristics (SmPC).</li><li>-The study design has been amended to use only a single written informed consent form (ICF) required to be signed by subjects at the start of the clinical trial, instead of two ICFs planned to be used in the earlier study design. The second ICF is therefore no longer required.</li><li>-Inclusion Criteria 4 has been altered to include subjects who had either (spirometric) post-bronchodilator OR pre-bronchodilator forced expiratory volume in 1 second (FEV1) in the last year, if the COPD diagnosis was confirmed with (spirometric) post-bronchodilator FEV1/forced vital capacity (FVC) &lt;0.7 in the past. The reason to change this inclusion criteria is to also allow subjects with a historical COPD diagnosis (&gt;1 year) to be included in the trial to reflect the routine medical practice in the participating countries.</li><li>-Exclusion criteria have been updated to reflect the contraception requirements as defined in the Clinical Trial Facilitation Group Recommendations related to contraception and pregnancy testing in clinical trials.</li><li>-Further changes were made to clarify study procedures, such as editorial changes related to data protection measures and reporting of Serious Adverse Device Event.</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
24 January 2019	The study was terminated early due to technical issues 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.	-

Notes:

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was prematurely terminated due to technical issues with the investigational Concept2 inhalers. Due to limited and inaccurate data, efficacy endpoints with respect to change in on-time and total treatment adherence were not evaluated.

Notes: