Sponsor

Novartis

Generic Drug Name

Not applicable, No investigational drug treatment in this study.

Trial Indication(s)

Chronic obstructive pulmonary disease (remote patient monitoring system, RPM)

Protocol Number

CIDD001D2401

Protocol Title

A 52-week multi-center randomized trial to evaluate remote patient monitoring using the EXACT patient-reported outcome tool on reduction of hospitalizations from exacerbations in patients with Chronic Obstructive Pulmonary Disease as compared to those managed by usual care

Clinical Trial Phase

Phase I

Phase of Drug Development

Not applicable, No investigational drug treatment in this study.

Study Start/End Dates

Study initiation date: 28-Jun-2012 (first patient first visit)
Early termination date: 5-Dec-2013
Study completion date: 27-Jan-2014 (last patient last visit)

Reason for Termination (If applicable)

The study was prematurely terminated on 5th December 2013 due to issues with the Telehealth system data connection which inhibited further testing of the primary efficacy hypothesis of the study.

Study Design/Methodology

This pilot study was planned to use two parallel groups of approximately 100 patients in each arm. After a maximum 2-week screening period to confirm eligibility, patients were randomized to either the usual care with RPM system group, or the usual care only group. Both groups were to be followed for 52 weeks until the end of study. There were 4 planned study visits (screening, baseline/randomization, interim visit after 6 months and end of study). The assessment to address the primary objective was to be performed at the end of the 52-week study period. The EXACT has identified changes from usual daily scores which have been associated with exacerbations; however, not all such deviations from baseline daily scores are necessarily followed by an exacerbation. The remote patient monitoring system issues an alert to the clinical site once the established threshold change has been reached; the alert notification requires the clinical site to contact the patient in order to determine the clinical significance associated with the change in score, and to treat the patient based on clinical judgment and clinical practice. Management of exacerbations was not otherwise mandated by the study protocol. Patients in the usual care arm had the identification and management of their exacerbations continue through their normally established procedures of nurse/physician contact and evaluation, as is considered standard for each individual practitioner in the study.
Note: On the 5th December 2013, the decision was taken by Novartis to terminate the study prematurely due to issues with the Telehealth system data connection (provided by an external vendor) which inhibited further testing of the primary efficacy hypothesis of the study.

Centers

A total of 20 centers in 2 countries enrolled at least one patient (number of centers in brackets): Sweden (7), Spain (13).

Publication

No Publications

Objectives:

Primary objective was to investigate whether the use of remote patient monitoring (RPM) system using the EXACT PRO tool (EXACT) can reduce the number of hospitalizations and/or emergency room visits from COPD exacerbations through early detection of clinical deterioration and triggering timely outpatient intervention, as compared to usual care.
Secondary objectives were:
• To evaluate the effect of the RPM system using EXACT on average length of hospital stay for COPD exacerbations compared to usual care.
• To evaluate the effect of the RPM system using EXACT on time to first occurrence of hospitalization for COPD exacerbation compared to usual care.
• To evaluate the effect of the RPM system using EXACT on health care resource utilization (e.g., hospitalizations, unscheduled and scheduled office visits, frequency of telephone call contacts, medications) as compared to usual care.
• To evaluate the effect of the RPM system using EXACT on number of medical visits (e.g., hospitalizations, emergency room visits, unscheduled and scheduled office visits) for COPD management compared to usual care.
Note: due to the early termination of the study and the low sample size, most of the secondary and all of the exploratory objectives were not evaluated.

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

Not applicable, there was no investigational drug treatment in this study.

Statistical Methods

Data were analyzed by the Contract Research Organization (CRO) DATAMAP GmbH, Freiburg (Germany), according to the data analysis section 9 of the study protocol which is available in Appendix 16.1.1. Important information is given in the following sections.
The primary objective of this study was to demonstrate if the use of remote patient monitoring (RPM) system using the EXACT PRO tool (EXACT) can reduce the number of hospitalizations and/or emergency room visits from COPD exacerbations through early detection of clinical deterioration and triggering timely outpatient intervention, as compared to usual care.

On 5th December 2013 the decision was taken by Novartis to terminate the study prematurely due to issues with the data connection of the Telehealth system and because the primary efficacy hypothesis of the study could no longer be tested. At that time point only 120 patients had entered the trial, 6 of those patients had already completed the trial and 38 patients were observed for 6 months or longer. The study was designed to recruit approximately 200 patients. Therefore, the available data were limited and it was decided to report the study data in an abbreviated Clinical Study Report (CSR) with descriptive tabulations of the main available data and patient data listings. No inferential statistical analysis was performed.
Safety was assessed based on adverse events suspected to be related to the RPM system device, and serious adverse events, as well as vital signs.
In general categorical data are presented as frequencies and percentages. For continuous data, either the number of non-missing observations, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum is presented, or the continuous data were collapsed

into categorical data and summarized as categorical data.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and females adults aged ≥ 40 years
3. Outpatients with a diagnosis of COPD, GOLD grade 2 or higher as classified by the GOLD guidelines, Updated 2011 (Appendix 1), including:
   - Current or ex-smokers with a smoking history of at least 10 pack years
   - Post-bronchodilator FEV1 < 80% of the predicted normal value within 12 months prior to screening* or at screening
   - Post-bronchodilator FEV1/FVC < 70% within 12 months prior to screening* or at Screening

     (Post refers to within 10-15 minutes of inhalation of 400 µg (4 x 100 µg) of salbutamol, equivalent to 4 x 90 µg albuterol delivered at the mouthpiece)

     *Historical pulmonary function data within 12 months of the screening visit will be accepted.
4. A documented history of at least 2 COPD exacerbations requiring treatment with systemic corticosteroids and/or antibiotics in the previous 12 months prior to the screening visit, at least one of which required hospitalization.
5. Study subjects must be able to read and understand study instructions and questionnaires in the local language of the participating country.

Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study:
1. Use of investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer
2. Patients who have a COPD exacerbation not clinically resolved within 30 days prior to screening (Visit 1).
3. Patients with a history of asthma (at Visit 1), indicated by (but not limited to) the onset of respiratory symptoms suggestive of asthma (such as cough, wheezing, shortness of breath) prior to age 40 years.
4. Patients who are unable or unwilling to use the RPM system.
No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

Participant Flow Table

Patient disposition and time in study (All patients)

	RPM system n (%)	Usual care n (%)	Total n (%)
Screened	-	-	131
Randomized	61 (100)	59 (100)	120 (100)
Completed	2 (3.3)	4 (6.8)	6 (5.0)
Completion status not databased[1]	1 (1.6)	0	1 (0.8)
Discontinued	58 (95.1)	55 (93.2)	113 (94.2)
Primary reason for premature discontinuation			
Adverse event(s)	0	1 (1.7)	1 (0.8)
Exacerbation adverse event	0	1 (1.7)	1 (0.8)
Non-exacerbation adverse event	0	0	0
Administrative problems[2]	44 (72.1)	45 (76.3)	89 (74.2)
Patient withdrew consent	10 (16.4)	5 (8.5)	15 (12.5)
Lost to follow-up	3 (4.9)	4 (6.8)	7 (5.8)
Death	1 (1.6)	0[3]	1 (0.8)

	RPM system n (%)	Usual care n (%)	Total n (%)
Abnormal laboratory value(s)	0	0	0
Abnormal test procedure result(s)	0	0	0
Protocol deviation	0	0	0
Time in study (days)			
n	61	59	120
Mean	114.3	139.2	126.5
SD	99.30	105.37	102.66
Median	85.0	119.0	103.5
Min - Max	1-366	1-444	1-444
Time in study - n (%)			
<= 3 months	31 (50.8)	24 (40.7)	55 (45.8)
4-6 months	14 (23.0)	13 (22.0)	27 (22.5)
6-12 months	15 (24.6)	20 (33.9)	35 (29.2)
>12 months	1 (1.6)	2 (3.4)	3 (2.5)

One patient received a randomization number assigned by IVRS. According to an Investigator comment; this patient withdrew consent after randomization and no assessments were performed. Later on this case was identified as an error of randomization process because the patient did not perform any screening assessments. This patient was not included in any of the analyses in this study.

Administrative problems refer to issues with data connection.

One patient randomized to Usual care was discontinued from the study due to Adverse Event Lung Cancer and later died.

Baseline Characteristics

Demographic summary (Full analysis set)

		RPM system N=61	Usual care N=59	Total N=120
Age (years)	n	61	59	120

		RPM system N=61	Usual care N=59	Total N=120
	Mean	70.0	68.2	69.1
	SD	7.65	8.08	7.88
	Median	70.0	69.0	70.0
	Min - Max	48-91	48-84	48-91
Age group - n (%)	40 - 64 years	9 (14.8)	19 (32.2)	28 (23.3)
	>= 65 years	52 (85.2)	40 (67.8)	92 (76.7)
Sex - n (%)	Male	43 (70.5)	47 (79.7)	90 (75.0)
	Female	18 (29.5)	12 (20.3)	30 (25.0)
Race - n (%)	Caucasian	61 (100)	59 (100)	120 (100)
Ethnicity - n (%)	Hispanic/Latino	20 (32.8)	25 (42.4)	45 (37.5)
	Other	41 (67.2)	34 (57.6)	75 (62.5)
Weight (kg)	n	60	59	119
	Mean	73.1	72.2	72.7
	SD	16.44	15.21	15.79
	Median	69.5	70.0	70.0
	Min - Max	43.0-121.0	44.0-110.0	43.0-121.0
Height (cm)	n	60	59	119
	Mean	166	165	166
	SD	7.6	7.0	7.3
	Median	165	165	165
	Min - Max	141-182	152-182	141-182
BMI (kg/m2)	n	60	59	119
	Mean	26.5	26.3	26.4
	SD	5.69	5.01	5.34
	Median	25.5	25.9	25.8
	Min - Max	15.8-42.9	16.4-39.0	15.8-42.9
BMI category - n (%)	<= 30.0 kg/m^2	44 (72.1)	44 (74.6)	88 (73.3)

		RPM system N=61	Usual care N=59	Total N=120
	> 30.0 kg/m^2	16 (26.2)	15 (25.4)	31 (25.8)
	Missing	1 (1.6)	0	1 (0.8)

BMI = Body mass index (= weight [kg] / height (m2)]

Summary of Efficacy

Efficacy was not powered for analysis

Safety Results

Serious AEs by primary system organ class and preferred term - n (%) of patients (Full analysis set)

	RPM system N=61 n (%)	Usual care N=59 n (%)
Patients with any serious (AE)s*	19 (31.1)	15 (25.4)
Primary system organ class and preferred term		
Cardiac disorders	3 (4.9)	3 (5.1)
Cardiac failure	3 (4.9)	1 (1.7)
Atrial fibrillation	1 (1.6)	0
Angina pectoris	0	1 (1.7)
Right ventricular failure	0	1 (1.7)
General disorders and administration site conditions	1 (1.6)	0
Non-cardiac chest pain	1 (1.6)	0
Infections and infestations	4 (6.6)	5 (8.5)
Respiratory tract infection	2 (3.3)	1 (1.7)
Endocarditis	1 (1.6)	0
Viral infection	1 (1.6)	0
Bronchitis bacterial	0	1 (1.7)
Neutropenic infection	0	1 (1.7)
Pneumonia	0	2 (3.4)
Injury, poisoning and procedural complications	2 (3.3)	0
Contusion	1 (1.6)	0
Femur fracture	1 (1.6)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (1.6)	2 (3.4)
Lung adenocarcinoma	1 (1.6)	0

	RPM system N=61 n (%)	Usual care N=59 n (%)
Lung neoplasm malignant	0	2 (3.4)
Nervous system disorders	1 (1.6)	1 (1.7)
Cerebrovascular accident	1 (1.6)	0
Tension headache	0	1 (1.7)
Renal and urinary disorders	1 (1.6)	0
Renal failure chronic	1 (1.6)	0
Respiratory, thoracic and mediastinal disorders	15 (24.6)	14 (23.7)
Chronic obstructive pulmonary disease	15 (24.6)	13 (22.0)
Respiratory failure	2 (3.3)	2 (3.4)
Dyspnea	1 (1.6)	0
Acute respiratory failure	0	1 (1.7)
Vascular disorders	1 (1.6)	1 (1.7)
Hypotension	1 (1.6)	0
Embolism	0	1 (1.7)

*There were a few discrepancies identified in clinical database when compared to safety database, after the database lock. All discrepancies have been investigated and there is no impact on the primary efficacy variable because all hospitalizations were reported and there are few missing SAEs in the clinical database. All SAEs are captured and reported in the safety database (ARGUS). Please see below for details of individual discrepancies;

One patient (RPM system) experienced a serious adverse event of Diverticulitis which was not included in the clinical database. The event was considered as not related to study device. The event was reported in the safety database.

One patient (Usual care) had a hospitalization but no corresponding SAE was included in clinical database. Upon inquiry site confirmed that the patient was hospitalized for an elective hernia operation and it was not deemed serious by the investigator.

One patient (RPM system) had a hospitalization but no corresponding severe COPD exacerbation was included in the clinical database. The event was reported in the safety database.

One patient (Usual care) had a hospitalization but no corresponding severe COPD exacerbation was included in the clinical database. The event was reported in safety database.

Primary system organ classes are sorted alphabetically; preferred terms are sorted within each primary system organ class in descending order of frequency in the RPM group.

Conclusion:

The primary objective of this pilot study was to demonstrate whether the use of remote patient monitoring (RPM) system using the EXACT PRO tool (EXACT) can reduce the number of hospitalizations and/or emergency room (ER) visits from COPD exacerbations through early detection of clinical deterioration and triggering timely outpatient intervention, as compared to usual care.

However, the decision was taken by Novartis to terminate the study prematurely due to issues with the data connection of the Telehealth system and because the primary efficacy hypothesis of the study could no longer be tested. At that time point (5th December 2013) only 120 patients had entered the trial, 6 of those patients had completed the trial and 38 patients were observed for 6 months or longer. The actual total observation time in this study was 41 patient-years which is only approximately 20% of the theoretically possible 200 patient-years. Therefore, the available data were very limited which has to be taken into consideration when interpreting the results.

Although the proportion of patients with hospitalizations or emergency room visits from COPD exacerbations was numerically higher for patients in the remote patient monitoring group compared to patients in the usual care (31.1% vs. 23.7%, corresponding to 19 and 14 patients, respectively), this finding has to be interpreted considering the before-mentioned limitations of available data; in particular the low difference in the absolute number of patients with such events does not allow any firm conclusion. The same applies for the difference in the number of hospitalizations or emergency room visits which was slightly higher in the remote patient monitoring group compared to the usual care group (26 vs. 23 events, respectively), and for the higher event rate per 100 patient years in the remote patient monitoring group compared to the usual care group (136.2 vs. 102.3).

Two deaths were reported during the study. One patient randomized to the remote patient monitoring system user group died due to respiratory failure; this event was not suspected to be related to the study device. Another patient who randomized into the usual care group died due to lung cancer.
Overall, no meaningful differences between both study arms were seen for any safety investigations.
Conclusion:
• Because of the premature termination of the study, the available data is very limited and the primary efficacy hypothesis of the study (to detect a 50% reduction in the rate of hospitalizations and/or emergency room visits from COPD exacerbations in the remote patient monitoring system incorporating EXACT arm compared to the usual care arm) could not be tested.
• The number of hospitalizations or ER visits as well as the proportion of patients with hospitalizations or ER visits from COPD exacerbations were numerically higher for patients using the remote patient monitoring compared to patients using usual care. Also the event rate per 100 patient years was higher in the RPM group compared to the usual care group.
• No meaningful differences between both study arms were seen for any safety investigations.

Date of Clinical Trial Report
02-Jul-2014 (content final)

Date of Initial Inclusion on Novartis Clinical Trial Results website
24-Nov-2014

Date of Latest Update
Not applicable

Reason for Update

Not applicable