Non-Interventional Study (NIS) Results

Correlation Between Patient Perception Of The Ability To Perform Morning Activities And Findings On Clinical Examination In COPD Patients – RELIEF Study

ROMANIA

Protocol: NIS-RRO-ATC-2012/1

Version: 1.1

1. List of abbreviations and definition of terms

Abbreviation or special term	Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
CDLM	Capacity of Daily Living during the Morning
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form (electronic/paper)
FAS	Full Analysis Set
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
Group C	patients with high risk and fewer symptoms (GOLD classification)
Group D	patients with high risk and more symptoms (GOLD classification)
LABA/ICS	Long acting β2-agonist/inhaled corticosteroid combination
NIS	Non-Interventional Study
PP	Per-Protocol Population
SD	Standard deviation

2. Objectives

(a) Primary objective

To evaluate if there is positive correlation between improvement on the CDLM score and improvement of the general health status visual scale (assessed by clinician during the regular physical exam).

(b) Secondary objectives

1. To evaluate the percentage of patient which register improvement, using CDLM and general health status visual scale.

2. To evaluate adherence to ICS/LABA treatment in general in COPD patients based on group C and D categorization according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines Revised 2011. Group C patients are those with high risk and few symptoms; Group D patients have high risk and more symptoms.

3. To evaluate the effort tolerance of patients with COPD, group C and D according to GOLD Guidelines Revised 2011, by using a pedometer to measure the dynamics of daily walking distance .

4. To evaluate the incidence and impact of COPD exacerbation during the study.

3. Study Design and Subject Population

This was a multi-center, prospective, non-interventional study to evaluate, in daily clinical practice, systematic treatment for 12 weeks of combined therapy (LABA/ICS) administered in COPD patients groups C and D, according to GOLD Guidelines Revised 2011.

The study consisted of a Baseline visit and 3 follow-up visits.

Patients in the study were aged 40 years of age or older diagnosed with grade C or D COPD according to the GOLD Guidelines Revised 2011 who had smoked for at least 10 pack years and who were receiving inhaled combined therapy for their COPD. The inhaled combined therapy (corticosteroid / LABA/ICS) treatment was initiated at least 1 month before entering in the study.

The study sites were located in Romania.

3.1. Variables

3.1.1. Primary variables

- Total CDLM score

- Physician evaluation of patient general health status visual scale

3.1.2. Other variables

- Demographic patient characteristics (age, gender, date of diagnosis, patient group at diagnosis, co-morbidities, concomitant medications, and relevant supportive therapies
- Unscheduled visit (exacerbations, emergency visits)
- Measurement of walking steps (by using pedometers)
- Registration and evaluation of administered combined therapy (inhaled corticosteroid/ LABA/ICS)
- Patient adherence to treatment (by using visual 5 point scale).

3.1.3. CDLM Questionnaire

At Visit 1, each subject was instructed as to how to complete the questionnaires, and completed the first CDLM at this visit (this constituted the baseline evaluation), and also received the questionnaires that they were to complete by the next study visit.

Subjects were instructed to fill in the CDLM questionnaires at a specific time each day, (preferably at about noon). In the interval between study visits, subjects completed the CDLM questionnaire on 7 consecutive days per month, specifically in weeks 4, 8 and 12 of the study period.

In order to complete the self-administered CDLM questionnaires, the patients were required to:

1) Report on their ability to carry out 6 different morning activities and
2) Rank the difficulty of performing each of these activities on a 5-point Likert-type scale ranging from 0 (not at all difficult) to 4 (extremely difficult).

There was no weighting of the different morning activities; the total CDLM score was calculated as the average of all morning activities. The total CDLM score was calculated as described in Statistical Methods.

3.1.4. Registration of walking steps

The pedometers registered the total daily walking steps. On the morning of the days when the CDLM was completed, the subject reset the device and at the end of the day recorded the number of steps that had been walked in the daily activities monitoring calendar.

4. Reporting of Adverse Events

Only spontaneously mentioned adverse events were reported. No specific safety evaluations were performed in this study.

5. Statistical Methods

This study evaluated the potential positive correlation between improvement perceived by the patient (as measured by the CDLM total score) and improvement observed by the treating physician (as measured by the patient general health status score), using the bivariate correlation test.

The statistical analysis was mainly descriptive. If statistical tests were used, they were performed 2-sided on a 5% level. No adjustment for multiple testing was done. Appropriate methods were used to derive confidence intervals, depending on the nature of the data and distribution.

Continuous data were described by their mean, standard deviation (SD), median, lower and upper quartile, minimum and maximum and valid cases. Categorical data were described by absolute and percentage number of subjects per category.

5.1. Main Summary Measures

5.1.1. Analysis Sets

The All Subjects population was defined as all enrolled subjects.

The Full Analysis Set (FAS) is defined as all enrolled and eligible subjects.

The Per-Protocol Population (PP) is defined as all enrolled and eligible subjects who had non-missing primary variables up to Visit 4.

The FAS was used for all tables except the primary variables tables where PP was used.

5.1.2. CDLM Score evaluation

Patients were instructed to complete the questionnaire once all morning activities were performed . The responses from the 2 questions for each morning activity were used to calculate a score that can vary from 0 (so difficult that the activity could not be carried out by the patient on their own) to 5 (activity was not all difficult to carry out).

For each of the six morning activities the score was calculated using the responses from the 2 questions for each morning activity.

The daily score of CDLM was calculated as mean score of all 6 activities with non-missing answers. A daily score was set to missing if more than 1 answer was missing. The CDLM total score was calculated as the mean of the non-missing daily scores. The CDLM total score was set to missing if more than 2 daily scores were missing

5.1.3. Measurements of study variables

5.1.3.1. Primary variables

The correlation between improvement perceived by the patient (CDLM total score) and improvement observed by the treating physician (evaluation on the patient general health status score) was calculated using the bivariate correlation (Kendall tau-b) test at all visits for the PP population.

5.1.3.2. Secondary variables

1. To evaluate the percentage of patient which registered improvement, descriptive statistics of the CDLM total score and general health status score were tabulated per visit.
2. To evaluate adherence to ICS/LABA treatment in general in COPD patients group C and D according to GOLD Guidelines Revised 2011 descriptive statistics were tabulated per visit.
3. To evaluate the effort tolerance of patients with COPD, descriptive statistics of the daily average of the number of steps recorded by the pedometer were tabulated per visit.
4. To evaluate the incidence of COPD exacerbation during the study descriptive statistics were tabulated per visit.

5.2. Study Population Characteristics

5.2.1. Subject Disposition

Subject Disposition data was summarized using absolute counts (n) and percentages (%). Percentages were based on the number of subjects with data. The descriptive statistics were used for the patient number of different visits and the patient number signed the informed consent.

5.2.2. Demographics and Subject Characteristics

Subject demographics were assessed in a descriptive manner for the analysis population. The following sections describe the variables that were analyzed.

5.2.2.1. Enrolment Summary

The numbers of subjects enrolled and eligible for the analysis population were summarized; the reasons for exclusion from the analysis population were presented in a data listing.

5.2.2.2. Demographics

All demographic and background data were summarized using contingency tables for the qualitative variables (sex) and the mean, SD, median, minimum and maximum for the quantitative variables (age, physical examination, vital signs). The following demographic information were summarized: sex, age (years), year of COPD diagnosis, actual stage of COPD.

5.2.2.3. Medical History

Medical history is provided in a data listing.

5.2.2.4. Prior Medications administrated for COPD

Medications that subjects received were tabulated and also provided in a data listing.

6. Results

6.1. Study Population

A total of 505 subjects participated in the study. Overall, 489 subjects (96.8%) completed the study (ie, attended Visit 4), as summarized in Table 1.

Table 1. Number of patients at each visit

Visit	Number (%) of patients
1	505 (100)
2	499 (98.8)
3	492 (97.4)
4	489 (96.8)

The reasons for discontinuation from the study are summarized in Table 2. The most frequently reported reason for discontinuation was the investigator's decision.

Table 2. Reasons for Discontinuation

Reason for study termination	Number (%) of patients
Patient's consent withdrawal	3 (0.6)
Investigator's decision	10 (2)
Sponsor's decision	0 (0)
Death	2 (0.4)

All 505 subjects were included in the FAS population (Table 3). A total of 259 subjects (51.3%) were eligible for inclusion in the Per-Protocol Population due to incomplete data.

Table 3. Populations for Analysis

Population	Number (%) of patients
All Patients Population	505 (100)
FAS	505 (100)
PP	259 (51.3)

6.2. Demographics and Baseline Characteristics

The majority of subjects were male (430 subjects, 85.1%) and a total of 75 subjects were female (14.9%). The average age of the subjects was 65 years (range: 40 to 88 years). Mean height at baseline was 170 cm (range: 145 to 189 cm) and mean body weight was 76.92 kg (range: 45 to 145 kg). The majority of subjects (74.7%) self-reported as ex-smokers, with the remainder being largely current smokers (24.8%). A small proportion of subjects failed to answer the question (0.6%).

Among subject who smoked, the mean was 1 pack (20 cigarettes) per day (9). The maximum number of cigarettes per day was 90. This correlated to a mean number of pack years of 34.69 (range: 10 to 300).

The average duration of COPD was 5.31 years, ranging from 0 to 40 years .

Overall, the majority of subjects were in group C (308 subjects, 61%); a total of 197 subjects were in group D (39%).

Most of the subjects (363, 71.9%) had experienced at least 1 exacerbation of their COPD within the previous 12 months. The mean number of exacerbations was 2 (range: 1 to 12).

With regards to COPD medications, the majority of subjects (54.3%) were using salmeterol/fluticasone, while 45.7% were taking budesonide/formoterol. The mean duration of combined inhaled therapy was 36.18 months (range: 1 to 151.7 months).

Other COPD medications (ie, not combined inhaled therapy) are summarized in Table 4. The most frequently reported was long acting anticholinergic for 199 subjects (39.4%).

Table 4. Other COPD medications

Other COPD medications	Number (%) of patients
Short acting β_2 - agonist	142 (28.1)
Long acting β_2 - agonist	8 (1.6)
Short acting anticholinergic	12 (2.4)
Long acting anticholinergic	199 (39.4)
Methylxanthines	131 (25.9)
Inhaled corticosteroids	1 (0.2)
Systemic corticosteroids	0 (0)
Combination short acting β_2 – agonist plus anticholinergic in one inhaler	28 (5.5)
Phosphodiesterase-4 inhibitor	10 (2)

6.3. Changes from Baseline

6.3.1. Comorbidities

The change in the proportion of subjects reporting comorbidities from Visit 1 through Visit 4 was small, as summarized in Table 5. At Visit 1, 67.9% of patients reported comorbidities, and this proportion was 65.8% at Visit 4.

Table 5. Summary of Proportions of Subjects With Comorbidities at all Study Visits

	Visit 1	Visit 2	Visit 3	Visit 4
No comorbidities	162 (32.1)	167 (33.5)	167 (33.9)	167 (34.2)
With comorbidities	343 (67.9)	332 (66.5)	325 (66.1)	322 (65.8)

The most frequent comorbidity was Hypertension for 190 subjects (38.2%) at Visit 1. The most frequently reported comorbidities are summarized in Table 6.

Table 6. Most frequent comorbidities

	Visit 1	Visit 2	Visit 3	Visit 4
Atrial fibrillation	18 (3.6)	17 (3.4)	17 (3.5)	17 (3.5)
Cardiac failure	16 (3.2)	15 (3)	15 (3)	14 (2.9)
Chronic obstructive pulmonary disease	35 (6.9)	34 (6.8)	33 (6.7)	33 (6.7)
Cor pulmonale	53 (10.5)	52 (10.4)	51 (10.4)	51 (10.4)
Diabetes mellitus	32 (6.3)	30 (6.3)	29 (5.9)	29 (5.9)
Hypercholesterolaemia	20 (4)	19 (3.8)	19 (3.9)	19 (3.9)
Hypertension	193 (38.2)	189 (37.9)	186 (37.8)	184 (37.6)
Myocardial ischaemia	104 (20.6)	102 (20.4)	99 (20.1)	99 (20.2)

The most frequently used medication used for comorbidities was trimetazidine (54 subjects, 10.7%).

In general, the proportions of subjects reporting signs of obstruction decreased from Visit 1 to Visit 4, as summarized in Table 7.

Table 7. Proportions of subjects with signs of obstruction, Visit 1 to 4

	Visit 1	Visit 2	Visit 3	Visit 4
Prolonged expiration	438 (86.7%)	407 (81.6%)	403 (81.9%)	405 (82.8%)
Sibilant rales	223 (44.2%)	169 (33.9%)	152 (30.9%)	152 (31.1%)
Sonorous rales	273 (54.1%)	183 (36.7%)	190 (38.6%)	169 (34.6%)

The percentages of patients with signs of hyperinflation did not significantly chance from Visit 1 to Visit 4, as summarized in Table 8.

Table 8. Signs of hyperinflation

	Visit 1	Visit 2	Visit 3	Visit 4
Increased antero-posterior chest diameter	385 (76.2%)	371 (74.3%)	363 (73.8%)	363 (74.2%)
Hypersonority at percution	347 (68.7%)	318 (63.7%)	330 (67.1%)	310 (63.4%)
Diminished vesicular murmur	329 (65.1%)	329 (65.9%)	327 (66.5%)	319 (65.2%)
Attenuation of cardiac sounds	203 (40.2%)	178 (35.7%)	180 (36.6%)	171 (35%)

The percentages of patients with signs of cor pulmonale decreased from Visit 1 to Visit 4, as summarized in Table 9. The change in Oedemas was a significant decrease: -4.3% (p-value: 0.0391).

Table 9. Signs of cor pulmonale

	Visit 1	Visit 2	Visit 3	Visit 4
Oedemas	170(13.9%)	44(8.8%)	49(10%)	47 (9.6%)
Right ventricular gallop	44(8.7%)	33 (6.6%)	35(7.1%)	36(7.4%)
Hepatomegaly	103 (20.4%)	90 (18%)	86(17.5%)	82(16.8%)

The percentages of patients with respiratory insufficiency slightly decreased from Visit 1 to Visit 4, as summarized in Table 10. However, there were no significant changes from Visit 1 to Visit 4 regarding respiratory insufficiency.

Table 10. Signs of respiratory insufficiency

	Visit 1	Visit 2	Visit 3	Visit 4
Turgid jugular veins	108 (21.4%)	101 (20.2%)	93 (18.9%)	91 (18.6%)
Central Cyanosis	131 (25.9%)	117 (23.4%)	112 (22.8%)	114 (23.3%)
Tremor	85 (16.8%)	72 (14.4%)	69 (14%)	73 (14.7%)
Altered consciousness	3 (0.6%)	0 (0%)	2 (0.4%)	1 (0.2%)

With regards to the LABA/ICS treatment and other COPD treatments during the study, there was very little change from Visit to Visit 4.

6.3.2. Primary Objective

The correlation between the CDLM total score and the 5-scale general health status score was investigated at every visit using the Kendall tau-b correlation test (Table 11). A significant positive correlation was identified on every visit, with a range from 0.2269 to 0.3181 of Kendall tau-b values, implying a weak-to-moderate positive connection between the 2 parameters.

Table 11. **CDLM vs general health status score**

	tau-b value	p-value
Visit 1	0.3181	<.0001
Visit 2	0.2620	<.0001
Visit 3	0.2269	<.0001
Visit 4	0.2537	<.0001

6.3.3. Secondary Objectives

Secondary objectives are analysed in the FAS population (N=505 subjects). However, CDLM and health status, adherence to treatment changes, and p-values between visits are calculated within the PP population (N=259).

6.3.3.1. CDLM Questionnaire

In the FAS analysis, at Visit 1, the mean CDLM score was 3.68, increasing to 3.96 at Visit 4 (Table 12).

Table 12. CDLM total score (FAS)

	Visit 1	Visit 2	Visit 3	Visit 4
n	394	395	396	373
Mean (std)	3.68 (0.97)	3.89 (0.87)	3.97 (0.91)	3.96 (0.89)
Median	3.8	3.93	4.065	4.03
Q1, Q3	3, 4.5	3.25, 4.63	3.36, 4.81	3.46, 4.78
Min, Max	0.83, 5	1.05, 5	0.6, 5	0.48, 5

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In the PP population analysis, at Visit 1, the mean CDLM score was 3.79, increasing to 3.95 at Visit 4 (Table 13).

Table 13. CDLM total score (PP)

	Visit 1	Visit 2	Visit 3	Visit 4
n	259	259	259	259
Mean (std)	3.79 (0.93)	3.94 (0.86)	3.96 (0.93)	3.95 (0.92)
Median	4	4.04	4.06	4.03
Q1, Q3	3, 4.5	3.33, 4.74	3.33, 4.85	3.33, 4.83
Min, Max	1.17, 5	1.05, 5	0.6, 5	0.48, 5

The change of the CDLM total score between visit 1 and visit 4 was significant (based on the Wilcoxon signed rank test), with a mean change of 0.16 (p-value 0.0015).

6.3.3.2. General health status

The general health status for the patients was indicated using a scale of 5 levels (1= very bad, 5= very good) as evaluated by the investigators at each visit.

For the FAS analysis, at Visit 1, 41.2% of patients had a score of 4/5. The proportion increased at each visit, and reached 57.4% at Visit 4, as summarized in Table 14.

Table 14. General health status score (FAS)

General health status score [N(%)]	Visit 1	Visit 2	Visit 3	Visit 4
1	6 (1.2)	5 (1)	7 (1.4)	2 (0.4)
2	50 (9.9)	43 (8.6)	29 (5.9)	36 (7.4)
3	241 (47.7)	205 (41.1)	194 (39.4)	170 (34.8)
4	143 (28.3)	156 (31.3)	167 (33.9)	183 (37.4)
5	65 (12.9)	90 (18)	95 (19.3)	98 (20)

Results were similar for the PP population analysis, with the percentage of patients with a score of 4/5 of 50.9% at Visit 1, increasing to 64.8% at Visit 4.

The improvement in health status improvement from Visit 1 to Visit 4 was significant (based on the Wilcoxon signed rank test).

6.3.3.3. Adherance to ICS/LABA treatment

The level of adherence to ICS/LABA treatment by the patients was indicated on a scale of 5 levels (from 0% to 100%) by the investigators following a discussion with the patient.

In the FAS analysis, at Visit 1, 93.1% of subjects were considered to be adhering to their treatment from 75%/100%. At Visit 4, this proportion had increased to 98.2%.

Results were similar for the PP population analysis, with 95.8% of patients adhering at the level of 75%/100%, increasing to 98.5% by Visit 4. The analysis of the changes at each visit (by number and % of subjects) showed a significant improvement for the PP population (based on the Wilcoxon signed rank test).

6.3.3.4. Effort Tolerance

Patients used a pedometer to measure their daily walking distance on 7 consecutive days between the visits. The mean of the daily averages of number of steps on Visit 2 was 3014.65 and decreased to 2695.26 on Visit 4.

The difference of daily averages of number of steps between the visits was significant (based on Wilcoxon signed rank test).

6.3.3.5. COPD Exacerbations During the Study

The change in incidence and impact of COPD exacerbations was small, with the percentage of subjects with exacerbations ranging from 8% to 9.6% across all visits. Less than 1% of subjects reported to the ER for COPD exacerbations; ≤1.1% of subjects required hospitalization because of a COPD exacerbation, and less than 1.5% of subjects visited a physician due to a COPD exacerbation .