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2. SYNOPSIS

Name of Company: Chiesi Farmaceutici S.p.A. **Name of Finished Product:** NEXThaler® **Name of Active Ingredient:** NA	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(for National Authority Use only)*
Title of Study: An Open Label Placebo Study To Assess The Inhalation Profile Obtained By Acoustic Monitoring In COPD Patients Using The NEXThaler® Dry Powder Inhaler (DPI) Device		
Investigators: One Principal Investigator in Italy		
Study Centre(s): One investigational study site in Italy		
Publication (reference): None		
Studied Period: FPFV: 03 Dec 2013; LPLV: 26 Jun 2014	**Phase of development:** IIa	

Objectives:

Primary:

The primary objective of this study was to assess the inspiration profile through the NEXThaler® device in COPD patients with varying degrees of airflow limitation as per GOLD 2013 (updated) spirometric classification of disease severity.

Secondary:

The secondary objective of the study was to evaluate the potential correlation between the lung function parameters measured by spirometry at clinic and the variables measured by acoustic monitoring technology during the inspiratory manoeuvre.

Methodology (Study Design):

This was a phase IIa, single-centre, open-label, single-arm, investigational, placebo study, to evaluate the inspiration profile through the NEXThaler® device in COPD patients with varying degrees of airflow limitation as per GOLD 2013 (updated) spirometric classification of disease severity. The study plan included one visit at clinic. After the signature of the informed consent form, the patient was instructed to the correct use of NEXThaler® and inclusion/exclusion criteria were checked. If the patient was eligible, the lung function parameters were evaluated. The patient then subsequently inhaled through the device and the inspiration profile was measured.

Number of patients (planned and analyzed):

A minimum of 70 to a maximum of 80 completed patients were planned to be recruited, ensuring the following distribution in terms of COPD Stage as per GOLD 2013 (updated) spirometric classification of disease severity:

- 10 to 20 COPD GOLD Stage I patients
- 20 patients in each of the COPD GOLD Stage II to IV.

72 patients were actually enrolled divided in the four GOLD stage groups as shown below:

	GOLD stage I	GOLD stage II	GOLD stage III	GOLD stage IV	Total
Enrolled	21	20	21	10	72
Safety population	21	20	21	10	72
Per-protocol population	19	20	20	10	69
Completed	21	20	21	10	72

Diagnosis and main criteria for inclusion:

1. Written informed consent obtained from the patient and/or the legal representatives;
2. Inpatients and outpatients of both sexes, aged ≥ 40 years;
3. Documented clinical diagnosis of COPD with varying degrees of airflow limitation based on spirometric classification of disease severity according to GOLD 2013 (updated) guidelines with a smoking history of at least 10 pack years (pack-years = the number of cigarette packs smoked per day multiplied by the number of years). Current smokers and ex-smokers were eligible;

4. A cooperative attitude and ability to use DPIs and to be trained in the proper use of the NEXThaler® as confirmed by the activation of breath actuated mechanism (BAM) of the NEXThaler® training device.

Test product, dose and mode of administration, batch number:

Placebo NEXThaler® DPI (Chiesi Farmaceutici S.p.A.). At the study visit all patients received 2 inhalations.

Batch numbers: refer to Appendix 16.1.6.

Duration of treatment: Single dose

Reference therapy, dose and mode of administration, batch number: [redacted]

Criteria for evaluation:

Analysis variables:

- Variables measured by acoustic monitoring technology through the NEXThaler® during the inspiratory manoeuvre:
  - Flow and time to BAM firing;
  - Peak inspiratory flow (PIF) and time to PIF;
  - Initial acceleration (rate of change of flow at inhalation start);
  - Total inhaled volume and inhalation time;
  - Inspiratory flow rate by time.
- Pulmonary function by spirometry: FEV_1, FEV_1 percent of predicted normal value, FVC, FVC percent of predicted normal value, FEV_1/FVC ratio, PEF, PEF percent of predicted normal value and PIF.
- Device usability by means of a physician-assessed questionnaire.

Safety variables:

The safety variable of the study was:

- Adverse events (AEs).

Statistical methods

Analysis variables

The following populations were considered for data analysis: Safety population, which included all patients who received the study medication; Per-Protocol population (PP), which included all patients from the Safety population, excluding patients without any valid evaluation of inhalation profile or with major protocol deviations significantly affecting this assessment. Acoustic monitoring and spirometry variables, and device usability, were analysed on the PP population. Analysis of safety variables was performed in the Safety population.

All the analyses were performed separately for the first and the second inhalation.

Acoustic monitoring variables (flow at and time to BAM firing, PIF and time to PIF, initial acceleration, total inhaled volume and inhalation time, inspiratory flow rate by time) and spirometry variables (FEV_1, FEV_1 % of predicted normal value, FVC, FVC % of predicted normal value, FEV_1/FVC ratio, PEF, PEF % of predicted normal value and PIF) were summarised using descriptive statistics and the 95% confidence interval (CI) of the mean, overall and by COPD GOLD stage.

Correlations between PIF from spirometry and PIF measured by acoustic monitoring technology, and between the variables measured by acoustic monitoring technology, were evaluated separately for the first and the second inhalation using Spearman's rank correlation coefficient, presented with its 95% CI and p-value.

The number and percentage of patients with positive/negative answers to the usability evaluation questionnaire were presented overall and by COPD GOLD stage.

Safety variables

The number and percentage of patients experiencing AEs, adverse drug reactions (ADRs), serious AEs (SAEs) and AEs leading to study withdrawal were to be summarised by System Organ Class and Preferred Term.

Study population:

Seventy-two patients in total were enrolled in the study. Twenty-one patients were in COPD GOLD stage I, 20 in stage II, 21 in stage III and 10 in stage IV. All enrolled patients completed the study.

Extent of exposure and compliance:

Extent of exposure: each patient performed at least 2 inhalations of placebo using the NEXThaler® DPI device.

Compliance: patients underwent the study procedures under supervision of the study personnel.

Summary – Conclusions:

Baseline spirometry measurements

The mean FEV_1 % predicted was 73.4 in GOLD stage I, 50.5 in GOLD stage II, 36.5 in GOLD stage III, and 22.4 in GOLD stage IV. The mean FEV_1/FVC ratio was 0.61 in GOLD stage I, 0.56 in GOLD stage II, 0.47 in GOLD stage III, and 0.36 in GOLD stage IV. The same trend (i.e. a decrease in mean values with increasing severity) was observed for the other spirometric parameters (FVC, PEF and PIF).

Results of acoustic monitoring

The profiles of mean inspiratory flow rate over time up to BAM firing were consistent across all GOLD stage groups. The curve profile in the first and in the second inhalation was similar in all subgroups of patients based on GOLD stage, except for patients in GOLD stage IV, in which mean values after BAM firing were higher in the first inhalation than in the second one.

The results of acoustic monitoring are presented in the table below.

The mean flow at BAM firing was similar in patients in all GOLD stages at both the first (mean values in the range 40.27 – 44.76 L/min) and the second (mean values in the range 40.79 – 43.59 L/min) inhalation.

At the first inhalation, the mean PIF was slightly higher in patients in GOLD stages I and II than in patients in GOLD stages III and IV (74.08 L/min in stage I, 69.13 L/min in stage II, 63.47 L/min in stage III, and 63.51 L/min in stage IV). At the second inhalation, the mean PIF was lower in patients in GOLD stage IV than in the other subgroups (71.87 L/min in stage I, 70.51 L/min in stage II, 66.43 L/min in stage III, and 55.28 L/min in stage IV).

No relevant differences between GOLD stages were found in time to BAM firing and time to PIF.

Mean values for initial acceleration were consistent across all GOLD stages without any significant difference between first and second inhalation. Mean values for this parameter were in the range of 140.3 – 158.7 L/min/s for the first inhalation and of 124.8 – 143.5 L/min/s for the second inhalation.

The mean total inhaled volume was higher and the median total inhalation time was longer in patients in GOLD stage I than in patients in the other subgroups at both the first and the second inhalation.

Results of acoustic monitoring variables (PP population)

	GOLD stage I N=19	GOLD stage II N=20	GOLD stage III N=20	GOLD stage IV N=10	Total N=69
Flow at BAM firing, *L/min*					
First inhalation					
Mean ± SD	42.90 ± 6.38	40.27 ± 4.20	41.05 ± 7.04	44.76 ± 7.52	41.87 ± 6.29
Median (range)	42.00 (28.8-52.1)	40.45 (33.8-50.9)	42.15 (18.1-51.4)	46.50 (29.2-56.2)	41.50 (18.1-56.2)
Second inhalation					
Mean ± SD	43.59 ± 7.38	40.79 ± 5.56	43.39 ± 5.24	41.03 ± 6.92	42.38 ± 6.20
Median (range)	42.95 (32.5-57.1)	39.50 (26.6-47.4)	43.35 (34.1-56.5)	40.50 (30.1-48.6)	42.95 (26.6-57.1)
PIF, *L/min*					
First inhalation					
Mean ± SD	74.08 ± 20.79	69.13 ± 17.67	63.47 ± 14.96	63.51 ± 20.15	68.04 ± 18.38
Median (range)	72.40 (47.7-125.4)	66.60 (45.3-103.4)	61.20 (40.5-97.5)	63.00 (31.5-104.5)	66.30 (31.5-125.4)
Second inhalation					
Mean ± SD	71.87 ± 22.12	70.51 ± 12.91	66.43 ± 17.84	55.28 ± 14.31	67.57 ± 17.92
Median (range)	66.20 (45.1-135.9)	69.80 (45.4-90.7)	63.20 (41.3-101.7)	54.20 (32.0-82.3)	64.60 (32.0-135.9)
Time to BAM firing, *s*					
First inhalation					
Mean ± SD	0.17 ± 0.14	0.17 ± 0.12	0.18 ± 0.12	0.20 ± 0.14	0.18 ± 0.13
Median (range)	0.10 (0.06-0.49)	0.14 (0.05-0.49)	0.16 (0.02-0.63)	0.14 (0.07-0.49)	0.13 (0.02-0.63)
Second inhalation					
Mean ± SD	0.20 ± 0.12	0.15 ± 0.07	0.22 ± 0.16	0.17 ± 0.08	0.19 ± 0.12
Median (range)	0.21 (0.06-0.53)	0.13 (0.05-0.31)	0.16 (0.07-0.72)	0.15 (0.05-0.31)	0.16 (0.05-0.72)
Time to PIF, *s*					
First inhalation					
Mean ± SD	0.72 ± 0.34	0.64 ± 0.26	0.63 ± 0.30	0.57 ± 0.17	0.65 ± 0.28
Median (range)	0.58 (0.38-1.56)	0.54 (0.36-1.17)	0.54 (0.11-1.46)	0.53 (0.42-0.99)	0.54 (0.11-1.56)
Second inhalation					
Mean ± SD	0.71 ± 0.35	0.63 ± 0.21	0.68 ± 0.31	0.53 ± 0.24	0.65 ± 0.29
Median (range)	0.56 (0.38-1.70)	0.60 (0.36-1.31)	0.63 (0.11-1.37)	0.45 (0.19-1.05)	0.59 (0.11-1.70)
Initial acceleration, *L/min/s*					
First inhalation					
Mean ± SD	155.6 ± 65.5	140.3 ± 55.1	140.4 ± 37.4	158.7 ± 42.4	147.2 ± 51.8
Median (range)	158.4 (38.7-296.5)	160.7 (42.1-238.7)	134.5 (89.0-219.1)	163.1 (91.9-214.3)	153.9 (38.7-296.5)
Second inhalation					
Mean ± SD	143.5 ± 64.6	133.8 ± 51.7	136.9 ± 53.6	124.8 ± 22.6	136.2 ± 52.6
Median (range)	143.3 (42.3-297.6)	138.4 (17.7-202.6)	148.4 (15.4-222.8)	125.5 (93.3-170.4)	139.8 (15.4-297.6)
Total inhaled volume, *L*					
First inhalation					
Mean ± SD	2.28 ± 0.67	1.70 ± 0.60	1.75 ± 0.73	1.51 ± 0.62	1.85 ± 0.70
Median (range)	2.27 (1.27-4.05)	1.68 (0.51-2.66)	1.82 (0.38-3.65)	1.57 (0.31-2.26)	1.79 (0.31-4.05)
Second inhalation					
Mean ± SD	2.15 ± 0.76	1.73 ± 0.54	1.73 ± 0.56	1.23 ± 0.62	1.78 ± 0.67
Median (range)	2.05 (1.18-4.36)	1.87 (0.68-2.42)	1.88 (0.65-2.83)	1.45 (0.17-1.97)	1.84 (0.17-4.36)
Total inhalation time, *s*					
First inhalation					
Mean ± SD	2.90 ± 0.68	2.29 ± 0.60	2.39 ± 0.79	2.12 ± 0.80	2.47 ± 0.75
Median (range)	2.73 (1.86-4.24)	2.38 (0.96-3.34)	2.33 (0.98-4.03)	2.21 (0.77-3.20)	2.51 (0.77-4.24)
Second inhalation					
Mean ± SD	2.77 ± 0.62	2.28 ± 0.63	2.37 ± 0.68	1.91 ± 0.88	2.39 ± 0.72
Median (range)	2.68 (1.87-4.30)	2.33 (1.18-3.50)	2.40 (1.45-3.78)	2.11 (0.46-3.09)	2.44 (0.46-4.30)

Analysis of correlation

Significant correlations at both the first and second inhalation were detected between the following variables (see Table below):

Variables	First inhalation		Second inhalation	
	Spearman correlation coefficient	p-value	Spearman correlation coefficient	p-value
Flow at BAM firing – PIF from acoustic monitoring	0.43	<0.001	0.36	0.003
Flow at BAM firing – Total inhaled volume	0.34	0.003	0.30	0.012
Time to BAM firing – Time to PIF	0.61	<0.001	0.58	<0.001
Time to BAM firing – Initial acceleration	-0.32	0.006	-0.33	0.006
PIF from acoustic monitoring – Total inhaled volume	0.64	<0.001	0.61	<0.001
Time to PIF – Total inhalation time	0.24	0.043	0.42	<0.001
Total inhaled volume – Total inhalation time	0.79	<0.001	0.83	<0.001

The strongest levels of correlation were observed between total inhaled volume and total inhalation time, PIF from acoustic monitoring and total inhaled volume and time to BAM firing and time to PIF.

Device usability

There were generally no concerns reported in regard to the functionality and usability of the study device. Only for one patient overall (1.4%) in the GOLD stage II subgroup it was reported by the physician that the mouthpiece size did not well fit to user.

Safety Results

No AEs were reported in this study.

Conclusions:

- All patients in all GOLD stage subgroups had a PIF above the BAM activating value, indicating that all subjects regardless of their functional limitation were able to effectively use the device.
- The profiles of mean inspiratory flow rate over time up to BAM firing were consistent across all GOLD stage groups. Since in vitro testing has shown that once the BAM is activated, all the powder is effectively released, our results confirm that such critical activation event is triggered independently of patient functional limitation.
- No substantial differences between the inspiratory profiles measured in the first and in the second inhalation manoeuvres were found in all subgroups of patients based on GOLD stage, except for patients in GOLD stage IV, in which the mean flow rate after BAM firing was generally higher in the first inhalation. Since this difference is observed only after BAM activation, its relevance is to be considered rather negligible in regards to the effective delivery of the drug, further highlighting that all patients are capable of effectively activating the device regardless of their functional limitation.
- All patients, irrespective of functional status, reached consistent values of acceleration, an additional critical factor in determining effective powder de-aggregation further confirming the device flow-independent characteristics
- The overall acceptability of the device was very high further supporting the ease of use of NEXThaler® in the target population.
- The inhalation of placebo via the NEXThaler® DPI did not lead to any AEs.

Date of the report: 15 December 2014