2. SYNOPSIS

Name of Company: Chiesi Farmaceutici S.p.A.	**Individual Study Table Referring to Part of the Dossier**	*(for National Authority Use only)*
Name of Finished Product: NEXThaler® DPI	**Volume:**	
Name of Active Ingredient: Not applicable (placebo)	**Page:**	

Title of Study: An open label placebo study to assess the inhalation profile obtained by acoustic monitoring in asthmatic patients using the NEXThaler® dry powder inhaler (DPI) device

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Publication (reference): Not applicable

Studied Period:	**Phase of development:** IIa
FPFV: 27/JUN/2012 LPLV: 17/SEP/2012	

Objectives:

The primary objective of this study was to assess the inspiratory flow profile through the NEXThaler® device in adult asthmatics with different degrees of disease control.

Methodology *(Study Design):*

This was a phase IIa, single-centre, open-label, single-arm study, to evaluate the inspiration profile through the NEXThaler® device in adult asthmatic patients with different degrees of disease control.

The study included one visit at the clinic. Following the signature of the informed consent form, the inclusion/exclusion criteria were checked and lung function parameters were evaluated. If the subjects met the inclusion/exclusion criteria, they were instructed to use the NEXThaler®. The patients subsequently inhaled through the device and the inspiration profile was measured.

Number of patients *(planned and analysed)*:

Planned:

40 patients (20 with controlled stable disease and 20 with partly controlled or uncontrolled disease according to GINA guidelines, 2011)

44 patients were to be screened in order to have 40 patients completed (assuming a screening

failure/drop-out rate of 10%; a drop-out patient was defined as an enrolled patient who did not perform two evaluable inhalations)

Analysed:

Safety population: 41 patients (21 patients with controlled disease and 20 patients with partly controlled or uncontrolled disease)

Per Protocol (PP) population: 40 patients (20 patients with controlled disease and 20 patients with partly controlled or uncontrolled disease)

Diagnosis and main criteria for inclusion:

Written informed consent obtained from the patient and/or the legal representatives was required. Inpatients and outpatients of both sexes, aged ≥ 18 years and with a clinical diagnosis of asthma according to GINA guidelines (2011) were eligible. 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 the training device BAM) were required.

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

Test product:

NEXThaler® dry powder inhaler containing placebo

Dosing regimen:

two inhalations in the morning during the visit at the clinic

Batch number:

[redacted]

Duration of treatment:

Two inhalations during one visit

Reference therapy, dose and mode of administration, batch number:

Not applicable.

Criteria for evaluation :

- Variables measured by acoustic monitoring technology through the NEXThaler® during the inspiratory manoeuvre:
  - inspiratory flow rate by time;
  - flow at 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.
- Pulmonary function by spirometry: FEV_1, FEV_1 percent of predicted normal value, FVC, FVC percent of predicted normal value, PEF, PEF percent of predicted normal value and PIF.
- Device usability by means of a physician-assessed questionnaire.

Safety:

- Adverse events

Statistical methods:

Analysis variables

- The inspiratory flow rate by time was summarised using descriptive statistics and the 95% confidence interval (CI) of the mean. Individual time profile plots of the inspiratory flow rate and time profile plots of the mean inspiratory flow rate were presented.
- Flow at and time to BAM firing, PIF and time to PIF, initial acceleration, total inhaled volume and inhalation time were summarised using descriptive statistics and the 95% CI of the mean.
- Time to BAM firing and time to PIF were submitted to Kaplan-Meier analysis and plots were presented.
- FEV_1, FEV_1 percent of predicted normal value, FVC, FVC percent of predicted normal value, PEF, PEF percent of predicted normal value and PIF from spirometry were summarised using descriptive statistics and the 95% CI of the mean.
- Relevant correlations between variables were evaluated using the Spearman's rank correlation coefficient and graphically using scatter plots.
- Device usability was summarised using descriptive statistics.

All the analyses (except for the evaluation of correlations) were performed stratifying by disease control and overall. Variables measured by the acoustic monitoring technology during the inspiratory manoeuvre were analysed separately for the first and second inhalation.

Safety variables

According to the protocol, the number and percentage of patients experiencing adverse events (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 using the MedDRA dictionary.

Summary – Conclusions:

Baseline spirometry measurements

Patients with controlled asthma had a mean FEV_1 % of predicted normal value of 95.1% (range 70.3-112.0%) compared to 89.8% (range 55.2-111.0%) in patients with partly controlled or uncontrolled asthma. The mean FVC % of predicted normal value was 107.8% and 105.9%, respectively, and the mean PEF % of predicted normal value was 95.1% and 88.0%, respectively. The mean PIF was 350.67 L/min (controlled asthma) and 280.14 L/min (partly controlled / uncontrolled asthma).

Acoustic monitoring results

Superimposable time profiles of inspiratory flow rate were obtained in the two inhalations.

In both inhalations, generally higher inspiratory flow rates were observed over time in patients with controlled asthma compared to patients with partly controlled or uncontrolled asthma.

Patients with controlled asthma reached higher PIF rates as compared to patients with partly controlled or uncontrolled asthma during the first (mean: 70.46 vs. 58.82 L/min) and second inhalation (mean: 72.10 vs. 63.04 L/min). Also the mean initial acceleration was higher in

patients with controlled asthma vs. patients with partly controlled/uncontrolled asthma at both the first (136.82 vs. 123.52 L/min/s) and second (146.58 vs. 134.40 L/min/s) inhalation. An increased total inhaled volume (mean) was observed in patients with controlled asthma as compared to patients with partly controlled or uncontrolled asthma (first inhalation: 1.73 vs. 1.39 L; second inhalation: 1.68 vs. 1.39 L). No relevant differences were observed in the other variables measured by acoustic monitoring technology, including flow at and time to BAM firing.

Overall, the median time to BAM firing and time to PIF were 0.07 and 0.48 s in both inhalations. The mean flow at BAM firing and PIF in the overall population were 34.95 and 64.64 L/min in the 1st inhalation, and 35.36 and 67.57 L/min in the 2nd inhalation.

Acoustic monitoring variables, PP population

		Controlled asthma (N=20)	Partly controlled /uncontrolled asthma (N=20)	Total (N = 40)
Flow at BAM firing [L/min]				
First inhalation	Mean	35.39	34.51	34.95
	95% CI	(30.94, 39.83)	(30.47, 38.55)	(32.08,37.81)
	Median	37.40	33.15	36.10
Second inhalation	Mean	34.57	36.16	35.36
	95% CI	(30.27, 38.86)	(31.95, 40.36)	(32.48,38.24)
	Median	35.60	35.75	35.60
Time to BAM firing [s]				
First inhalation	Mean	0.11	0.13	0.12
	95% CI	(0.05, 0.16)	(0.07, 0.19)	(0.08,0.16)
	Median	0.06	0.08	0.07
Second inhalation	Mean	0.09	0.10	0.09
	95% CI	(0.04, 0.13)	(0.07, 0.12)	(0.07,0.12)
	Median	0.07	0.08	0.07
PIF [L/min]				
First inhalation	Mean	70.46	58.82	64.64
	95% CI	(57.25, 83.67)	(49.39, 68.24)	(56.67,72.60)
	Median	62.05	55.25	56.45
Second inhalation	Mean	72.10	63.04	67.57
	95% CI	(60.11, 84.09)	(55.16, 70.91)	(60.57,74.57)
	Median	66.50	59.95	61.60
Time to PIF [s]				
First inhalation	Mean	0.62	0.66	0.64
	95% CI	(0.48, 0.75)	(0.44, 0.89)	(0.51,0.77)
	Median	0.47	0.50	0.48
Second inhalation	Mean	0.59	0.61	0.60
	95% CI	(0.44, 0.73)	(0.50, 0.73)	(0.51,0.69)
	Median	0.46	0.56	0.48
Initial acceleration [L/min/s]				
First inhalation	Mean	136.82	123.52	130.17
	95% CI	(104.99, 168.65)	(99.83, 147.21)	(111.12,149.22)
	Median	116.30	121.45	117.80
Second inhalation	Mean	146.58	134.40	140.49
	95% CI	(122.28, 170.88)	(112.54, 156.25)	(124.77,156.20)
	Median	134.90	128.25	131.45
Total inhaled volume [L]				
First inhalation	Mean	1.73	1.39	1.56
	95% CI	(1.28, 2.17)	(1.13, 1.65)	(1.31,1.81)

	Median	1.59	1.34	1.52
Second inhalation	Mean	1.68	1.39	1.53
	95% CI	(1.28, 2.07)	(1.13, 1.65)	(1.30,1.76)
	Median	1.45	1.27	1.39
Total inhalation time [s]				
First inhalation	Mean	2.03	2.04	2.04
	95% CI	(1.64, 2.42)	(1.60, 2.49)	(1.75,2.32)
	Median	1.93	1.80	1.83
Second inhalation	Mean	1.97	1.90	1.93
	95% CI	(1.60, 2.33)	(1.51, 2.29)	(1.68,2.19)
	Median	2.00	1.68	1.82

Analysis of correlation

Significant correlations were detected between the following variables (variable 1 and variable 2) at both the first and second inhalation.

Variable 1	**Variable 2**	**Correlation coefficient**		**p-value**	
		1st inhal.	**2nd inhal.**	**1st inhal.**	**2nd inhal.**
Flow at BAM firing	Time to BAM firing	0.46	0.67	0.002	<.001
Flow at BAM firing	Initial acceleration	0.38	0.42	0.015	0.006
Time to BAM firing	PIF*	-0.49	-0.36	<.001	0.021
Time to BAM firing	Time to PIF	0.53	0.53	<.001	<.001
PIF*	Initial acceleration	0.86	0.73	<.001	<.001
PIF*	Total inhaled volume	0.51	0.34	<.001	0.029
Time to PIF	Total inhalation time	0.49	0.50	<.001	<.001
Total inhaled volume	Total inhalation time	0.81	0.90	<.001	<.001

* Measured by acoustic monitoring.

The strongest correlations were observed between PIF measured by acoustic monitoring and initial acceleration, and between total inhaled volume and total inhalation time.

Device usability

There were generally no concerns reported in regard to the functionality and usability of the study device. Only for one patient (2.5%) it was reported by the physician that the number on the device counter was not clearly readable.

Safety Results

No AEs were reported in this study.

Conclusions

- The results of this study describe the complete inhalation profile through our device in a population of asthmatic patients with different degrees of disease control and pulmonary function.
- Superimposable inspiratory profiles were observed for first and second inhalation manoeuvres in either group of patients indicating consistency in device performance.

- Numerically higher PIF, initial acceleration and total inhaled volume were observed for patients with controlled asthma as compared to patients with partly controlled or uncontrolled asthma.
- However, no relevant differences were observed for flow at and time to BAM firing between the two groups of patients indicating that activation of the BAM was achieved independently of asthma control or flow limitation.
- A strong correlation was observed between PIF measured by acoustic monitoring and initial acceleration and between total inhalation volume and total inhalation time indicating a close relationship between these key parameters of device performance.
- No relevant NEXThaler® device usability concerns were detected.
- Inhalation of placebo via the NEXThaler® DPI did not lead to any AEs.

Date of report: *2 April 2013*