Clinical Study Report Synopsis

Drug Substance	Not applicable
Study Code	NIS-RGR-DUM-2009/1
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A cross sectional study for the assessment of the words used by patients and physicians to express asthma symptoms and the limitations of daily activities in primary care – The "Asthma language" study

Study dates: First subject enrolled: *14 September2009*
                          Last subject last visit: *10 December 2009*

Phase of development: Not applicable

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
ACQ-5	Asthma Control Questionnaire 5-item version
CHF	Congestive Heart Failure
CHD	Coronary Heart Disease
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
ER	Emergency Room
GERD	Gastroesophageal Reflux Disease
ICS	Inhaled Corticosteroids
LABA	Long-Acting β_2 Agonist
LTRA	Leukotriene Receptor Antagonist
PEF	Peak Expiratory Flow
SD	Standard Deviation

Study centres

The study was conducted in Greece by 87 office-based physicians. The majority of the investigators were pneumonologists (58.6 %) and the mean age was 46.8±6.2 years. Thirty four point five per cent (34.5 %) of the study sites were in the Attica region, and 50.6% of the investigators were male. Table 1 summarizes the main investigator characteristics.

Table 1: Investigators characteristics

	Mean	SD
Age (years)	46.8	6.2
	N	**%**
Sex		
Male	44	50.6
Female	40	46.0
Missing	3	3.4
Specialty		
Pneumonologist	51	58.6
Internist	31	35.6
Missing	5	5.7

Publications

None at the time of writing this report.

Objectives

Primary

- The evaluation of the concordance of the most frequently used words by the patients and the physicians to express asthma symptoms and the limitations of daily activities caused by asthma.

Secondary

- To describe the most frequently used words (lexical intensity) by the patient and the physician to express asthma symptoms and the limitations of daily activities.

- To describe the concordance of words used by physicians and patients to express asthma symptoms and the limitations of daily activities according to the level of asthma control (as assessed by ACQ-5).

- To describe the asthma control level associated with the words used by the patient.

- To describe the actions recommended by the physician or those initiated by the patient and are associated with words that express symptoms.

- To describe the symptom severity level as experienced by the patient and the symptom severity level as assessed by the investigator

- To describe the most frequently used words (lexical intensity) by the patient and the physician when there's a use of an inhaled reliever treatment.

- Factors associated with the use of these words by the patients when expressing their asthma symptoms and the limitations of daily activities.

Study design

The "Asthma Language" survey was a multicentre, observational, single visit, cross-sectional study.

Each physician completed a questionnaire with personal data (specialty, age, sex, size of community in which he/she practices medicine and number of asthma patients treated last year) as well as a CRF. This captured patient information including demographics, disease history, level of asthma control, words used to express the patient's asthma symptoms (choice of 4 words maximum among a list of 21 words), actions/therapeutic recommendations associated with each chosen word, severity of symptoms as assessed by him/her and finally words used to express the patient's daily limitations due to asthma (choice of 4 words maximum among a list of 20 words).

Each patient completed the ACQ-5 questionnaire, answered a direct question about asthma control level, selected the words used to express asthma symptoms (choice of 4 words maximum among a list of 21 words) and the limitations of daily activities caused by asthma (choice of 4 words maximum among a list of 20 words), checked the severity of symptoms and selected the actions associated with each chosen words used to express symptoms.

The lists used by the physicians and the patients were identical.

Target subject population and sample size

The study enrolled patients aged ≥18 years old with a diagnosis of persistent asthma treated with ICS-based maintenance treatment for more than 6 months. Patients were followed up by the investigator for at least the same period of time and should have been able to answer the questionnaire by themselves.

Patients with heart diseases such as CHF, CHD as well as patients with a respiratory disease other than asthma (COPD, sleep apnoea syndrome) were excluded.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

No investigational products were used in this study.

Duration of treatment

Not Applicable

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Primary

- Concordance of words used by the patients and their physicians to express asthma symptoms and limitations of daily activities

Secondary

- Words (frequency) used by the patients and their physicians

- Concordance or words used by the patients and their physicians per ACQ-5 score

- ACQ-5 score in relation to the frequency words used by the patients

- Recommended actions by physician, actions taken by patients according to words that express symptoms

- Symptoms severity score

- Words used by the patients/physicians when relieving therapy is sued.

- Factors associated with words.

Patient-reported outcomes (PROs)

All study subjects completed the patient-specific study questionnaire which included the following:

- The ACQ-5 questionnaire

- Their perception of asthma control level

- The words used to express asthma symptoms (choice of 4 words maximum among a list of 21 words).

- The words used to express daily limitations due to asthma (choice of 4 words maximum among a list of 20 words).

- Severity of symptoms

- Actions associated with each chosen words to express asthma symptoms.

Criteria for evaluation - safety

No safety data were collected in the present study. Participating investigators were required to report adverse reactions according to national requirements for post-marketing reporting.

Statistical methods

Descriptive analyses were provided for all data. Continuous data were described in terms of mean, median, standard deviation, minimum and maximum. Categorical data were described using numbers and percentages. All analyses presented used all subjects who met the inclusion/exclusion criteria.

Pearson chi square test and Fisher's exact test were used, whenever appropriate, for comparing the categorical variables. On the other hand, in order to compare continuous variables the Independent Sample T Test or Mann Whitney U Test, were used, whenever appropriate.

Summary of results

Demographics and baseline characteristics

Out of the 696 enrolled patients 695 were eligible and were included in the analysis. One patient who was younger than 18 years old was excluded from the analysis.

Distribution by sex was 42.6%male /57.3% female. Mean age was 46.9 years. Mean time since asthma diagnosis was 13 years (table 2).

Table 2. Patients' demographics and baseline characteristics

		Mean	SD
Age (years)		46.8	14.8
Time since asthma diagnosis (years)		12.9	9.4
		N	**%**
Sex	Male	296	42.6
	Female	398	57.3
	Missing	1	0.3
Occupation	Farmer	26	3.7
	Civil servant	151	21.8
	Private employee	164	23.7
	Technician	42	6.0
	Trader/businessman	64	9.2
	Household duties	115	16.5
	Unemployed	20	2.9
	Pensioner	79	11.4
	Student	31	4.5
	Missing	3	0.4

Smoking and relevant medical history

The majority of the study population were non-smokers (62.2% non-smokers/22.9% current smokers/14.7% ex-smokers).

Patients' smoking and relevant medical history is shown in table 3.

Table 3. Patients' smoking and relevant medical history

	N	%
Smoking history		
Non-smoker	432	62.2
Ex-smoker	102	14.7
Smoker	159	22.9
Missing	2	0.3
Allergic rhinitis		
No	294	42.3
Yes	377	54.2
Missing	24	3.5
GERD		
No	509	73.2
Yes	124	17.8
Missing	62	8.9
Obesity		
No	534	76.8
Yes	93	13.4
Missing	68	9.8

Treatment for asthma

The majority of patients (59.1%) were treated with the combination of ICS+LABA while 22.9% of them were treated with ICS+LABA+LTRA as shown in table 4.

Table 4. Asthma treatment

	N	%
ICS single agent	44	6.3
ICS+LABA	411	59.1
ICS+LTRA	39	5.6
ICS+LABA+LTRA	159	22.9
Other	15	2.2
Missing	27	3.9

ACQ-5 score

ACQ-5 score (mean ± SD) for the study population was 1.5±1.1.

Primary variable (concordance of words used to express asthma symptoms)

In order to analyze the concordance of the words used to describe asthma symptoms as well as limitations of daily activities caused by asthma, 3 categorical variables were generated: Full concordance (both physician and patient checked the same words), (b) partial concordance (physician and patient checked 1-3 words in common), and (c) disaccord (all words checked by physician and patient were different).

Full concordance was observed in 4.3% of the cases, whereas partial concordance was observed in 75.4% (table 5).

Table 5: Concordance of words used to express asthma symptoms

	N	%
Disaccord	141	20.3
Partial concordance	524	75.4
Full concordance	30	4.3
Total	695	100.0

A second analysis was performed which assessed word concordance following word grouping. Words expressing practically the same symptom (eg breathlessness and dyspnoea) were grouped together as illustrated in table 6.

Table 6: Word grouping

Expectoration	Wheezing	Tiredness	Dyspnoea	Others (ungrouped)
• Bronchitis	• Wheezing	• Tiredness	• Dyspnoea	• Cough
• Cold	• Whistling	• Rapid onset tiredness	• Bronchospasm	• Nasal congestion
• Phlegm	• Cat's meow		• Breathlessness	• Chest tightness
	• Chest sounds		• Crisis/attack	• Awakening during the night
			• Chest discomfort	
			• Suffocation	
			• Insufficient air breathing	
			• Breathing difficulty	

In this analysis, full concordance was observed in 21.7% of the cases, whereas partial concordance was observed in 71.9% (table 7).

Table 7: Concordance of words used to express asthma symptoms following word grouping

	N	**%**
Disaccord	44	6.3
Partial concordance	500	71.9
Full concordance	151	21.7
Total	695	100.0

Primary variable (concordance of words used to express limitations of daily activities)

Limitation of daily activities was reported in 390 (65.5%) pairs of physicians-patients, whereas 382 of them specified the type of activity that was limited. Full concordance was observed in 19.1% of the cases, whilst partial concordance was observed in 74.9% (table 8).

Table 8: Concordance of words used to express limitations of daily activities

	N	**%**
Disaccord	23	6.0
Partial concordance	286	74.9
Full concordance	73	19.1
Total	382	100.0

Secondary variables

Most frequently used words (lexical intensity) to express asthma symptoms and the limitations of daily activities

The words most frequently cited (>35%) by both patients and physicians included "dyspnoea", "wheezing", "cat's meow" and "cough". The word "bronchospasm" was infrequently reported by patients (table 9).

Table 9: Frequency of words used to express asthma symptoms

	Physicians		Patients	
Words	**N**	**%**	**N**	**%**
Bronchitis	73	11.68	39	6.24
Whistling	117	18.72	183	29.28
Dyspnoea	331	52.96	233	37.28
Wheezing	244	39.04	90	14.4
Chest sounds	93	14.88	183	29.28
Cat's meow	94	15.04	222	35.52
Cough	349	55.84	332	53.12
Tiredness	68	10.88	129	20.64
Awakening during the night	43	6.88	74	11.84
Nasal congestion	84	13.44	87	13.92
Chest tightness	72	11.52	109	17.44
Bronchospasm	210	33.6	30	4.8
Phlegm	88	14.08	126	20.16
Breathlessness	84	13.44	154	24.64
Crisis/attack	37	5.92	19	3.04
Chest discomfort	89	14.24	96	15.36
Cold	25	4	36	5.76
Suffocation	13	2.08	51	8.16
Insufficient air breathing	22	3.52	82	13.12
Breathing difficulty	59	9.44	82	13.12
Rapid onset tiredness	89	14.24	76	12.16

The words most frequently cited (40.5% - 52%) by both patients and physicians were "climbing stairs", "fast walking", and "uphill walking" (table 10).

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Table 10: Frequency of words used to express limitations of daily activities

	Physicians		Patients	
Activity	**N**	**%**	**N**	**%**
Climbing stairs	214	50.83	234	52.94
Fast walking	175	41.57	179	40.50
Uphill walking	222	52.73	230	52.04
Housekeeping	78	18.53	67	15.16
Sports	123	29.22	86	19.46
Shopping	22	5.23	25	5.66
Difficulty at work	56	13.30	50	11.31
Weight lifting	53	12.59	44	9.95
Visits to friends	4	0.95	4	0.90
Entertainment	14	3.33	12	2.71
Strong smells	93	22.09	112	25.34
Playing with children	2	0.48	11	2,49
Difficulty in a smoking area	124	29.45	166	37.56
Difficulty in speaking	17	4.04	26	5.88
Difficulty in singing	3	0.71	13	2.94
Difficulty in laughing	15	3.56	29	6.56
Hobby	10	2.38	9	2.04
Sexual activity	8	1.90	9	2.04
Difficulty at cold environments	49	11.64	64	14.48
Difficulty in humid environments	112	26.60	164	37.10

<u>Concordance of words used to express asthma symptoms and the limitations of daily activities according to the level of asthma control (as assessed by ACQ-5)</u>

Regarding words expressing symptoms, the highest proportions for the "Disaccord" and "Partial concordance" groups (42.4% and 44.7% respectively) reported ACQ-5 scores > 1.5, whereas in the "Full concordance" group category, the highest proportion (43.3%) reported ACQ-5 scores between 0.76 and 1.5 (table 11).

Table 11: Concordance of words used to express asthma symptoms according to ACQ-5 score

		ACQ-5 score			Total
		ACQ-5 <0.75	**ACQ-5 0.76-1.5**	**ACQ-5 >1.5**	
Disaccord	**N**	39	41	59	139
	%	28.1	29.5	42.4	100.0
Partial concordance	**N**	161	125	231	517
	%	31.1	24.2	44.7	100.0
Full concordance	**N**	6	13	11	30
	%	20.0	43.3	36.7	100.0
Total	**N**	206	179	301	686
	%	30.0	26.1	43.9	100.0

In terms of words used to express limitations of daily activities caused by asthma, the highest proportions for all groups, (43.5%, 59.4% and 59.7% respectively) reported ACQ-5 scores > 1.5 (table 12).

Table 12: Concordance of words used to express limitations of daily activities per ACQ-5 score

		ACQ-5 score			Total
		ACQ-5 <0.75	ACQ-5 0.76-1.50	ACQ-5 >1.50	
Disaccord	N	4	9	10	23
	%	17.4	39.1	43.5	100.0
Partial concordance	N	63	51	167	281
	%	22.4	18.1	59.4	100.0
Full concordance	N	14	15	43	72
	%	19.4	20.8	59.7	100.0
Total	N	81	75	220	376
	%	21.5	19.9	58.5	100.0

Asthma control level associated with the words used by the patient

Analysis of asthma words used to express symptoms according to the level of asthma control as reported by the patients showed that there is no prevalent word or group of symptoms characteristic for the level of asthma control. Interestingly, the 3 most commonly reported words "dyspnoea", "cat's meow" and "cough" were reported with almost the same frequency among all 3 levels of asthma control, as measured with ACQ-5.

Actions recommended by physicians or those initiated by patients and are associated with words that express symptoms.

The 3 most common actions recommended by the physician were: "to inhale rescue medication", "to increase maintenance dose" and "to call him/her". The most critical symptoms for these recommendations were "dyspnoea", "awakening during the night", "wheezing", "cat's meow", "bronchospasm", "crisis/attack", "insufficient air breathing" and breathing difficulty (table 13).

Table 13: Actions recommended by physicians associated with words expressing asthma symptoms

Words used to express asthma symptoms	Actions recommended by physicians															
	No specific advice		Inhale rescue medication		Increase maintenance dose		Measure PEF		Administration of systemic corticosteroids		Call him/her		Visit the hospital ER		Decide on his/her own what to do	
	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N
Bronchitis	5.56	4	41.67	30	44.44	32	4.17	3	8.33	6	30.56	22	1.39	1	0.00	0
Whistling	5.13	6	62.39	73	45.30	53	11.11	13	3.42	4	27.35	32	0.00	0	0.00	0
Dyspnoea	1.84	6	58.28	190	54.29	177	17.48	57	9.20	30	53.07	173	3.99	13	0.31	1
Wheezing	2.92	7	56.67	136	51.67	124	15.42	37	7.92	19	42.08	101	2.92	7	0.83	2
Chest sounds	6.67	6	53.33	48	45.56	41	10.00	9	5.56	5	40.00	36	1.11	1	0.00	0
Cat's meow	5.49	5	50.55	46	52.75	48	10.99	10	4.40	4	32.97	30	0.00	0	0.00	0
Cough	10.00	34	51.47	175	47.94	163	13.53	46	7.06	24	42.06	143	0.88	3	0.59	2
Tiredness	13.24	9	39.71	27	50.00	34	7.35	5	5.88	4	47.06	32	1.47	1	1.47	1
Awakening during the night	4.76	2	57.14	24	64.29	27	14.29	6	11.90	5	50.00	21	4.76	2	2.38	1
Nasal congestion	10.98	9	35.37	29	32.93	27	10.98	9	8.54	7	41.46	34	2.44	2	4.88	4
Chest tightness	5.71	4	51.43	36	48.57	34	18.57	13	10.00	7	42.86	30	7.14	5	0.00	0
Bronchospasm	2.93	6	60.49	124	49.27	101	16.10	33	10.24	21	51.22	105	3.41	7	0.49	1
Phlegm	17.24	15	40.23	35	37.93	33	16.09	14	6.90	6	47.13	41	1.15	1	2.30	2
Breathlessness	12.05	10	49.40	41	44.58	37	12.05	10	8.43	7	32.53	27	2.41	2	0.00	0
Crisis/attack	2.94	1	50.00	17	44.12	15	17.65	6	20.59	7	52.94	18	32.35	11	0.00	0
Chest discomfort	11.49	10	47.13	41	48.28	42	9.20	8	9.20	8	36.78	32	5.75	5	0.00	0
Cold	12.50	3	29.17	7	29.17	7	20.83	5	4.17	1	62.50	15	8.33	2	4.17	1
Suffocation	0.00	0	14.29	6	16.67	7	2.38	1	7.14	3	21.43	9	2.38	1	0.00	0
Insufficient air breathing	4.55	1	40.91	9	59.09	13	13.64	3	27.27	6	50.00	11	9.09	2	0.00	0
Breathing difficulty	3.51	2	47.37	27	50.88	29	7.02	4	19.30	11	54.39	31	14.04	8	0.00	0
Rapid onset tiredness	17.86	15	28.57	24	42.86	36	22.62	19	7.14	6	46.43	39	2.38	2	1.19	1

The most common responses of patients to a symptom were to take emergency rescue medication and to call their physicians, as shown in table 14.

Table 14: Actions initiated by patients associated with words expressing asthma symptoms

Words used to express asthma symptoms	Actions initiated by patients												
	I do nothing. I just wait until resolution		I take emergency medication		I increase the dose of my inhaled drug		I measure my PEF		I take cortisone tablet or injection		I call my doctor		I visit the hospital ER	
	%	N	%	N	%	N	%	N	%	N	%	N	%	N
Bronchitis	28.95	11	28.95	11	36.84	14	2.63	1	2.63	1	34.21	13	2.63	1
Whistling	18.71	32	60.82	104	26.32	45	3.51	6	2.34	4	28.07	48	1.17	2
Dyspnoea	9.22	20	63.13	137	35.48	77	5.07	11	3.69	8	42.86	93	3.23	7
Wheezing	18.29	15	56.10	46	34.15	28	2.44	2	1.22	1	21.95	18	1.22	1
Chest sounds	14.86	26	46.86	82	34.29	60	4.00	7	2.86	5	39.43	69	1.71	3
Cat's meow	12.86	27	51.90	109	40.48	85	4.29	9	3.81	8	38.10	80	1.43	3
Cough	24.35	75	43.18	133	25.00	77	3.25	10	0.97	3	38.31	118	0.32	1
Tiredness	40.71	46	27.43	31	25.66	29	7.08	8	5.31	6	30.97	35	2.65	3
Awakening during the night	15.28	11	62.50	45	41.67	30	2.78	2	4.17	3	29.17	21	4.17	3
Nasal congestion	35.80	29	46.91	38	14.81	12	3.70	3	3.70	3	28.40	23	1.23	1
Chest tightness	14.14	14	55.56	55	37.37	37	3.03	3	6.06	6	38.38	38	5.05	5
Bronchospasm	4.00	1	44.00	11	48.00	12	8.00	2	0.00	0	56.00	14	8.00	2
Phlegm	29.81	31	34.62	36	25.00	26	3.85	4	0.96	1	36.54	38	2.88	3
Breathlessness	30.50	43	47.52	67	26.24	37	2.84	4	2.13	3	24.82	35	2.84	4
Crisis/attack	5.26	1	63.16	12	31.58	6	15.79	3	15.79	3	52.63	10	47.37	9
Chest discomfort	15.12	13	48.84	42	34.88	30	3.49	3	3.49	3	45.35	39	3.49	3
Cold	27.59	8	24.14	7	20.69	6	3.45	1	0.00	0	55.17	16	6.90	2
Suffocation	17.02	8	59.57	28	40.43	19	10.64	5	6.38	3	53.19	25	12.77	6
Insufficient air breathing	11.84	9	57.89	44	40.79	31	5.26	4	5.26	4	50.00	38	9.21	7
Breathing difficulty	11.69	9	49.35	38	32.47	25	2.60	2	2.60	2	55.84	43	3.90	3
Rapid onset tiredness	56.16	41	27.40	20	24.66	18	0.00	0	1.37	1	35.62	26	0.00	0

Regarding the most frequently cited words by patients and physicians ("dyspnoea", "wheezing", "cat's meow" and "cough"), the corresponding most frequently cited recommended actions (35%-54%) by physicians were to " inhale rescue medication", and to "increase maintenance dose", and similarly the most frequent actions initiated by patients were "I take emergency medication" and "I increase the dose of my inhaled drug".

Symptom severity level as experienced by patients and as assessed by physicians

Words associated with the highest level of severity (0-5, 0 lowest severity and 5 highest severity) were "bronchospasm", "crisis/attack" and "awaking during the night" for patients and "crisis/attack", "breathing difficulty" and "suffocation" for physicians (table 15).

Table 15: Symptom severity level as experienced by the patients and Physicians

Words used to express asthma symptoms	Physicians			Patients		
	N	Mean	SD	N	Mean	SD
Bronchitis	70	2.41	1.21	36	2.28	1.28
Whistling	111	2.15	0.96	170	2.55	1.13
Dyspnoea	317	2.85	1.15	220	3.09	1.24
Wheezing	229	2.62	1.09	84	2.56	1.17
Chest sounds	92	2.46	1.15	174	2.67	1.10
Cat's meow	90	2.33	1.04	212	2.55	1.12
Cough	339	2.47	1.12	310	2.70	1.29
Tiredness	65	2.40	1.20	122	2.61	1.31
Awakening during the night	42	2.98	1.09	71	3.52	1.13
Nasal congestion	80	2.48	1.20	82	2.55	1.50
Chest tightness	70	2.73	1.09	97	3.15	1.16
Bronchospasm	204	2.77	1.12	28	3.57	1.14
Phlegm	86	2.20	1.00	116	2.43	1.35
Breathlessness	80	2.48	1.10	145	2.53	1.26
Crisis/attack	36	3.64	1.13	19	4.05	1.08
Chest discomfort	88	2.45	1.18	91	2.96	1.19
Cold	24	2.42	1.18	30	2.87	1.25
Suffocation	13	3.31	1.11	48	3.38	1.10
Insufficient air breathing	22	2.91	1.23	75	3.52	1.12
Breathing difficulty	57	2.96	1.15	76	3.26	1.32
Rapid onset tiredness	84	2.50	1.25	74	2.73	1.30

<u>Most frequently used words by patients and physicians when there's a use of an inhaled reliever treatment</u>

When there is a use of an inhaled reliever medication, the words most frequently cited (12% - 13%) by patients were "dyspnoea" and "cough". Those most frequently cited (13% - 16%) by physicians were "dyspnoea" and "wheezing" (table 16).

Table 16: Frequency of the words when there's a use of an inhaled reliever treatment

Words used to express asthma symptoms	Patients		Physicians	
	N	**%**	**N**	**%**
Bronchitis	11	1.00	36	3.54
Whistling	97	8.84	56	5.51
Dyspnoea	142	12.94	161	15.83
Wheezing	50	4.56	140	13.77
Chest sounds	85	7.75	44	4.33
Cat's meow	112	10.21	53	5.21
Cough	143	13.04	137	13.47
Tiredness	28	2.55	20	1.97
Awakening during the night	43	3.92	23	2.26
Nasal congestion	36	3.28	34	3.34
Chest tightness	53	4.83	32	3.15
Bronchospasm	11	1.00	86	8.46
Phlegm	25	2.28	24	2.36
Breathlessness	61	5.56	34	3.34
Crisis/attack	13	1.19	18	1.77
Chest discomfort	43	3.92	38	3.74
Cold	5	0.46	6	0.59
Suffocation	27	2.46	7	0.69
Insufficient air breathing	52	4.74	10	0.98
Breathing difficulty	42	3.83	27	2.65
Rapid onset tiredness	18	1.64	31	3.05
Total	1097	100	1017	100

Summary of pharmacokinetic results

Not Applicable

Summary of pharmacodynamic results

Not Applicable

Summary of pharmacokinetic/pharmacodynamic relationships

Not Applicable

Summary of pharmacogenetic results

Not Applicable

Summary of safety results

Not Applicable