Clinical Study Report Synopsis

Drug Substance	Symbicort/Oxis
Study Code	D6256M00046
Edition Number	1.0
Date	Dec 12, 2013
EudraCT Number	NCT01257048

An open, randomised, parallel group multi-centre, methodology study, evaluating the Sensitivity of Oxygen-Enhanced Magnetic Resonance Imaging (OE-MRI) in detecting and comparing response to 8 weeks treatment with budesonide/formoterol Turbuhaler® (320/9 µg bid) and formoterol Turbuhaler® (9 µg bid) in patients with moderate to severe Chronic Obstructive Pulmonary Disease (COPD)

Study dates: First subject enrolled: 8 Aug 2011
Last subject last visit: 27 Jun 2012

Phase of development: Methodology Study

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

Study centres

Patients were recruited at two centres (one in the United Kingdom and one in Sweden).

Publications

The study was presented in part as a late-breaking abstract at ERS 2013:

Morgan AR, Parker GJ, Roberts C, Buonaccorsi GA, Maguire N, Hubbard PL, Singh D, Vestbo J, Bjermer L, Jögi J, Nordenmark LH, Taib Z, Sarv J, Bruijnzeel P, Waterton JC Evaluating dynamic oxygen-enhanced MRI biomarkers of lung function: Sensitivity to conventional COPD treatment, ERS 2013, September 7-11, Barcelona, Spain

A manuscript for a full paper is currently available in draft form.

Objectives and criteria for evaluation

Primary Objective

The primary objective was to evaluate, against standard lung function tests, the sensitivity of a new imaging-based method, OE-MRI, in quantifying changes in lung function in patients with moderate to severe COPD treated with either a long acting β_2 –agonist (formoterol) or the fixed combination of budesonide (an inhaled corticosteroid) and formoterol during 8 weeks. A single dose test with formoterol at visit 5 will examine the potential influence of the acute bronchodilating effect of formoterol.

Secondary objective

- to evaluate the feasibility of transferring OE-MRI to a centre that does not have any previous experience of this OE-MRI.
- to evaluate the relationship between change in OE-MRI-derived parameters of lung function and change in COPD symptoms recorded in patient's diary using the BCSS questionnaire, and use of reliever medication induced by pharmacological treatment of COPD, and between change in OE-MRI-derived parameters of lung function assessed daily by measurements of morning and evening PEF.

Exploratory objective

- to evaluate the sensitivity of impulse oscillometry in quantifying changes in ventilation induced by pharmacological intervention of COPD.

The table below summarizes the OE-MRI endpoints evaluated in the study.

Parameter	Description	Model	Units
ΔPO_2	Maximum change in partial pressure of oxygen in lung tissue when switching from air to 100% oxygen	Empirical	mmHg
τ_{up}	Time constant describing the exponential wash-in (upslope) dynamics of ΔPO_2	Empirical	s
τ_{down}	Time constant describing the exponential wash-out (downslope) dynamics of ΔPO_2	Empirical	s
EnF	Enhancing fraction of the lung	Empirical	%
K_{ux}	The rate of transfer of gas via the diffusing airways and membranes into the lung tissue water and blood plasma, where the MRI measurements of ΔPO_2 occur	Compartmental	s^{-1}
$E_{ox}F_b$	The regional extraction of gas from the lung by blood, a composite function of blood flow, blood plasma solubility and hemoglobin carriage of oxygen	Compartmental	(ml blood)/min/(ml lung)
T_{vent}	Effective mixing time of oxygen from the mouth, via the conducting airways, and into the bronchioles, which can be considered roughly as the time taken for oxygen within the conducting airways to reach a plateau concentration after switching from air to oxygen breathing, or vice versa	Compartmental	s

Note - median of parameters calculated in the enhancing portion of the lung only.

Study design

The study used established and well characterized treatments in COPD in order to evaluate the sensitivity of the oxygen enhance MRI (OE-MRI) technique:

- Single dose treatment with bronchodilator vs. placebo
- Long term treatment with bronchodilator vs. bronchodilator/ICS.

The design was an open, active-controlled, parallel-group, randomised study, with an initial ICS washout period of 14-19 days and a treatment period of 56(+7) days.

At visit 1, the patients received information about the study and signed the Informed Consent Form. At visit 2, inclusion and exclusion criteria were assessed and demography, vital signs, medical-, surgical- and COPD exacerbation history were collected. Oximetry was measured and physical examination and safety sampling were carried out. In addition, patients practised lung function procedures with no registration of data. At visit 3, an MSCT scan was performed in order to characterize the COPD phenotype in terms of level of emphysema. Visit 4 was the baseline visit, at which a physical examination, lung function tests as well as OE-MRI were performed.

Patients were randomly assigned (ratio 1:1) to receive either a single dose of formoterol or placebo in the morning of visit 5. Following the evaluations of the single dose treatment, patients were randomized 2:1 to receive 8 weeks of treatment with either budesonide/formoterol or formoterol only. The 2:1 randomization was used in order to maximize the confidence in the estimates of OE-MRI parameters in the budesonide/formoterol group, given the limitation in the total number of subjects.

In order to evaluate the sensitivity of the technique for single dose bronchodilator effects, changes in OE-MRI and lung function parameters were determined from baseline (visit 4) to follow-up (visit 5). The ability to detect changes with additional long-term ICS treatment was evaluated using the same baseline visit and follow-up visit 7.

Target subject population and sample size

Symptomatic patients with moderate to severe COPD at a stable state were included in the study. The inclusion criteria were as follows:

1. Provision of informed consent prior to any study specific procedures
2. Men and women ≥40 years of age
3. Clinical diagnosis of moderate to severe COPD according to GOLD guidelines, with COPD symptoms for ≥1 year prior to enrolment
4. Current or ex-smokers with a smoking history equivalent to at least 10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year)
5. A Modified Medical Research Council (MMRC) dyspnoea scale score of ≥2.
6. $FEV_1/FVC < 0.7$ (post-bronchodilator)
7. $FEV_1 > 40$ % PN and < 70 % PN (post-bronchodilator)

To facilitate recruitment, a protocol amendment was implemented on Dec 6, 2011. For the UK site only, the interval for FEV1 was changed to:

1. $FEV_1 > 30$ % PN and < 80 % PN (post-bronchodilator)

However, no subjects with FEV1 outside the originally specified interval (40-70 % PN) were subsequently recruited in the study.

The planned number of evaluable subjects was 36 (24 on budesonide/formoterol and 12 on formoterol).

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

On the morning of visit 5, eligible patients received one single dose of formoterol Turbuhaler 4.5 µg x 2 or placebo Turbuhaler, 2 inhalations. In the evening the same day, patients commenced an 8-week treatment period with either budesonide/formoterol Turbuhaler 160/4.5 µg x 2 inhalations bid or formoterol Turbuhaler 4.5 µg x 2 inhalations bid. During this period, patients used their ordinary short-acting bronchodilator(s) as reliever medication.

Batch numbers:

Formoterol Turbuhaler:	10-005255AZ / MD922, 12-000853AZ
Budesonide/Formoterol Turbuhaler:	10-005848AZ / MK3498, 10-005848AZ
Placebo Turbuhaler:	10-004810AZ / MH46, 11-003374AZ

Duration of treatment

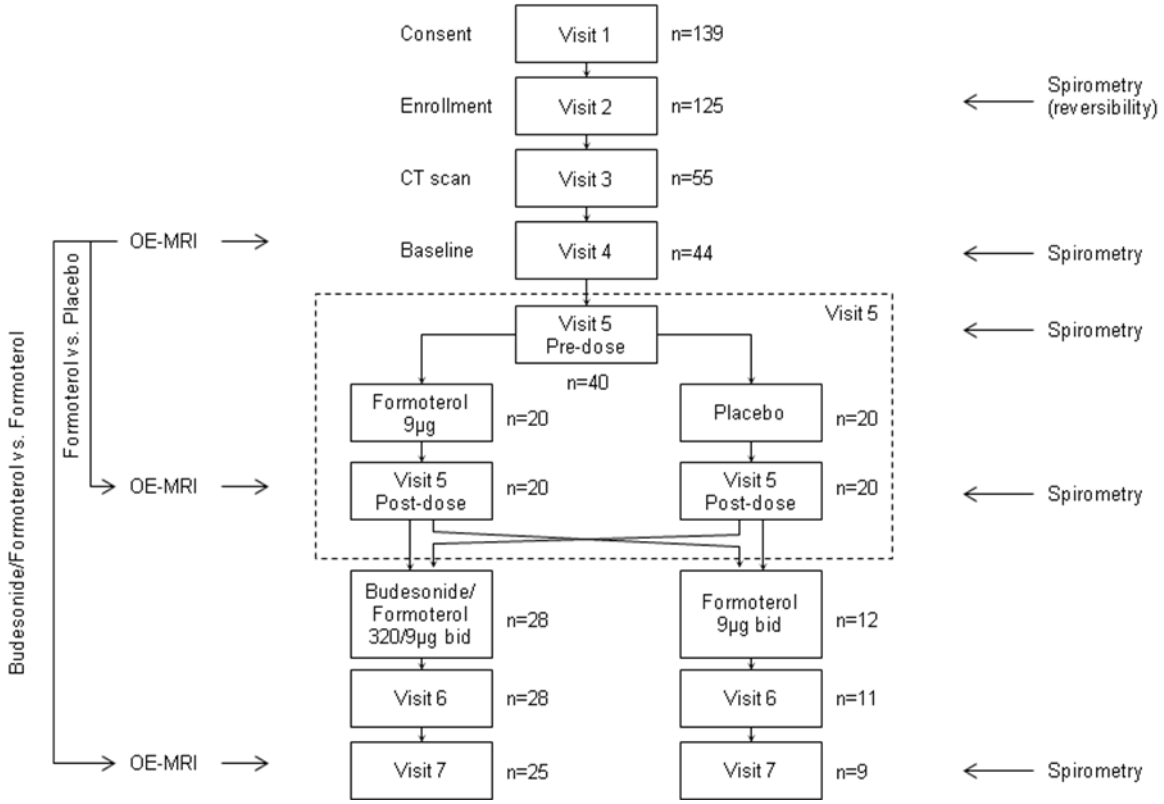
The initial ICS washout period was 14-19 days. Following the single dose of formoterol or placebo at visit 5, the treatment period with budesonide/formoterol or formoterol was 56(+7) days.

Statistical methods

The change from baseline in all measurements was analyzed in SAS (Version 8.2, SAS Institute Inc., Cary, NC, USA) using an ANCOVA statistical model, modelling the log difference, i.e. the log of the ratio of follow-up vs. baseline values. Model parameters used were the baseline value for the variable evaluated (log of value), treatment arm, sex, age, smoking status and emphysema index (log of EI -950HU). Significance was indicated by $p<0.05$.

Subject population

The flow chart below illustrates the total number of subjects enrolled and randomized by the two centres.



The table below summarizes the baseline characteristics for all subjects, as well as for the subjects randomized into each treatment arm for both single dose, and long-term treatments.

		Single-dose treatment effect groups		Long-term treatment effect groups	
	ALL (n = 40)	FORM (n = 20)	Placebo (n = 20)	BUD/FORM (n = 28)	FORM (n = 12)
Variable	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Age (years)	63.98 (7.55)	65.65 (7.13)	62.30 (7.77)	64.07 (7.82)	63.75 (7.21)
Sex F/M (%)	52.5/47.5	30/70	75/25	53.6/46.4	50/50
FEV_1 % pred.	58.01 (7.94)	55.75 (8.29)	60.26 (7.06)	58.55 (7.81)	56.74 (8.44)
FEV_1/FVC	0.46 (0.10)	0.43 (0.10)	0.48 (0.10)	0.46 (0.09)	0.45 (0.13)
TLC (L)	6.32 (1.39)	6.91 (1.40)	5.72 (1.11)	6.33 (1.30)	6.28 (1.64)
FRC (L)	4.12 (1.08)	4.50 (1.11)	3.75 (0.94)	4.13 (0.98)	4.12 (1.35)
RV (L)	3.29 (0.97)	3.56 (1.02)	3.02 (0.86)	3.31 (0.93)	3.24 (1.10)
sR_{AW} (s.kPa)	2.60 (1.25)	2.64 (1.26)	2.55 (1.28)	2.43 (1.02)	3.00 (1.66)
DL_{CO} (mmol/kPa.min)	4.62 (1.60)	4.58 (1.84)	4.66 (1.36)	4.59 (1.23)	4.70 (2.27)
EI_{-910HU} (%)	37.61 (12.71)	41.08 (14.28)	34.14 (10.11)	35.92 (12.30)	41.55 (13.32)
EI_{-950HU} (%)	14.33 (9.56)	16.55 (11.17)	12.12 (7.26)	12.21 (7.52)	19.30 (12.13)
PD_{15} (HU)	-945.34 (20.09)	-948.65 (22.83)	-942.02 (16.86)	-940.87 (17.80)	-955.77 (21.99)
ATI (%)	45.13 (15.01)	47.46 (16.51)	42.81 (13.36)	44.52 (15.10)	46.57 (15.37)

SD = standard deviation
PFTs: FEV_1 = forced expiratory volume in 1 s, FVC = forced vital capacity, TLC = total lung capacity, FRC = functional residual capacity, RV = residual volume, sR_{AW} = specific airway resistance, DL_{CO} = diffusing capacity of carbon monoxide
MSCT: EI_{-910HU} = emphysema index with threshold -910HU, EI_{-950HU} = emphysema index with threshold -950HU, PD_{15} = 15th percentile density, ATI = air trapping index
FEV_1 % predicted normal and FEV_1/FVC measures post-bronchodilator

In general there was an even balance between the treatment groups. However, baseline characteristics indicate an uneven gender split for the single-dose formoterol and placebo groups, resulting in slightly larger group mean TLC and FRC values in the formoterol group.

Higher emphysema levels were also found in the formoterol group than in the placebo group, and also in the formoterol group compared to the budesonide/formoterol group.

Summary of efficacy results

The relative changes in OE-MRI parameters and FEV1 from baseline to follow-up are listed in the table below.

	Relative change from baseline with single-dose treatment			Relative change from baseline with 8 weeks treatment		
Variable	**FORM**	**Placebo**	**FORM / Placebo**	**BUD+FORM**	**FORM**	**BUD+FORM/ FORM**
FEV1	+12%*** (n=20)	+1% (n=20)	+11%*	+18%*** (n=25)	+11% (n=9)	+7%
ΔPO_2	-10% (n=14)	-8% (n=16)	-2%	-13%* (n=21)	-5% (n=5)	-8%
τ_{up}	-34% (n=14)	+19% (n=16)	-44%	+13% (n=21)	0% (n=5)	+13%
τ_{down}	+47%* (n=12)	+19% (n=13)	+24%	-31%* (n=19)	+46% (n=5)	-53%*
EF	-5% (n=14)	-3% (n=16)	-2%	-1% (n=21)	-1% (n=5)	0%
K_{ox}	+10% (n=12)	-19% (n=13)	+35%	-10% (n=19)	+11% (n=5)	-18%
$E_{ox}F_b$	+41% (n=12)	+11% (n=13)	+27%	+58%* (n=19)	+16% (n=5)	+36%
T_{vent}	+47%* (n=12)	-26% (n=13)	+98%**	+1% (n=19)	+21% (n=5)	-17%

* = $p<0.05$, ** = $p<0.001$, *** = $p<0.001$

Mean improvements in FEV1 are in agreement with published data.

ANCOVA analysis showed a significant increase from baseline in both τ_{down} and T_{vent} in the single-dose formoterol group. For T_{vent}, the difference in change from baseline was statistically significant from placebo.

A significant reduction in τ_{down} from baseline was observed with 8 weeks of budesonide/formoterol treatment, with a significant difference in change from baseline between the formoterol group and the budesonide/formoterol group.

ΔPO_2 was significantly reduced in the budesonide/formoterol group. In the same group, there was also a significant increase in $E_{ox}F_b$ with 8 weeks of treatment.

No significant changes were found in the τ_{up} and K_{ox} parameters with either treatment.

Data acquisition was successful at both study sites, with no differences observed in the proportion of valid results.

An analysis of the correlation between change in BCSS breathing score and OE-MRI parameters showed a weak correlation.

Summary of safety results

The following AEs (all AEs) were reported: viral upper airway infection, common cold, cough, sore throat, abrasion on back, boil in groin, COPD exacerbation, dizziness, epistaxis, TIA, headache, increased hypertension, infected sebaceous cyst, metatarsalgia, palpitations, toothache, infective exacerbation, brief blackout during spirometry, secondary bacterial upper airway infection and bronchoalveolar carcinoma. Dependent on the degree of symptoms they could be categorized as mild , moderate and severe (see table below). The person that experienced a blackout during spirometry was withdrawn from the study. 2 SAEs were reported: a TIA and a bronchoalveolar carcinoma. None of the AEs or SAEs were drug related. One AE was procedure related.

Number of Patients		**Oxis (n=12)**		**Symbicort (n=28)**	
		SWE	**UK**	**SWE**	**UK**
Any AE		**0**	**7**	**1**	**7**
	Mild	0	2	0	4
	Moderate	0	4	0	2
	Severe	0	1	1	1
Any SAE (no deaths)		**0**	**1**	**0**	**1**
Leading to withdrawal		**0**	**2**	**0**	**1**
	SAE	0	1	0	1

Maximum level of AE given, if patient had several AEs.