UPLIFT – an overview Understanding Potential Long-term Impacts on Function with Tiotropium

Laura Price

CSF Medical Communications Ltd, Cheltenham, UK

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UPLIFT – an overview
Understanding Potential Long-term Impacts on Function with Tiotropium

Laura Price

CSF Medical Communications Ltd, Cheltenham, UK

OBJECTIVES

UPLIFT is a large, 4-year, double-blind, randomised, placebo-controlled, parallel-group study designed to show whether long-term treatment with tiotropium reduces the decline in lung function and hence disease progression in people with COPD.

CONTEXT

The World Health Organization predicts that chronic obstructive pulmonary disease (COPD) will become the third-leading cause of death worldwide by 2030.[1] Three million people died from COPD in 2005; 210 million people were estimated to have the disease in 2007.[1]

Tobacco smoke – inhaled either directly or via passive exposure – is the primary risk factor for the development of COPD in countries of high or middle incomes.[1] In low-income countries, exposure to indoor air pollution such as that from the use of wood and other biomass fuels, accounts for the greatest burden of COPD.[1]

Although COPD is characterised by chronic airflow limitation and pathological changes in the lung, the significance of the extrapulmonary effects of the disease has become increasingly well recognised in recent years. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) urges that while COPD should be regarded as a pulmonary disease, the significant comorbidities should also be addressed when assessing severity and selecting appropriate treatment options.[2] To reflect this position, GOLD has proposed the following working definition.

> *Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.*[2]

Management of COPD centres on reducing exposure to risk factors, relieving symptoms and preventing complications and exacerbations. The 2004 guideline from the National Institute for Health and Clinical Excellence (NICE) recommended, for those suffering frequent exacerbations, optimising bronchodilator therapy with one or more long-acting bronchodilators ($beta_2$-agonist or anticholinergic), and adding inhaled corticosteroids if the forced expiratory volume in 1 second (FEV_1) is at or below 50% and the person has two or more exacerbations in a 12-month period.[3] Guidelines from GOLD state that, in stable COPD, the choice between $beta_2$-agonists, anticholinergics and theophylline, or combination therapy depends on availability and individual response (i.e. symptom relief and side-effects). Historically, evidence underpinning the value of pharmacological interventions on slowing the rate of decline in lung function has been weak.

Bronchoconstriction and mucus hypersecretion occur in COPD, and both are regulated by the autonomic nervous system. Acetylcholine mediates both processes via muscarinic receptors:

- The M_1 and M_3 receptors mediate bronchoconstriction and stimulate mucus secretion.
- The M_2 receptors control acetylcholine release from M_1 and M_3 receptors through a negative feedback mechanism.[4]

Anticholinergic bronchodilators such as tiotropium and ipratropium act by blocking the action of acetylcholine at the muscarinic receptors and inducing relaxation of smooth muscle in the airways. Tiotropium shows selectivity for the M_1 and M_3 receptors over M_2 receptors, and it has an extended duration of action without increasing acetylcholine production.[5]

Short- and medium-term studies have shown that treatment with tiotropium benefits lung function and exercise tolerance in patients with COPD.[6–15] Time to first exacerbation and numbers of exacerbations have also been shown to be significantly reduced with tiotropium compared with placebo.[10,16,17] A 1-year study comparing the efficacy of tiotropium with that of the short-acting anticholinergic agent ipratropium found that treatment with tiotropium significantly reduced the use of rescue medication, the number of exacerbations and dyspnoea compared with ipratropium.[18] One 6-month comparison of tiotropium with the long-acting beta$_2$-agonist salmeterol found tiotropium to be associated with significantly less dyspnoea and use of rescue medication than salmeterol.[9] A second study found no significant differences between tiotropium and salmeterol in the outcomes of use of rescue medication, dyspnoea, health-related quality of life (HRQoL) or exacerbations, however.[10]

Preliminary data from the INSPIRE study (Investigating New Standards for Prophylaxis In Reduction of Exacerbations), which compared the efficacy of salmeterol/fluticasone propionate 50/500 μg twice daily (SFC) with tiotropium, 18 μg once daily, show the two treatments to have a similar impact on the overall exacerbation rate defined as exacerbations requiring extra healthcare resource utilisation (1.28 for SFC and 1.32 for tiotropium).[19] At 2 years, the mean HRQoL score, assessed by the same instrument as used in UPLIFT, was significantly lower with SFC than with tiotropium (–2.1 units; $p = 0.038$).[20] A 52% reduction in risk of on-therapy all-cause mortality at any time during the 2-year study period has also been reported for SFC compared with tiotropium (Hazard ratio 0.48, $p = 0.012$).[20] There were no differences in post-dosing FEV_1 between the two treatments.[20]

STUDY DESIGN

Inclusion and exclusion criteria

UPLIFT started recruiting from 470 sites in 37 countries across all the continents in December 2002. The broad inclusion criteria (Table 1) were designed to capture a cross-section of patients with COPD.[21] Reversibility to bronchodilator was not an entry criterion. Patients with confounding medical conditions or an inability to participate meaningfully in the trial were not enrolled. Other exclusion criteria are shown in Table 2.[24]

Participants were able to continue to use all respiratory medications prescribed previously with the exception of inhaled anticholinergic agents, as long as the prescription had not changed in the 6 weeks before randomisation. Medications prescribed for exacerbations were not restricted.

Screening period/smoking cessation

Prior to randomisation, smokers were advised to stop smoking and offered a cessation programme, once written consent had been obtained. Two

Table 1. Inclusion criteria for UPLIFT.[21]

- Clinically diagnosed COPD according to American Thoracic Society standards (1995)[22]
- Age ≥ 40 years
- Smoking history of ≥ 10 pack-years
- Willing to provide written informed consent
- Maximal post-bronchodilator FEV_1 ≤ 70% FVC predicted from European criteria[23]
- FEV_1 ≤ 70% FVC
- Ability to perform satisfactory spirometry

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 2. Exclusion criteria for UPLIFT.[24]

- Respiratory infection or COPD exacerbation in the 4 weeks before screening
- History of asthma or pulmonary resection
- Use of supplemental oxygen for more than 12 hours a day
- Significant other disease that may influence the outcome or ability to participate
- Myocardial infarction in the previous 6 months
- Unstable or life-threatening arrhythmia in the previous year
- Hospitalisation for heart failure, New York Heart Association classification class III or IV, in the previous year
- Active tuberculosis
- Malignancy treated with chemotherapy or radiotherapy within the previous 5 years
- Known hypersensitivity to anticholinergic drugs or components
- Known moderate to severe renal impairment
- Known narrow-angle glaucoma
- Significant symptomatic benign prostatic hyperplasia or bladder neck obstruction
- Use of oral corticosteroids at unstable doses or > 10 mg/day.

weeks after the first session, contact was made (phone or visit), with potential participants to attend a final session at or before randomisation. Pharmacological intervention to support smoking cessation was allowed.

Randomisation and monitoring schedule

Following the screening period, participants were randomised to receive either the tiotropium inhalation capsule, 18 μg, delivered via the HandiHaler® device, or placebo. Participants attended visits:

- after 1 month on study treatment – results obtained here are taken as the baseline values, as the pharmacokinetic steady state is reached only after several weeks of taking tiotropium;[25]
- every 6 months until the double-blind treatment period ended (i.e. at 4 years) (Figure 1).

Once the double-blind treatment period ended, all participants received open-label ipratropium for 30 days. The final visit occurred 30 days after treatment.

Endpoints

The primary endpoint is the rate of decline in FEV_1 (trough and peak) in people with COPD.

The secondary endpoints include:

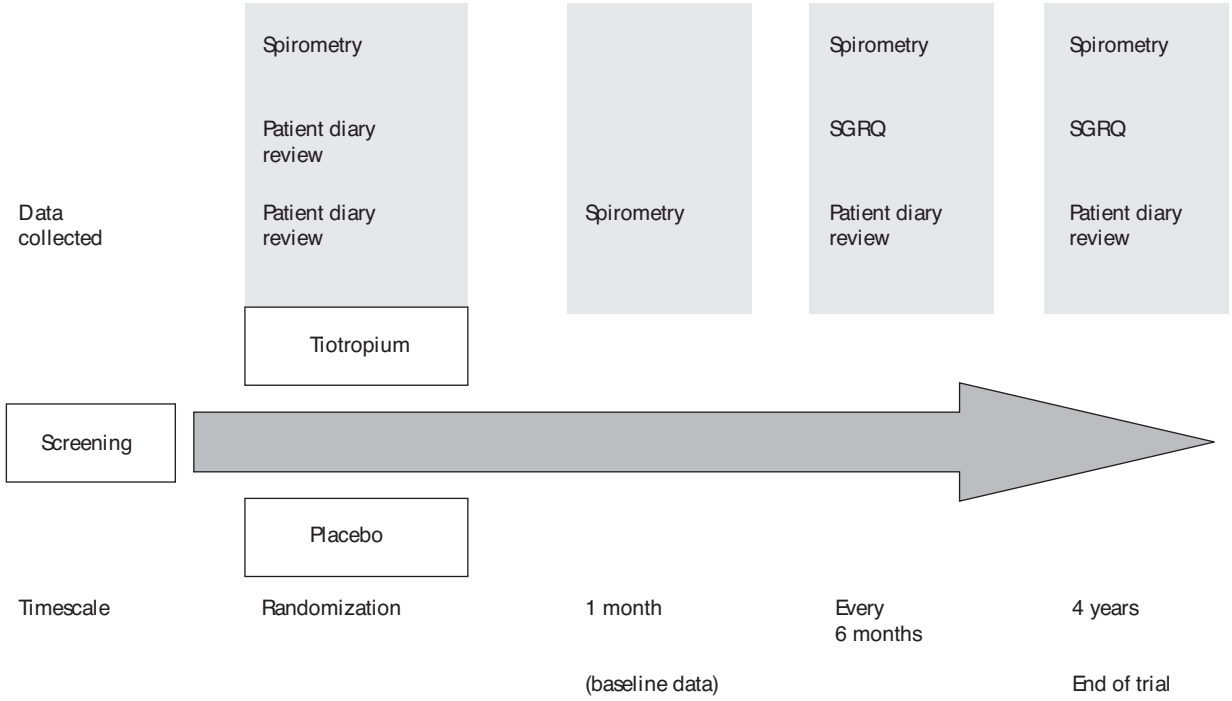
- the mean yearly rate of decline in pre- and post-bronchodilator FEV_1, FVC (forced vital capacity) and SVC (slow vital capacity) from day 1 until the end of the trial, and for FVC and SVC from day 30 to the end of the double-blind study period;
- the decline in health-related quality of life;
- exacerbations of COPD and associated hospitalisations;
- mortality (respiratory and all cause).

Evaluation of lung function and health status

Spirometry

Lung function was assessed using spirometry. FEV_1, FVC and SVC were measured in the morning at approximately the same time during each visit. Spirometry was performed pre- and post-bronchodilator at each visit. Following the pre-bronchodilator tests, the participant had four inhalations of ipratropium bromide (80 μg via metered dose inhaler [MDI]) followed by, 60 minutes later, four inhalations of salbutamol (400 μg via MDI). The post-bronchodilator spirometry was carried out 30 minutes after salbutamol administration. Once participants had been randomised to tiotropium or placebo, the study drug was administered immediately before the ipratropium bromide. The highest

Figure 1. Design of the UPLIFT trial.[21]



acceptable FEV_1 (out of three acceptable efforts) and the highest FVC that met the American Thoracic Society criteria[26] were taken as the data for that particular test set. SVC was recorded first, and was performed by slow exhalation manoeuvre. The dataset SVC was taken as the highest SVC recorded from triplicate manoeuvres.

A quality-assurance programme was developed to support the collection of spirometry data in UPLIFT, in an attempt to overcome potential variability in testing. Regular feedback was given to sites soon after testing, and this was associated with maintenance of acceptable spirometry over time.[27]

Health status

The St George's Respiratory Questionnaire (SGRQ) was used to assess impact on overall health, daily life, and perceived well-being. The questionnaire comprises 50 items (76 responses) that produce three domain scores and one overall score measuring:

- symptoms (frequency and severity) (completed on a 5-point scale);
- activity (activities that cause or are limited by breathlessness) (completed on a 'yes/no' basis);
- impacts (social functioning, psychological disturbances resulting from airways disease) (completed on a 'yes/no' basis).

Participants completed the questionnaire before spirometry was performed at the randomisation visit and then at every 6-month visit thereafter until the double-blind study period ended.

Exacerbations of COPD

An exacerbation was defined as an increase in or onset of a respiratory symptom (cough, sputum, sputum purulence, wheezing, dyspnoea) that lasted for 3 days or longer and that needed pharmacological treatment (antibiotic, systemic steroid or both). The categorisation of exacerbations is shown in Table 3. A specific data-capture form was designed to record exacerbations in the trial.

Table 3. Classification of COPD exacerbations as applied in UPLIFT.[21]

Mild

- Treated at home without seeing a healthcare practitioner

Moderate

- Visited healthcare practitioner but did not require admission to hospital

Severe

- Hospitalisation required

Analysis of data

The primary endpoints in the two treatment groups (tiotropium and placebo) are being compared using random regression analysis, with data from all participants with at least three sets of spirometry results from at least three visits post randomisation included.

The effects of age, gender, smoking status and baseline FEV_1 on the yearly decline in FEV_1 are also being analysed. The recorded numbers of exacerbations, associated hospitalisations, and exacerbation and hospitalisation days per participant are being normalised by the extent of exposure and compared between the two treatment groups using the Wilcoxon (Mann-Whitney) rank sum test. The time to the first exacerbation and associated hospitalisation are being compared across treatment groups using the log-rank test. The results from UPLIFT are expected in the second half of 2008.

STUDY POPULATION

A total of 5993 people were randomised to receive either tiotropium or placebo. Baseline demographics and other patient characteristics are shown in Table 4. Patient characteristics have been investigated and stratified according to a number of variables to provide additional information on COPD and patient characteristics.

Another long-term (3-year) study – Towards a Revolution in COPD Health (TORCH) – enrolled approximately 6200 patients from 450 centres worldwide, and randomised participants to placebo, salmeterol, 50 μg twice daily, fluticasone, 500 μg twice daily, or a combination of salmeterol 50 μg and fluticasone 500 μg twice daily. The baseline demographics and patient characteristics were similar to those of the UPLIFT participants, although far fewer of the patients enrolled in TORCH were using other respiratory medication (49% compared with 99% in UPLIFT, see below).[28]

Use of respiratory medications

Nearly all (99%) of the UPLIFT participants were using one or more respiratory medications at randomisation (Table 4). Stratifying participants by COPD severity revealed that the proportion of participants receiving long-acting bronchodilators increased with COPD severity (Table 5).[29] Most participants with stage II COPD were using inhaled corticosteroids, contrary to the current GOLD guidelines. This pattern was seen across all regions (Table 6).[30] Theophyllines were used commonly in Asia, less

Table 4. Baseline demographics and patient characteristics of the 5993 participants randomised in the UPLIFT trial.[31,36,38,39]

Mean age	65 years
Proportion of men	75%
Mean FEV_1	1.10 L
Percentage of predicted FEV_1	39%
Smoking history	49 pack-years (mean)
Proportion still smoking	30%
Body mass index	26
Proportion of racial subgroup*:	
Black 1.6%	
Asian 6.3%	
White 89.7%	
Proportion using other respiratory medication	99%
COPD severity:	
Moderate (FEV_1 50–79% of predicted)	44.5%
Severe (FEV_1 30–49% of predicted	44.8%
Very severe (FEV_1 < 30% of predicted)	10.7%

*No information for 17 participants.
FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 5. Use of respiratory medication according to COPD severity at baseline in the UPLIFT trial.[29]

	Proportion of patients taking medication (%)			
	Stage II (n = 2483)	Stage III (n = 2501)	Stage IV (n = 593)	Total* (n = 5583)
Long-acting bronchodilators (anticholinergics and/or beta$_2$-agonists)	61.8	67.3	69.3	65.1
Short-acting anticholinergics	41.7	50.7	59.9	47.6
Short-acting beta-agonists	68.8	76.3	78.9	73.2
Inhaled corticosteroids	63.7	67.2	72.5	66.2
Theophylline	24.7	34.9	36.1	30.5

*Includes 6 patients with stage I COPD.

Table 6. Use of respiratory medication by participants with stage II COPD by region at baseline in the UPLIFT trial.[30]

	Proportion of patients with stage II COPD in each region taking medication (%)				
	USA (n = 648)	Latin America (n = 182)	Europe* (n = 1793)	Asia (n = 130)	Total (n = 2753)
Any respiratory medication	81.3	76.9	95.0	92.3	90.5
Long-acting bronchodilators (anticholinergics and/or beta$_2$-agonists)	43.4	40.1	63.8	33.1	56.0
Short-acting anticholinergics	40.3	18.7	38.1	43.8	37.6
Short-acting beta-agonists	69.1	54.9	60.2	66.2	62.3
Inhaled corticosteroids	46.6	38.5	65.0	38.5	57.7
Theophylline	4.9	15.9	26.9	52.3	22.2

*Includes Australia, New Zealand and South Africa.

so in Latin America and Europe, and much less commonly in the USA.

Prevalence of psychiatric disorders

Psychiatric disorders tend to be more prevalent in people with chronic diseases than in healthy comparators. Of the participants in the UPLIFT trial, 17.2% had a concomitant psychiatric diagnosis at baseline (Table 7).[31] The prevalence was higher among women and slightly lower among older participants (≥ 65 years of age), but no patterns were observed when results were analysed according to COPD severity.

FEV_1 and tobacco use according to racial subgroup

Differences in susceptibility to the effects of cigarette smoke between different racial subgroups have been suggested in some studies,[32–34] but not in another.[35] When the baseline FEV_1 data from the UPLIFT trial were analysed according to racial subgroup, there was no correlation between pre- or post-bronchodilator FEV_1 and number of pack-years of smoking for the racial subgroups (Table 8).[36] Susceptibility indices ([race-adjusted post-bronchodilator FEV_1 % predicted −100]/pack-years) for each racial subgroup did suggest, however, a greater loss of lung function per pack-year among Blacks than among Whites or Asians (−1.63, −1.57, −1.47, respectively; $p < 0.05$).

Acute bronchodilator responsiveness

Baseline data were analysed to investigate the acute improvement in lung function after staged bronchodilator inhalation (i.e. with ipratropium followed by, 60 minutes later, salbutamol).[37] FEV_1 response to bronchodilator was assessed using three different criteria:

- ≥ 12% and ≥ 200 mL improvement
- ≥ 15% increase over baseline
- ≥ 10% absolute increase in the percentage predicted value.

Table 7. Prevalence of psychiatric disorders at baseline in the UPLIFT trial.[31]

	Gender (%)		Age (%)		COPD stage (%)			Total (%)
	Male	Female	< 65 years	≥ 65 years	II	III	IV	
Any psychiatric diagnosis	13.7	27.3	18.2	16.2	17.1	17.1	19.2	17.2
Depression	5.9	16.2	10.2	6.9	8.7	8.2	9.6	8.5
Anxiety	4.0	8.9	5.4	5.1	5.1	5.3	6.5	5.9
Sleep disorder	5.1	8.4	5.2	6.5	5.8	6.2	5.6	5.9
Alcohol use	0.5	0.3	0.5	0.4	0.4	0.4	0.8	0.4
PTSD	0.3	0.1	0.4	0.1	0.3	0.2	0.8	0.3

PTSD, post-traumatic stress disorder.

Table 8. Baseline characteristics by racial subgroup.[36]

	White (n = 5378)	Asian (n = 380)	Black (n = 98)	Total (n = 5976)
Mean age (years)	64.3	66.2	64.2	64.5
Proportion of males	73.1	93.7	66.3	74.3
Proportion of active smokers	31.5	17.1	32.7	30.6
Smoking history (mean pack-years)	48.9	50.7	41.8	48.9
COPD duration (years)	10.1	6.8	7.6	9.8
Mean pre-bronchodilator FEV_1 (L) (% predicted)	1.12 (39.6)	0.84 (36.5)	0.96 (38.5)	1.10 (39.3)
Mean post-bronchodilator FEV_1 (L) (% predicted)	1.34 (47.7)	1.04 (44.7)	1.16 (46.6)	1.32 (47.5)

FEV_1, forced expiratory volume in 1 second.

To investigate the influence of COPD severity on bronchodilator responsiveness, improvements in FEV_1 and FVC were analysed by severity of COPD (GOLD stage) using the first two criteria listed above.

Following bronchodilator administration, the mean FEV_1 increased from 1.10 L to 1.329 L and the mean FVC increased from 2.63 L to 3.10 L ($p < 0.0001$ versus pre-bronchodilator rate in both instances). The percent predicted FEV_1 increased by 8.3%, from 39.3% to 47.6%.

The proportion of participants judged to be responsive to bronchodilator differed according to the criterion used:

- 53.9% showed ≥ 12% and ≥ 200 mL improvement in FEV_1
- 65.6% had an increase over baseline FEV_1 ≥ 15%
- 38.6% had an absolute increase in the percentage predicted FEV_1 ≥ 10%.

The proportion of patients with a flow response according to the ≥ 12% and ≥ 200 mL criterion decreased increasingly with disease progression, whereas the proportions with responses judged by the other criteria remained relatively stable across the GOLD stages. The proportion of patients who showed a volume response (FVC) without a significant flow response ranged from 5% to 49%, depending on criteria and stage, and increased with disease severity.

PREDICTING EXACERBATIONS AND MORTALITY

Exacerbations

The baseline data for the UPLIFT cohort were used to assess potential predictors of the occurrence of an exacerbation in the following year.[38] The analysis revealed that the likelihood of having an exacerbation in the following year was significantly associated with several baseline characteristics (Table 9). Occurrence in the previous year of unscheduled physician visits, emergency department visits, hospitalisation, or prescription of antibiotics or corticosteroids were found to be significantly associated with the occurrence of an exacerbation in the

Table 9. Baseline characteristics by occurrence of exacerbations in the year after randomisation in the UPLIFT trial.[38]

	Number of exacerbations in the year after randomisation		
	None (n = 3426)	≥ 1 (n = 2567)	*p* value
Mean age (years)	64.4	64.7	ns
Male (%)	75.2	73.9	ns
Mean FEV_1 (L)*	1.15	1.03	<0.0001
Mean FEV_1 (% predicted)*	41.0	37.2	<0.0001
Mean FVC (L)*	2.67	2.55	<0.0001
GOLD stage II, III, IV (%)*†	26/55/19	17/53/29	<0.0001
Smoking (mean pack-years)	48.0	49.6	0.0319
Smoking (%ex/%current)	68/32	72/29	0.0037
Mean body mass index	26.1	26.8	0.0041
Mean SGRQ total score	44.1	48.5	<0.0001

*Pre-bronchodilator.

†% patients in each GOLD stage with 0 or ≥ 1 exacerbation.

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; SGRQ, St George's Respiratory Questionnaire; ns, not significant.

Table 10. Association between baseline characteristics and short-term mortality in patients enrolled in UPLIFT.[39]

	All-cause mortality		
	Survived (n=5744)	Deceased (n=249)	p value
Mean age (years)	64.3	68.2	<0.0001
Male (%)	74.2	85.5	<0.0001
Mean FEV_1 (L)*	1.10	0.98	<0.0001
Mean FEV_1 (% predicted)*	39.5	35.9	<0.0001
Mean FVC (L)*	2.63	2.49	0.0084
GOLD stage II, III, IV (%)*†	22/54/23	15/52/33	0.0002
Smoking (mean pack-years)	48.6	50.7	ns
Mean body mass index	26.0	25.1	0.0101
Mean SGRQ total score	45.8	51.1	<0.0001
Home oxygen use (%)	4.6	8.4	0.0063
Use of inhaled corticosteroids (%)	31.2	37.8	0.0155

*Pre-bronchodilator.

†% of patients in each GOLD stage.

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ns, not significant; SGRQ, St George's Respiratory Questionnaire.

following year, in addition to those factors shown in Table 9.

Mortality

Data on all-cause mortality from trial initiation in January 2003 to October 2005 were analysed according to the baseline characteristics of the UPLIFT participants. Several baseline characteristics were significantly associated with short-term survival/mortality (Table 10).[39]

SAFETY

Boehringer Ingelheim, the manufacturer of tiotropium, informed the Food and Drug Administration (FDA) in the USA of a possible increased risk of stroke in patients taking tiotropium.[40] This was based on pooled analysis of safety data from 29 clinical studies (approximately 13,500 patients). The estimated excess risk of any type of stroke associated with use of tiotropium was 2/1000 patients. UPLIFT will provide additional long-term safety data and, once it has the data from UPLIFT, the FDA will make recommendations on the use of tiotropium.

KEY POINTS

- COPD is predicted to become the third leading cause of death worldwide by 2030.
- Good-quality long-term evidence to support the role of pharmacological intervention in COPD is lacking.
- UPLIFT is a 4-year, placebo-controlled multinational trial involving nearly 6000 patients with COPD. It has been designed to test the effect of maintenance treatment with the once-daily inhaled anticholinergic tiotropium on the rate of decline in FEV_1.
- UPLIFT will also provide data on the effect of tiotropium on health-related quality of life, exacerbations of COPD and hospitalisations, and mortality.
- Initial analyses of baseline demographic data and patient characteristics have revealed that certain characteristics may predict the likelihood of exacerbations or death in the short term.
- Safety data from UPLIFT will be considered by the FDA, which has been notified of a potential increase in the risk of stroke among people using tiotropium by the manufacturer.
- The results from UPLIFT may be presented later in 2008.

REFERENCES

1 World Health Organization. Chronic obstructive pulmonary disease (COPD). Available from www.who.int/respiratory/copd/en. Last accessed 26 June 2008.

2 Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention Of Chronic Obstructive Pulmonary Disease (Updated 2007).* MCR Vision, Inc, 2007.

3 NICE. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Clinical Guideline 12*. London: NICE, 2004.

4 Beeh KM, Welte T, Buhl R. Anticholinergics in the treatment of chronic obstructive pulmonary disease. *Respiration* 2002; 69: 372–379.

5 Maesen FP, Smeets JJ, Sledsens TJ *et al.* Tiotropium bromide, a new long-acting antimuscarinic bronchodilator: a pharmacodynamic study in patients with chronic obstructive pulmonary disease (COPD). Dutch Study Group. *Eur Respir J* 1995; 8: 1506–1513.

6 Littner MR, Ilowite JS, Tashkin DP *et al.* Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva) in stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161: 1136–1142.

7 Casaburi R, Briggs DD, Jr, Donohue JF *et al.* The spirometric efficacy of once-daily dosing with tiotropium in stable COPD: a 13-week multicenter trial. The US Tiotropium Study Group. *Chest* 2000; 118: 1294–1302.

8 Casaburi R, Mahler DA, Jones PW *et al.* A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002; 19: 217–224.

9 Donohue JF, van Noord JA, Bateman ED *et al.* A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 2002; 122: 47–55.

10 Brusasco V, Hodder R, Miravitlles M *et al.* Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax* 2003; 58: 399–404.

11 O'Donnell DE, Fluge T, Gerken F *et al.* Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004; 23: 832–840.

12 Casaburi R, Kukafka D, Cooper CB *et al.* Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. *Chest* 2005; 127: 809–817.

13 Niewoehner DE, Rice K, Cote C *et al.* Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med* 2005; 143: 317–326.

14 Maltais F, Hamilton A, Marciniuk D *et al.* Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. *Chest* 2005; 128: 1168–1178.

15 Verkindre C, Bart F, Aguilaniu B *et al.* The effect of tiotropium on hyperinflation and exercise capacity in chronic obstructive pulmonary disease. *Respiration* 2006; 73: 420–427.

16 Casaburi R, Mahler DA, Jones PW *et al.* A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002; 19: 217–224.

17 Dusser D, Bravo ML, Iacono P. The effect of tiotropium on exacerbations and airflow in patients with COPD. *Eur Respir J* 2006; 27: 547–555.

18 Vincken W, van Noord JA, Greefhorst AP *et al.* Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. *Eur Respir J* 2002; 19: 209–216.

19 Seemungal, T, Stockley R, Calverley P *et al.* Effect of salmeterol/fluticasone proprionate versus tiotropium bromide on exacerbations: the INSPIRE study (investigating new standards for prophylaxis in reduction of exacerbations). Presented at the annual congress of the European Respiratory Society, Stockholm, Sweden, 15–19 September 2007:688s.
20 Stockley R, Calverley P, Seemungal T *et al.* Effect of salmeterol/fluticasone proprionate versus tiotropium bromide on withdrawal rate, health status, lung function and mortality: INSPIRE (investigating new standards for prophylaxis in reduction of exacerbations) study. Presented at the annual congress of the European Respiratory Society, Stockholm, Sweden, 15–19 September 2007:34s.
21 Decramer M, Celli B, Tashkin DP *et al.* Clinical trial design considerations in assessing long-term functional impacts of tiotropium in COPD: the UPLIFT trial. *COPD* 2004; 1: 303–312.
22 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 152: S77–121.
23 Quanjer PH. standardised lung function testing of the European community for coal and steel. *Euro Physiopathol Respir* 1983; 19: 7.
24 Anonymous. Evaluation of the long-term effects of Spiriva on lung function in COPD patients. Available from http://clinicaltrials.gov/ct2/show/NCT00144339?term=long-term+and+spiriva&rank=2. Last accessed 26 June 2008.
25 van Noord JA, Smeets JJ, Custers FL *et al.* Pharmacodynamic steady state of tiotropium in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2002; 19: 639–644.
26 Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 1995; 152: 1107–1136.
27 Decramer M, Tashkin D, Celli B *et al.* Use of regular feedback on spirometry testing in a long-term multinational COPD trial. Presented at the annual meeting of the American Thoracic Society, Toronto, Canada, May 16–21 2008:A145.
28 Tashkin DP. The role of patient-centered outcomes in the course of chronic obstructive pulmonary disease: how long-term studies contribute to our understanding. *Am J Med* 2006;119:63–72.
29 Tashkin D, Celli B, Decramer M *et al.* Prescribing patterns according to COPD treatment guidelines in patients enrolled in a global clinical trial. Presented at the annual meeting of the American Thoracic Society, San Diego, California, May 19–24 2006: A111.
30 Decramer M, Celli B, Tashkin DP *et al.* Regional differences in the treatment of patients with moderate COPD enrolled in a global clinical trial. Presented at the annual meeting of the American Thoracic Society, San Diego, California, May 19–24 2006: 526S.
31 Tashkin D, Decramer M, Celli B *et al.* Prevalence of psychiatric disorders at baseline in a global respiratory trial. Presented at the annual meeting of the American Thoracic Society, Toronto, Canada, May 16–21 2008: A136.
32 Seltzer CC, Siegelaub AB, Friedman GD *et al.* Differences in pulmonary function related to smoking habits and race. *Am Rev Respir Dis* 1974; 110: 598–608.
33 Horne SL, To T, Cockcroft DW. Ethnic differences in the prevalence of pulmonary airflow obstruction among grain workers. *Chest* 1989; 95: 992–996.
34 Chatila WM, Wynkoop WA, Vance G *et al.* Smoking patterns in African Americans and whites with advanced COPD. *Chest* 2004; 125: 15–21.
35 Vollmer WM, Enright PL, Pedula KL *et al.* Race and gender differences in the effects of smoking on lung function. *Chest* 2000; 117: 764–772.
36 Celli B, Decramer M, Tashkin DP *et al.* Differences in baseline FEV1 and tobacco use in COPD patients from different racial subgroups. Presented at the annual meeting of the American Thoracic Society, San Diego, California, May 19–24 2006: A849.
37 Tashkin DP, Celli B, Decramer M *et al.* Bronchodilator responsiveness in patients with COPD. *Eur Respir J* 2008; 31: 742–750.
38 Decramer M, Tashkin D, Celli B *et al.* Predictors of exacerbations of COPD in a large global clinical trial. Presented at the annual meeting of the American Thoracic Society, San Diego, California, May 19–24 2006: A271.
39 Celli B, Decramer M, Tashkin D, Menjoje S, Burkhart D, Cassino C, Kesten S. Predictors of mortality in a large global COPD clinical trial. Presented at the annual meeting of the American Thoracic Society, San Diego, California, May 19–24 2006: A726.
40 US Food and Drug Administration. Early communication about an ongoing safety review of tiotropium (marketed as Spiriva HandiHaler). Issued 18 March 2008. Available from www.fda.gov/cder/drug/early_comm/tiotropium.htm. Last accessed 25 June 2008.