Economic Evaluation of Aclidinium Bromide in the Management of Moderate to Severe COPD

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Introduction

- Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterized by persistent airflow limitation that is usually progressive, irreversible, and associated with considerable morbidity and mortality.[1,2]
- COPD poses a significant economic burden via health care costs and resource utilization.[3]
- Long-acting bronchodilator medications, such as the widely prescribed long-acting muscarinic antagonist (LAMA) tiotropium, are central to symptom management in COPD.[1]
- Aclidinium bromide is a new LAMA indicated for long-term maintenance treatment of bronchospasm associated with COPD.

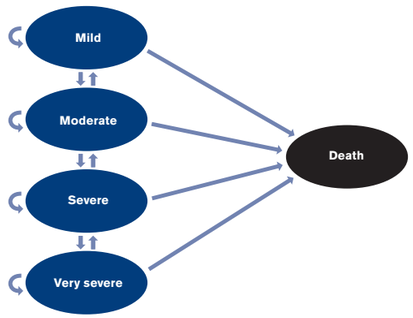
Objective

- To evaluate the cost-effectiveness of aclidinium 400 µg twice daily (BID) as an alternative to tiotropium 18 µg once daily for maintenance treatment of COPD in the United States

Methods

- A third-party-payer perspective, cost-utility, cohort model was developed using Microsoft Excel 2010, with 5 main health states: mild, moderate, severe, or very severe COPD, or death (Figure 1).
- Severity of COPD is depicted in line with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2006 classification.[4] Although this classification has been modified in the updated GOLD guidelines[1] to include assessment of symptoms and history of exacerbations, the model was created according to the previous classification, as utilities, costs, and exacerbation rates in all available publications are reported according to the former.

Figure 1. Basic concept of the model indicating health states in COPD



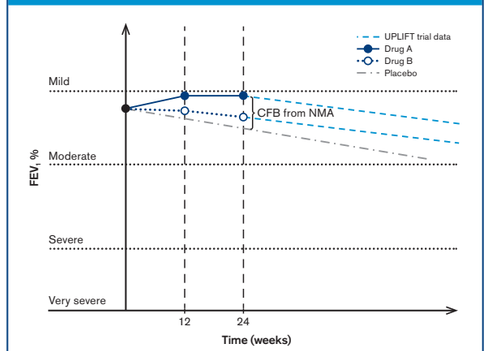
COPD, chronic obstructive pulmonary disease

- Each severity health state reflects the risk of experiencing a severe or nonsevere exacerbation, as well as the corresponding level of utility, resource use, and costs.
- The model has a 4-week cycle and a time horizon of 5 years.
- At the end of a cycle, patients may remain in a health state or move to another state according to their estimated forced expiratory volume in 1 second (FEV_1) % of predicted value at that time.

FEV_1 estimation

- Subanaylsis results of a network meta-analysis (NMA) were used to estimate the decline of the FEV_1 % of predicted during the first 24 weeks of the time horizon as a result of the efficacy of treatments.[5]
- After the first 24 weeks, the estimation of the long-term FEV_1 % of predicted evolvement was based on long-term data on LAMAs taken from the literature (UPLIFT study[7] for both arms and Reference 6).
  - UPLIFT is a 4-year, randomized, controlled trial comparing tiotropium versus placebo.
  - Thus, after 24 weeks, both treatment arms experience the same rate of decline (see Figure 2).
- This model assumes that at each time point, the FEV_1 % of predicted is normally distributed with a mean value estimated as described above (NMA before 24 weeks, UPLIFT after; Table 1 and Figure 2) and a standard deviation of 13.3% (baseline of ACCORD COPD I study,[8] a phase 3 aclidinium study conducted primarily in the United States), which does not change over time.
- With this assumption, we can estimate the percentage of patients in each health state (COPD stage) by using the estimated FEV_1 % values to classify the severity of COPD (Figure 2).

Figure 2. Basic concept of the model indicating efficacy for both treatment arms



CFB, change from baseline; FEV_1, forced expiratory volume in 1 second; NMA, network meta-analysis

- Quality of life was assessed using utility scores of US patients from UPLIFT.[7]
- Cost-effectiveness was defined as incremental cost per quality-adjusted life-year (QALY) gained.

Table 1. Model assumptions

Trough FEV_1 is assumed to be the main indicator for the classification of disease severity in COPD.
Long-term rate of decline for FEV_1 % is considered identical for all treatments (based on estimations from the UPLIFT study).
Exacerbation rates correspond to disease severity and are considered treatment independent.
Utility corresponds to disease severity and is considered treatment independent.
Treatment efficacy data observed in multinational clinical trials are assumed to be generalizable in the United States.
Disease-specific mortality is considered based on hazard ratio (COPD mortality vs natural mortality) from the UPLIFT study.
Adverse events are not considered.

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second

- The patient population used is in-line with the licensed indication of aclidinium 400 µg BID and reflects patients randomized to receive aclidinium 400 µg BID in the pivotal LAS-MD-33 (ACCORD I) trial.[8]
  - Inclusion criteria included: age ≥40 years, stable moderate to severe COPD, current smokers or ex-smokers (≥10 pack-years), postbronchodilator FEV_1 ≥30% and <80% of predicted normal value, FEV_1/forced vital capacity <70% (Table 2).

Table 2. Patient characteristics used to inform the model[a]

Characteristic	
Age, years, mean (SD)	64.3 (9.4)
Male, %	53
Postbronchodilator FEV_1 baseline data, L	1.55
Baseline FEV_1 % predicted and monthly decline, L	2.87 and -0.0023 (both calculated[b])
FEV_1, % of predicted (SD)	54 (13.35)
COPD-related mortality vs natural mortality,[7] HR	1.8

[a]All values presented except COPD mortality[7] are from the ACCORD I trial[8]
[b]Baseline FEV_1 % predicted was calculated at the starting point of the model[8]; monthly decline was based on Reference 6
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; HR, hazard ratio; SD, standard deviation

Scenario Analyses

- The following scenario analyses were performed (Table 3, column "varied in scenario"):
  - Using discount factors of 0% and 6% for benefits and costs
  - Using time horizon of one year
  - Estimating utilities by mapping St. George's Respiratory Questionnaire (SGRQ) to EuroQol 5-Dimensions (EQ-5D)
  - Varying the cost of exacerbations
- Including the LAS-MD-38 (ACCORD COPD II[9]) trial on the NMA results for comparative efficacy, this study was excluded from the base-case NMA because of a high risk of bias due to an imbalance in patients' baseline characteristics.[10]

Table 3. Values used for each of the parameters in the model

Model parameters					Included in PSA	Varied in scenario
Discount factor[11]	3% cost and benefits				No	0% and 6%
Time horizon	5 years				No	1 and 3 years
Efficacy FEV_1, L	**Mean**	**Low**	**High**	**Distribution**	**Included in PSA**	**Varied in scenario**
Absolute CFB at 12 weeks[10,12]	0.068	0.027	0.110	Normal	Yes	-
Absolute CFB at 24 weeks[10,12]	0.047	-0.006	0.101	Normal	Yes	-
Absolute annual decline after 24 weeks[7]	-0.040	-0.042	-0.038	Normal	Yes	-
Difference in CFB FEV_1, L, aclidinium vs tiotropium						
Difference in CFB, 12 weeks[10,12]	0.001	-0.030	0.032	Normal	Yes	ACCORD II trial included
Difference in CFB, 24 weeks[10,12]	0.024	-0.023	0.071	Normal	Yes	-
Difference in annual decline after 24 weeks[a]	0.0	0.0	0.0	Normal	Yes	-
Exacerbations	**Mean**	**Low**	**High**	**Distribution**	**Included in PSA**	**Varied in scenario**
Proportion of patients experiencing exacerbations per months[b]						
Mild COPD; nonsevere exacerbation	5%	3%	12%	Beta	Yes	-
Mild COPD; severe exacerbation	1%	0%	59%	Beta	Yes	-
Moderate COPD; nonsevere exacerbation	5%	3%	12%	Beta	Yes	-
Moderate COPD; severe exacerbation	1%	0%	59%	Beta	Yes	-
Severe COPD; nonsevere exacerbation	7%	6%	12%	Beta	Yes	-
Severe COPD; severe exacerbation	1%	7%	26%	Beta	Yes	-
Very severe COPD; nonsevere exacerbation	8%	8%	13%	Beta	Yes	-
Very severe COPD; severe exacerbation	2%	13%	28%	Beta	Yes	-
Utilities	**Mean**	**Low**	**High**	**Distribution**	**Included in PSA**	**Varied in scenario**
Mild health state[13,c]	0.83	0.82	0.84	Beta	Yes	Mapping SGRQ total score[c] to EQ-5D
Moderate health state[13]	0.83	0.82	0.84	Beta	Yes	
Severe health state[13]	0.80	0.79	0.82	Beta	Yes	
Very severe health state[13]	0.73	0.70	0.76	Beta	Yes	
Nonsevere exacerbation[12,14-16]	15%	12%	18%	Beta	Yes	-
Severe exacerbation[12,14-16]	50%	40%	60%	Beta	Yes	-
Cost data	**Mean (US$)**	**Low**	**High**	**Distribution**	**Included in PSA**	**Varied in scenario**
Aclidinium[13,d]	7.25	-	-	-	-	-
Tiotropium[13,d]	8.03	-	-	-	-	-
Monthly cost of COPD management per health state[e]						
Mild	1,709	1,703	1,715	Gamma	Yes	1) All-cause cost minus pharmacy cost 2) COPD-related costs
Moderate	1,709	1,703	1,715	Gamma	Yes	
Severe	2,341	2,333	2,350	Gamma	Yes	
Very severe	3,247	3,236	3,259	Gamma	Yes	
Cost per exacerbation[18,f]						
Nonsevere	2,009	1,942	2,076	Gamma	Yes	Cost per exacerbation varied using data from References 14 and 19
Severe	13,195	13,021	13,370	Gamma	Yes	

[a]Assumption: equal annual decline
[b]Calculations based on Reference 12
[c]US utility value for mild health state assumed to be similar to moderate
[d]Assumed continues treatment (365 days treatment per year)
[e]Reference 14 reported quarterly health care costs for moderate COPD (assumed no exacerbations reflected the cost of moderate COPD); the all-cause medical costs were converted to monthly costs. Costs were price indexed from 2006-2012 values using CPI. A multiplier was used to estimate the COPD management costs for the Severe (1.37) and Very severe (1.90) stages, as suggested by Reference 13.
[f]Assumed the quarterly cost to be a monthly cost
CFB, change from baseline; COPD, chronic obstructive pulmonary disease; EQ-5D, EuroQoL 5-Dimensions; FEV_1, forced expiratory volume in one second; PSA, probabilistic sensitivity analyses; SE, standard error; SGRQ, St. George's Respiratory Questionnaire

Results

- Over 5 years, QALYs were 3.50 for aclidinium and 3.49 for tiotropium, with a similar accumulated number of life-years over 5 years (4.52; Table 4).
- Total health care costs: $126,274 for aclidinium and $128,591 for tiotropium (Table 4).

Table 4. Cost-effectiveness of aclidinium vs tiotropium over 5 years

Data	Aclidinium	Tiotropium
QALY over 5 years	3.50	3.49
Life-years accumulated over 5 years	4.52	4.52
Exacerbations over 5 years		
Nonsevere	3.364	3.390
Severe	0.565	0.574
Mean total health care costs, US$	126,274	128,591
Drug cost	11,162	12,361
Cost of COPD management	101,673	102,642
Cost of exacerbations	13,439	13,558

COPD, chronic obstructive pulmonary disease; QALY, quality-adjusted life-year

- All scenario analyses showed lower costs and marginally greater QALYs for aclidinium compared with tiotropium (Table 5).

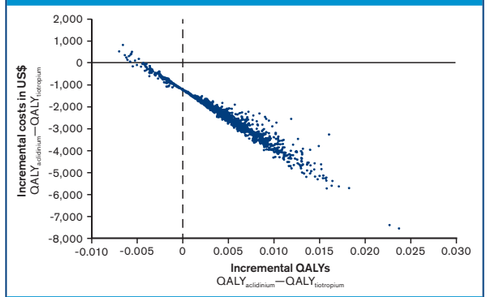
Table 5. Change in cost-effectiveness of aclidinium vs tiotropium with different scenarios (source data)

Base case value	Scenario	Change in cost with aclidinium vs tiotropium (US$)	Change in QALYs with aclidinium vs tiotropium	ICER
Base case	-	-2,137	0.0044	Dominant
Discount factor for benefits and costs (3%)	0% benefits and costs	-2,458	0.0047	Dominant
	6% benefits and costs	-2,191	0.0041	Dominant
Time horizon: 5 years	1 year	-444	0.0006	Dominant
	3 years	-1,425	0.0025	Dominant
Utilities per health state[12]	Mapping SGRQ from ACCORD I to EQ-5D dimensions	-2,137	0.0072	Dominant
Management cost COPD (all-cause medical)[17]	All-cause costs without pharmacy costs	-2,077	0.0044	Dominant
	COPD-related costs only	-1,482	0.0044	Dominant
Exacerbation cost from Reference 17	Reference 13	-2,252	0.0044	Dominant
	Reference 18	-2,217	0.0044	Dominant
Inclusion of ACCORD II data: difference mean CFB FEV_1 at 12 weeks: 0.001	Difference mean CFB FEV_1 at 12 weeks: -0.0135	-2,269	0.0042	Dominant

COPD, chronic obstructive pulmonary disease; CFB, change from baseline; EQ-5D, EuroQoL 5-Dimensions; FEV_1, forced expiratory volume in one second; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SGRQ, St. George's Respiratory Questionnaire

- The uncertainty in the evaluation was addressed by means of a probabilistic sensitivity analysis (Figure 3). Although the difference in QALYs is low, 84% of the iterations fall in the lower right quadrant, demonstrating the robustness of the base-case results.

Figure 3. Probabilistic sensitivity analyses – cost-effectiveness plane



QALY, quality-adjusted life-year

Limitations

- Because no long-term head-to-head clinical safety and efficacy studies have been conducted to compare treatment with aclidinium versus tiotropium, use of clinical trial data in an indirect treatment comparison was necessary in this study.
- Data after 24-weeks of treatment were extrapolated from the indirect treatment comparison results to predict expected costs and benefits in actual clinical practice over the 5-year time horizon.
- UPLIFT was used to estimate lung function decline after 24 weeks for both arms; however, UPLIFT differed from many of the studies used to estimate the first 24 weeks of treatment effect, as it allowed concomitant medications.
- Costs, utilities, and exacerbation rates were taken from published models; however, they are health state-related and not treatment-related (ie, exacerbation rates were not taken from the individual clinical trials included in the indirect treatment comparison).
- COPD severity is classified using GOLD 2006 guidelines instead of the more recent 2013 guidelines for reasons described in the methods. Although the updated guidelines also take symptoms and exacerbation history into account, they still use FEV_1 as one of the key components of assessing COPD severity.

Discussion

- This cost-utility analysis suggests that the use of aclidinium is potentially cost effective compared with tiotropium in the maintenance treatment of patients with moderate to severe COPD in the United States.
- The precision of this estimate is limited mainly due to the lack of long-term head-to-head trials between the treatments under consideration.

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