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Cost effectiveness of adding budesonide/formoterol to tiotropium in COPD in four Nordic countries

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Summary
Objective: Assess the cost effectiveness of budesonide/formoterol (BUD/FORM) Turbuhaler®+tiotropium (TIO) HandiHaler® vs. placebo (PBO)+TIO in patients with chronic obstructive pulmonary disease (COPD) eligible for inhaled corticosteroids/long-acting β_2-agonists (ICS/LABA).
Methods: The cost-effectiveness analysis was based on the 12-week, randomised, double-blind CLIMB trial. The study included 659 patients with pre-bronchodilator forced expiratory volume in 1 s $\leq$ 50% and $\geq$1 exacerbation requiring systemic glucocorticosteroids or antibiotics the

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preceding year. Patients received BUD/FORM 320/9 μg bid + TIO 18 μg qd or PBO bid + TIO 18 μg qd. Effectiveness was defined as the number of severe exacerbations (hospitalisation/emergency room visit/systemic glucocorticosteroids) avoided. A sub-analysis included antibiotics in the definition of an exacerbation. Resource use from CLIMB was combined with Danish (DKK), Finnish (€), Norwegian (NOK) and Swedish (SEK) unit costs (2010). The incremental cost-effectiveness ratios (ICERs) for BUD/FORM + TIO vs. PBO + TIO were estimated using descriptive statistics and uncertainty around estimates using bootstrapping. Analyses were conducted from the societal and healthcare perspectives in Denmark, Finland, Norway and Sweden.

Results: From a societal perspective, the ICER was estimated at €174/severe exacerbation avoided in Finland while BUD/FORM + TIO was dominant in the other countries. From the healthcare perspective, ICERs were DKK 1580 (€212), €307 and SEK 1573 (€165) per severe exacerbation avoided for Denmark, Finland and Sweden, respectively, while BUD/FORM + TIO was dominant in Norway. Including antibiotics decreased ICERs by 8–15%. Sensitivity analyses showed that results were overall robust.

Conclusion: BUD/FORM + TIO represents a clinical and economic benefit to health systems and society for the treatment of COPD in the Nordic countries. (ClinicalTrials.gov Identifier: NCT00496470).

Introduction

Population-based studies provide evidence of high prevalence of chronic obstructive pulmonary disease (COPD) within the Nordic countries, with age-dependant rates as high as 9% in Finland, 10% in Norway, 14% in Sweden and 17% in Denmark [1–9]. COPD entails a substantial economic burden. For example, the total annual societal costs of COPD in Finland in 2006 were €194 million, of which more than 50% were healthcare costs [10]. A study from Sweden estimated total costs of COPD to society at €982 million in 1999 [11]. Studies from the other Nordic countries emphasise the substantial costs related to COPD exacerbations [12–14]. In addition, repeated acute exacerbations of COPD have been shown to permanently affect lung function and patients' quality of life [15–17]. Therefore, reducing exacerbations and associated hospital admissions has been established as an important clinical and societal goal [18,19].

Budesonide/formoterol (BUD/FORM) is a combined long-acting β_2-agonist (LABA) and inhaled corticosteroid (ICS). When BUD/FORM twice daily (bid) was added to tiotropium (TIO; a long-acting muscarinic antagonist) once daily (qd) in the CLIMB trial, it significantly reduced the number of severe exacerbations by 62% [20]. Here, severe exacerbations were defined as requiring hospitalisation and/or emergency room (ER) visit and/or use of systemic glucocorticosteroids (GCS). An economic evaluation is required to investigate how this reduction relates to the increased costs of maintenance treatment.

In a cost-effectiveness analysis (CEA), the costs and effects of one healthcare intervention relative to another are assessed by calculating the incremental cost-effectiveness ratio (ICER). To determine whether a treatment is cost effective compared with an alternative, the cost per gained unit of effectiveness (e.g., cost per exacerbation avoided) as measured by the ICER must be compared with the payer's willingness to pay (WTP) for that particular gained unit of effectiveness. If the ICER is lower than the WTP, then the programme may be considered cost effective. A treatment is said to be dominant when it has a better outcome at a lower cost than the comparator. While cost-effectiveness studies for COPD treatments often estimate the cost per exacerbation avoided, a WTP value for an exacerbation avoided has not officially been agreed upon. Instead, results may be compared to ICERs and/or WTPs published and used in other studies, such as those by Najafzadeh et al. (2008) [21], Oostenbrink et al. (2004) [22] and Rutten-van Molken et al. (2007) [23].

A previous CEA of adding BUD/FORM to TIO has been performed for healthcare perspectives in Australia, Canada and Sweden [24], based on the clinical results from the CLIMB trial [20]. However, due to differences in healthcare systems, economic evaluations cannot easily be transferred and applied across countries. Our objective was to investigate the cost effectiveness associated with triple therapy (BUD/FORM + TIO) relative to single therapy (placebo [PBO]+TIO) from societal and healthcare perspectives in Denmark, Finland, Norway and Sweden. Hence, the present analysis builds on the methodology of the previous CEA [24], but also includes productivity losses since authorities in these countries also consider the societal perspective when making decisions relating to the economic value of healthcare treatments [25–28].

Methods

Study design

Resource use and effectiveness outcomes were based on the CLIMB study, a 12-week, randomised, double-blind, placebo controlled, parallel-group, multicentre study [20]. Patients were recruited from outpatient clinics and the study was conducted in 102 research sites in nine countries, including Australia (10 sites), Canada (16), France (12), Germany (12), Hungary (13), Poland (10), Slovakia (13), Spain (6) and Sweden (10). The study had a sample size of 659 patients, 329 in the BUD/FORM (320/9 μg bid)+TIO (18 μg qd) arm and 330 in the PBO + TIO arm. Terbutaline (TER; 0.5 mg/dose) was used as needed in both arms. All

patients were aged ≥40 years, had pre-bronchodilator forced expiratory volume in 1 s (FEV_1) not exceeding 50% of the predicted normal value and at least one exacerbation requiring systemic GCS and/or antibiotics in the preceding year. Based on post-bronchodilator FEV_1, approximately 25%, 64% and 11% of patients were classified as being Global initiative for chronic Obstructive Lung Disease (GOLD) stage II, III and IV [18], respectively. Baseline characteristics, treatment compliance and withdrawal rates over the trial period were comparable between the two treatment groups. A full description of the CLIMB study including the study design can be found in the clinical publication [20].

Time horizon and perspectives

The time horizon for the CEA, 3 months, was based on the duration of the CLIMB trial. The CEA considered results from both a societal perspective (which includes both the direct and indirect costs of COPD) and from a healthcare perspective (taking only direct costs into account) as stipulated in the Danish [25], Finnish [26], Norwegian [27] and Swedish [28] guidelines for economic evaluations.

Effectiveness

The effectiveness measure used in the economic analysis was the number of severe exacerbations avoided with BUD/FORM + TIO relative to PBO + TIO. In the CLIMB trial, a severe exacerbation was defined as one or more of the following: hospitalisation, ER visit or use of systemic GCS. Adjacent treatments were counted as one severe exacerbation while treatments that were at least 1 treatment-free day apart were counted as separate severe exacerbations. The number of severe exacerbations avoided was the effectiveness measure for this CEA. Antibiotic use, where exacerbation or COPD were stated as the reason for prescription by the investigator, was added to the definition of a severe exacerbation in a sub-analysis, as antibiotics are part of the exacerbation management in all countries in the analysis [29–32].

Healthcare resource use and costs

The resource use collected in the CLIMB trial and used in this CEA included hospitalisations (days), ER visits, BUD/FORM Turbuhaler® (Symbicort® Turbuhaler® 320/9 μg, bid, per protocol), TIO HandiHaler® (Spiriva® HandiHaler® 18 μg, qd, per protocol), TER Turbuhaler® (Bricanyl® Turbuhaler® 0.5 mg, as needed for rescue, actual use), systemic GCS (days) and antibiotics (days, when antibiotics were added to the definition of an exacerbation).

Although data on outpatient visits were not collected in the CLIMB trial, it was assumed that a general practitioner (GP) consultation had taken place when a patient was treated with systemic GCS or antibiotics if the treatment had not been initiated during an ER visit or a hospitalisation; if treatment was initiated during ER or hospitalisation, it was assumed that no GP resources were required. The first such treatment course was assumed to be associated with a GP visit, while any subsequent courses were assumed to be associated with a GP call. Only one GP consultation was applied if the patient started treatment with both systemic GCS and antibiotics at the same date. Cost per hospitalisation day was derived from official Diagnosis Related Group (DRG) data. The CLIMB data did not include the type of hospitalisation ward (intensive care unit [ICU] or general ward [GW]). Instead, the DRG costs applied were assumed to implicitly account for the distribution of ICU versus GW lengths of stay (LOS) of hospitalisations. In Norway, ER outpatient consultations rarely take place at hospitals but rather in GP-staffed urgent care centres. This was reflected in the relatively low unit cost of a Norwegian ER visit. For the other countries, the cost of an ER visit was assumed to be included in the DRG for patients hospitalised through the ER. The cost of an ER visit was added in Norway for such patients.

Pharmaceutical costs were based on pharmacy retail prices, excluding VAT but including any patient co-payment, and were collected from official databases [33–36]. The price per dose was applied to all protocol medications. For systemic GCS and antibiotics, the price per day based on average dose of the substance recommended by national guidelines and/or expert opinions was applied. In particular, the most commonly used systemic GCS was prednisolone in all countries (which was also the most frequently prescribed systemic GCS in the trial). Antibiotics were assumed to be amoxicillin plus clavulanic acid (Denmark), doxycycline (Finland and Sweden) and amoxicillin (Norway), based on expert opinion. If two or more antibiotic courses overlapped, the daily cost of the most common antibiotics was applied only once for all days of antibiotic treatment. When systemic GCS or antibiotics were administered in a hospital setting, drug costs were not added separately but were assumed to be covered by the hospitalisation cost.

Productivity losses

Sick leave due to severe COPD exacerbations was modelled in the analysis' societal perspective although these data were not collected within the CLIMB trial. The number of sick-leave days was based on severe exacerbation days from the CLIMB trial. Indirect costs were only applied to patients who were below the official retirement age in each country (Denmark and Sweden: 65 years, Finland: 63 years, and Norway: 67 years) [37]. Following the human capital approach (HCA), the national labour cost was used to calculate the cost of each day that patients were absent from their paid work.

Employment rates were based on the findings from a retrospective, non-interventional, epidemiological study in Sweden [38]. This study estimated that 36% of COPD patients in working ages (<65 years) in Sweden were full-time or part-time gainfully employed. The employment rate for patients with severe COPD was estimated at 22%. The same employment rate (36% in base case) was used for all Nordic countries and the patients were assumed to be full-time employed.

The national annual average labour cost (including employers' social contributions) for each country was used to estimate the unit cost per day. [39]. Since there was no information on whether the exacerbation days occurred on working days, the applied labour cost per day was based on the total annual labour compensation divided by 365 days (i.e. reflecting labour cost per day and not per working day).

This was then multiplied by the number of severe exacerbation days. Leisure time, house work and caregivers' productivity losses were not considered in this analysis.

Cost estimation

The healthcare perspective included direct costs (medication use and non-medication healthcare resource use) and the societal perspective included direct plus indirect costs (productivity loss due to severe COPD exacerbations). Costs were calculated by applying country-specific unit costs from Denmark (DKK), Finland (€), Norway (NOK) and Sweden (SEK) to the CLIMB trial's pooled resource use. All unit costs were year 2010 values (except medication costs which were collected in 2011 and not indexed) as presented in Table 1, indexed where necessary using each country's price indexes from national statistics [40—42]. Official price lists, DRG data and national databases as well as publications were used to cost hospitalisation days [43—46], ER visits [47—50], GP consultations [47,49—52], medication [33—36] and productivity loss [39]. Costs were not discounted due to the study time horizon of <1 year. Average annual exchange rates of year 2010 were applied to the individual country costs (€1 = DKK7.447, €1 = NOK8.007 and €1 = SEK9.541) [53—55].

Statistical methods and analyses

Mean values of the use for each resource type in each treatment arm and the corresponding mean difference between arms were calculated with descriptive statistics based on the full analysis set ($n = 659$), consisting of the pooled data from the CLIMB trial. All values were calculated as per patient 3 months' exposure by dividing the summed resource use across patients with the summed exposure time (yielding resource use per patient per day) and multiplied by 365.25/4. To estimate the uncertainty around the mean difference between treatment arms, 95% confidence intervals (CI) were estimated with bootstrapping. Bootstrapping is a non-parametric technique, which involves large numbers of repetitive computations to estimate the shape of a statistic's sampling distribution empirically. In this analysis, 1000 bootstrap samples, each consisting of $n = 659$ observations, were drawn with replacement from the full analysis set. For each of the bootstrap samples and for each resource type, the mean use in each treatment arm and the corresponding differences between treatment arms were calculated. Thus, the bootstrap procedure yields a distribution for each resource type consisting of 1000 observations of the difference between treatment arms. This distribution was used to estimate the 95% CI for that difference. The CI was estimated as the mean difference ± 1.96 multiplied by the standard deviation of the 1000 differences.

For each country, ICERs from the societal and healthcare perspectives were analysed separately, with and without antibiotics included in the definition of a severe exacerbation. ICERs were estimated by descriptive statistics (Δ mean cost/Δ mean severe exacerbation). To assess the uncertainty around the ICER estimates, the ICER was calculated for each of the bootstrap samples and the result is presented in cost-effectiveness scatter plots. The cost-effectiveness acceptability curves (CEACs) relate ICER estimates to potential WTP values. For each WTP, the CEAC shows the proportion of ICER estimates that are lower than the WTP, i.e. the estimated probability that BUD/FORM + TIO is cost effective relative to PBO + TIO for that particular WTP to avoid a severe exacerbation.

As parameters were estimated with uncertainty, one-way sensitivity analyses were performed to analyse the

Table 1 Unit costs 2010 [33—36,39,43—52].

	Unit costs			
	Denmark	Finland	Norway	Sweden
	DKK (€)	€	NOK (€)	SEK (€)
Healthcare costs				
Hospitalisation, day[a]	5376 (722)	499	5361 (670)	6005 (629)
ER, visit	1000 (134)	307	341 (43)[b]	2416 (253)
GP, visit	197 (27)	92	283 (35)	1300 (136)
GP, call	46 (6)	19	51 (6)	650 (68)[c]
Medication costs				
BUD/FORM 320/9 μg, inhalation	8.27 (1.11)	1.01	6.33 (0.79)	10.00 (1.05)
TIO 18 μg, inhalation	11.47 (1.54)	1.65	10.84 (1.35)	13.81 (1.45)
TER 0.5 mg, inhalation	0.67 (0.09)	0.08	0.57 (0.07)	0.81 (0.08)
Systemic GCS, day	5.12 (0.69)	0.48	5.22 (0.65)	9.78 (1.03)
Antibiotics, day	8.52 (1.14)	0.51	9.30 (1.16)	7.60 (0.80)
Indirect cost				
Labour cost, day	1017 (137)	116	1295 (162)	1137 (119)

ER: Emergency room, GP: General practitioner, BUD/FORM: Budesonide/formoterol Turbuhaler®, TIO: Tiotropium HandiHaler®, TER: Terbutaline Turbuhaler®, GCS: Glucocorticosteroid, LOS: Length of stay in hospital, COPD: Chronic obstructive pulmonary disease.

[a] For Finland, Norway and Sweden, the cost per day was based on the average cost per stay (DRG088) and average LOS DRG088 (COPD). For Denmark, costs were weighted based on complicated or uncomplicated exacerbations; codes DkDRG0423, DkDRG0424 and DkDRG0425 were used. Exchange rates (€1 = DKK7.447, €1 = NOK8.007 and €1 = SEK9.541).

[b] For Norway this cost is more accurately described as cost per 'urgent, unscheduled GP visit'.

[c] 50% of GP visit (expert opinion).

effect of changes to the parameters in the CEA on the ICER. The exacerbation rate scenarios served two distinct purposes. The first tested the effect of changing the baseline risk of severe exacerbation in either arm and the second changed the effectiveness of BUD/FORM in reducing that risk. Parameters that were changed in the one-way deterministic sensitivity analyses were related to:

- exacerbation rate:
  - exacerbation rate in each arm ± one standard deviation (SD)
  - exacerbations avoided between arms ± one SD
- resource use given exacerbation:
  - hospitalisation days in each arm ± one SD
  - systemic GCS days in each arm ± one SD
  - ER visits in each arm ± one SD
  - trial-based hospital LOS replaced by national averages
  - no GP consultations for systemic GCS/antibiotics prescriptions
  - no GP consultations for subsequent systemic GCS/antibiotic prescriptions
  - GP visit or GP call for all systemic GCS/antibiotics courses
  - addition of one GP (follow-up) visit or call for each exacerbation
- resource unit costs:
  - hospital unit cost ± 20%
  - ER unit cost ± 20%
  - ER unit cost equal to GP visit cost
- productivity losses:
  - employment rate of 100% or 22%
  - length of absenteeism ± 20%
  - labour costs ± 10%

Results

Effectiveness

In the CLIMB trial, 25 patients (7.6%) experienced at least one severe COPD exacerbation over the treatment period in the BUD/FORM + TIO group, compared with 61 patients (18.5%) in the PBO + TIO group [20]. In total, 0.18 (95% CI 0.09, 0.27) severe exacerbations were avoided per patient over 3 months of BUD/FORM + TIO treatment (Table 2). Including antibiotics in the definition of a severe exacerbation increased the mean difference between treatment arms to 0.19 (95% CI 0.09, 0.28).

Healthcare resource use

Treatment with BUD/FORM + TIO resulted in fewer healthcare visits, lower levels of non-protocol medication required and a reduced amount of productivity loss compared with PBO + TIO (Table 3).

Costs

A summary of the direct and indirect costs and their differences between treatment arms per patient using Danish, Finnish, Norwegian and Swedish unit costs is presented in Table 4 (the results from the sub-analysis including antibiotic use can be found in the online appendix). The major cost driver for the BUD/FORM + TIO group across all countries was the total cost of medication (67.1–74.9%). The major cost component for the PBO + TIO group across all countries was the total cost of healthcare visits (41.2–47.3%), which again was mainly due to the cost of hospitalisation days (75.4–94.7%, not shown). Direct costs were higher with BUD/FORM + TIO than with PBO + TIO in Denmark, Finland and Sweden. Total costs were lower with BUD/FORM + TIO in all countries except Finland (Table 4).

Incremental cost-effectiveness ratios

ICER values are presented in Table 5. From the societal perspective, the cost per severe exacerbation avoided for patients using BUD/FORM + TIO versus PBO + TIO was estimated at €174 for Finland. BUD/FORM + TIO was dominant for Denmark, Norway and Sweden. In the sub-analysis including antibiotics, the cost per severe exacerbation avoided was €149 for Finland; BUD/FORM + TIO was dominant for Denmark, Norway and Sweden.

Table 2 Three-month mean severe exacerbation rate per patient by treatment arm.

Exacerbation type	BUD/FORM + TIO (n = 329)	PBO + TIO (n = 330)	Mean difference[a] (95% CI)
Hospitalisation	0.02	0.04	0.02 (−0.01, 0.06)
ER (not associated with hospitalisation)	0.01	0.04	0.03 (0.00, 0.05)
ER (any exacerbation requiring ER)	0.02	0.05	0.03 (−0.00, 0.06)
Systemic GCS	0.10	0.27	0.17 (0.08, 0.25)
Total number of exacerbations	0.11	0.29	0.18 (0.09, 0.27)
Antibiotics[b]	0.11	0.18	0.07 (0.01, 0.14)
Total number of exacerbations (including antibiotics)	0.13	0.32	0.19 (0.09, 0.28)

ER: Emergency room, BUD/FORM: Budesonide/formoterol Turbuhaler®, TIO: Tiotropium HandiHaler®, PBO: Placebo, CI: Confidence interval, GCS: Glucocorticosteroid, COPD: Chronic obstructive pulmonary disease.

[a] Measures exacerbations avoided with BUD/FORM + TIO relative to PBO + TIO.

[b] Reason for antibiotic prescription: Exacerbation or COPD. All values in each treatment arm as well as differences between arms were calculated with descriptive statistics while the 95% CI were estimated with bootstrapping.

Table 3 Mean resource use and exacerbations per patient in three months.

	BUD/FORM+TIO (n = 329)	PBO + TIO (n = 330)	Mean difference (95% CI)
Healthcare visits			
Hospitalisation (days)	0.10	0.31	−0.21 (−0.48, 0.06)
ER visits (not associated with hospitalisation)	0.01	0.04	−0.03 (−0.05, −0.00)
ER visits (any exacerbation requiring ER)	0.02	0.05	−0.03 (−0.06, 0.01)
GP visits[a]			
Systemic GCS prescription	0.07	0.17	−0.10 (−0.15, −0.05)
Systemic GCS and/or antibiotics	0.09	0.21	−0.11 (−0.17, −0.06)
GP calls[a]			
Systemic GCS prescription	0.01	0.05	−0.03 (−0.07, 0.01)
Systemic GCS and/or antibiotics	0.02	0.06	−0.04 (−0.08, 0.01)
Medication			
BUD/FORM (inhalations)	182.63	0	182.63
TIO (inhalations)	91.31	91.31	0
TER (inhalations)	272.93	349.17	−76.24 (−115, −38)
Systemic GCS (days)[b]	0.91	2.08	−1.16 (−1.88, −0.44)
Antibiotics (days)	0.77	1.39	−0.61 (−1.14, −0.07)
Productivity loss			
<63 years: sick leave (days)	0.44	0.64	−0.20 (−0.61, 0.19)
<65 years: sick leave (days)	0.41	0.72	−0.32 (−0.68, 0.04)
<67 years: sick leave (days)	0.35	0.70	−0.36 (−0.68, −0.03)
Productivity loss including antibiotics			
<63 years: sick leave (days)	0.51	0.72	−0.21 (−0.65, 0.22)
<65 years: sick leave (days)	0.49	0.82	−0.33 (−0.74, 0.06)
<67 years: sick leave (days)	0.44	0.80	−0.36 (−0.71, −0.00)

All values in each treatment arm as well as differences between arms were calculated with descriptive statistics while the 95% CI were estimated with bootstrapping.
BUD/FORM: Budesonide/formoterol Turbuhaler®, TIO: Tiotropium HandiHaler®, PBO: Placebo, ER: Emergency room, GP: General practitioner, GCS: Glucocorticosteroid, TER: Terbutaline Turbuhaler®, CI: Confidence interval, CEA: Cost-effectiveness analysis.
[a] Systemic GCS/antibiotic treatments not initiated during hospitalisation or at an ER were assumed to be associated with GP consultations (a GP visit for the first prescription and a GP call for subsequent prescriptions).
[b] The number of systemic GCS days in this analysis is slightly different from those presented in the previous CEA [26], as all GCS days were included in the previous CEA regardless of when they occurred (i.e. they were also included even when occurring during hospitalisation).

From a healthcare perspective, the cost per severe exacerbation avoided for patients using BUD/FORM + TIO versus PBO + TIO was estimated at DKK 1580 (€212), €307 and SEK 1573 (€165) in Denmark, Finland and Sweden, respectively; BUD/FORM + TIO was dominant for Norway. In the sub-analysis including antibiotics, the cost per severe exacerbation avoided was estimated to be DKK1449 (€195), €281 and SEK1342 (€142) for Denmark, Finland and Sweden, respectively, and dominant for Norway. Thus, for both perspectives, inclusion of antibiotics in the definition of a severe exacerbation yielded results that were qualitatively similar, although ICERs were reduced by 8–15%.

Fig. 1 presents the cost-effectiveness scatter plots which show that BUD/FORM + TIO was associated with more severe exacerbations avoided for each sample realisation compared with PBO + TIO. From a societal perspective (not including antibiotics), the estimated probabilities that BUD/FORM + TIO was a dominant treatment option (lower-right quadrant) were 50% in Denmark, 32% in Finland, 74% in Norway and 52% in Sweden. The cost-effectiveness scatter plots for the sub-analysis where antibiotics treatment is included in the definition of a severe exacerbation can be found in the online appendix.

Fig. 2 shows the CEACs for the four countries with one diagram per country, each including four curves: healthcare versus societal perspective, both excluding and including antibiotics. The CEACs illustrate the relationship between the WTP to avoid a severe exacerbation and the probability of BUD/FORM + TIO being cost effective compared with PBO + TIO. As an example, using a WTP of €600 (DKK 4468; NOK 4804; SEK 5725) as in the previous CEA [24] yields probabilities of BUD/FORM + TIO being cost effective of 82%, 79%, 93% and 85% in Denmark, Finland, Norway and Sweden, respectively, from a societal perspective, excluding antibiotics. In addition, Fig. 2 shows that applying the societal perspective increases the probability of BUD/FORM + TIO being cost effective relative to applying the healthcare perspective. Including antibiotics in the definition of a severe exacerbation has little impact on the probability of the treatment being cost-effective.

Sensitivity analyses

Results from the one-way sensitivity analyses are presented in tornado diagrams, which illustrate how the ICER changes

Table 4 Total costs[a] per patient in 3 months (2010).

	Cost per patient		
	BUD/FORM+TIO (n = 329)	PBO + TIO (n = 330)	Mean difference (95% CI)
Denmark	DKK (€)	DKK (€)	DKK
Total cost of healthcare visits	554 (74)	1727 (232)	−1173 (−2642, 297)
Total cost of medication	2745 (369)	1292 (173)	1453 (1423, 1483)
Total direct cost	3299 (443)	3019 (405)	280 (−1219, 1779)
Total indirect cost	414 (56)	737 (99)	−323 (−696, 46)
Total costs	3713 (499)	3756 (504)	−42 (−1915, 1825)
Finland	€	€	€
Total cost of healthcare visits	59	182	−123 (−269, 24)
Total cost of medication	358	180	177 (174, 181)
Total direct cost	416	362	55 (−95, 204)
Total indirect cost	51	74	−24 (−71, 22)
Total costs	467	436	31 (−166, 227)
Norway	NOK (€)	NOK (€)	NOK
Total cost of healthcare visits	556 (69)	1716 (214)	−1160 (−2616, 295)
Total cost of medication	2306 (288)	1200 (150)	1106 (1080, 1132)
Total direct cost	2862 (357)	2916 (364)	−54 (−1536, 1427)
Total indirect cost	451 (56)	911 (114)	−460 (−884, −40)
Total costs	3313 (414)	3827 (478)	−514 (−2420, 1388)
Sweden	SEK (€)	SEK (€)	SEK
Total cost of healthcare visits	713 (75)	2187 (229)	−1474 (−3227, 280)
Total cost of medication	3317 (348)	1564 (164)	1753 (1714, 1791)
Total direct cost	4030 (422)	3751 (393)	279 (−1513, 2072)
Total indirect cost	463 (49)	824 (86)	−361 (−778, 51)
Total costs	4494 (471)	4575 (480)	−82 (−2291, 2122)

Exchange rates (€1 = DKK7.447, €1 = NOK8.007 and €1 = SEK9.541). All values in each treatment arm as well as differences between arms were calculated with descriptive statistics while the 95% CI were estimated with bootstrapping.
BUD/FORM: Budesonide/formoterol Turbuhaler®, TIO: Tiotropium HandiHaler®, PBO: Placebo, CI: Confidence interval.
[a] Excluding antibiotics. The corresponding table for the sub-analysis, which includes antibiotics in the definition of a severe exacerbation can be found in the online appendix.

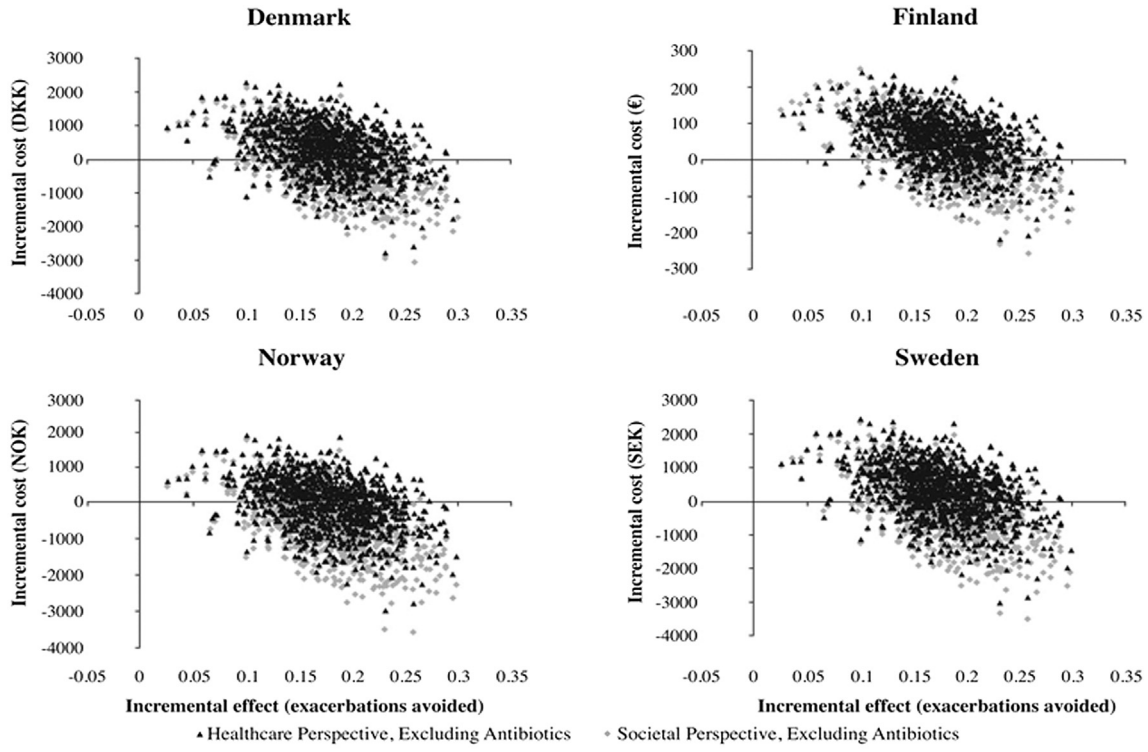
from the base-case under the different scenarios for each country. In total, 16 tornado diagrams (by country, by perspective and including vs. excluding antibiotics) were constructed, which show qualitatively similar results. The Swedish societal perspective including antibiotics (Fig. 3) is presented as an example of the results from this analysis. All 16 tornado diagrams are presented in the online appendix.

Sensitivity analyses indicated that results are overall robust and that most of the tested scenarios have only minor effects on the ICER estimates. From the societal perspective, the variables with the largest effect on the

Table 5 Incremental cost-effectiveness ratios of BUD/FORM + TIO relative to PBO + TIO.

	Societal perspective		Healthcare perspective	
	Excluding antibiotics	Including antibiotics	Excluding antibiotics	Including antibiotics
Denmark, DKK (€)	Dominant	Dominant	1580 (212)	1449 (195)
Finland, €	174	149	307	281
Norway	Dominant	Dominant	Dominant	Dominant
Sweden, SEK (€)	Dominant	Dominant	1573 (165)	1342 (141)

The effectiveness measure used was severe exacerbations avoided.
BUD/FORM: Budesonide/formoterol Turbuhaler®, TIO: Tiotropium Handihaler®, PBO: Placebo.



BUD/FORM: Budesonide/formoterol Turbuhaler®, TIO: Tiotropium Handihaler®, PBO: Placebo

Figure 1 Cost-effectiveness scatter plots of BUD/FORM + TIO relative to PBO + TIO.

ICERs were hospitalisations (cost, frequency, length) and employment rates for all four countries.

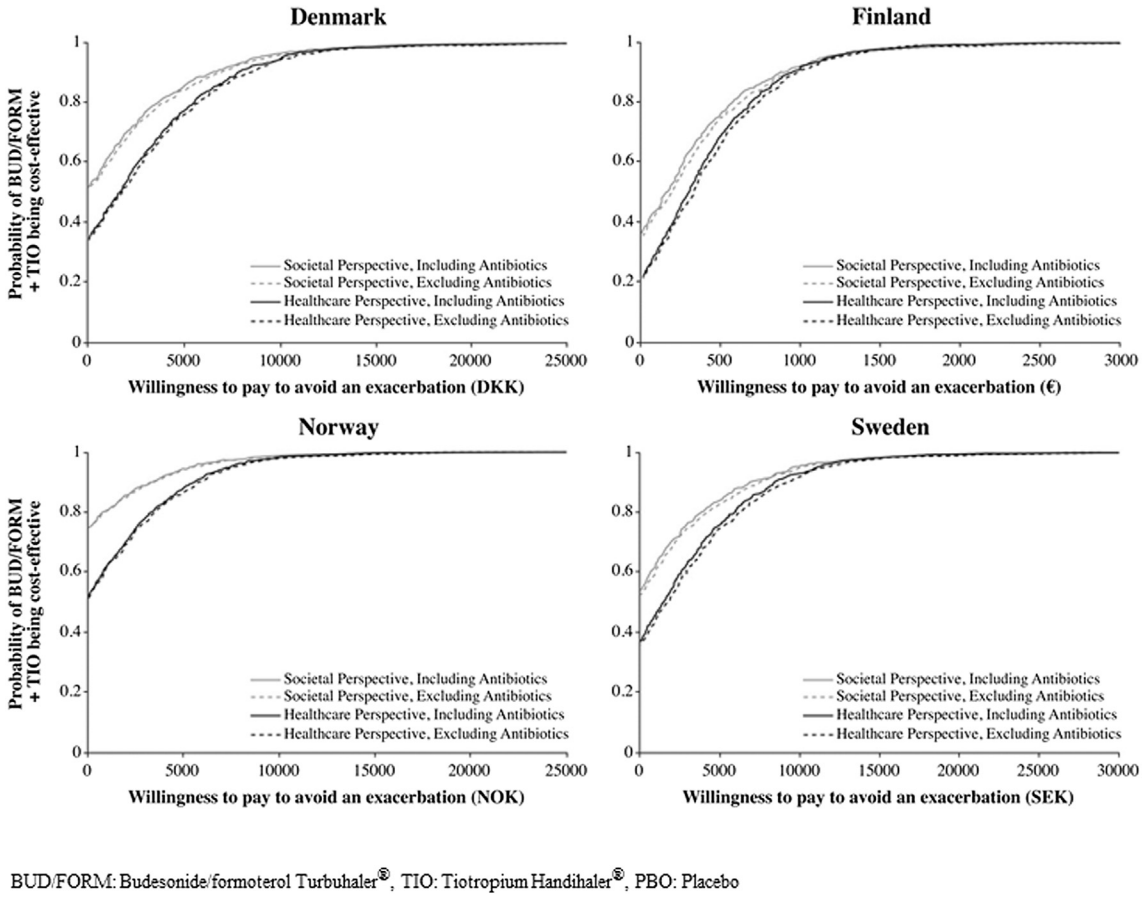
Discussion

The above analysis has shown that BUD/FORM + TIO compared with PBO + TIO from both societal and healthcare perspectives in the Nordic countries improves clinical outcomes at a low cost level or even at reduced costs over a 3-month time horizon. Results incorporating a societal perspective provided an ICER of €174 in Finland for BUD/FORM + TIO compared with PBO + TIO while BUD/FORM + TIO was the dominant treatment option in Denmark, Norway and Sweden. A sub-analysis incorporating antibiotic treatment in the definition of a severe exacerbation was shown to decrease ICERs by 8—15%. Sensitivity analyses revealed that results were overall robust, with parameters related to hospitalisation and employment rate being most influential.

There is no officially established WTP (for avoided exacerbations) with which to compare the estimated ICERs of our analysis. Instead, comparisons were made with WTP and/or ICERs from other published studies. However, one should be careful when comparing ICERs across studies as treatment alternatives, subject pools, resources costed, perspective used, study designs and inputs may differ considerably.

The only other analysis to have estimated the cost effectiveness of BUD/FORM + TIO is the previous CEA based on the CLIMB trial [24]. As mentioned, that analysis used a WTP of €600 and found probabilities of BUD/FORM + TIO being cost effective of 96%, 83% and 74% from Australian, Canadian and Swedish healthcare perspectives, respectively. The corresponding probabilities in the present analysis (healthcare perspective without antibiotics) using the WTP of €600 (DKK 4468; NOK 4804; SEK 5725) were 73%, 74%, 86% and 77% in Denmark, Finland, Norway and Sweden, respectively. One reason why BUD/FORM + TIO might have a higher probability of being cost effective in Australia than in the Nordic countries is the higher hospitalisation cost in Australia relative to the cost of BUD/FORM.

Other studies have estimated the cost effectiveness (all measuring the incremental cost per exacerbation avoided) of alternative triple and monotherapies in COPD. Based on a 52-week trial, Najafzadeh et al. (2008) [21] estimated the cost effectiveness of adding the fixed combination of fluticasone/salmeterol (FLU/SAL) to TIO for COPD from a Canadian healthcare perspective. Exacerbations were defined as events requiring treatment with steroids/antibiotics. The ICER of FLU/SAL + TIO was estimated at CAN$6510 per exacerbation avoided, which was not deemed cost effective. Potential explanations for the higher ICER compared with the current analysis include the higher maintenance costs and the smaller relative reduction in the exacerbation rate. For example, FLU/SAL + TIO was shown to reduce exacerbations by about 13% (from 1.56 per year to 1.35 per year) whereas BUD/FORM + TIO in CLIMB was found to reduce severe exacerbations by about 62% (from 0.29 to 0.11 per three months, see Table 2). These differences in

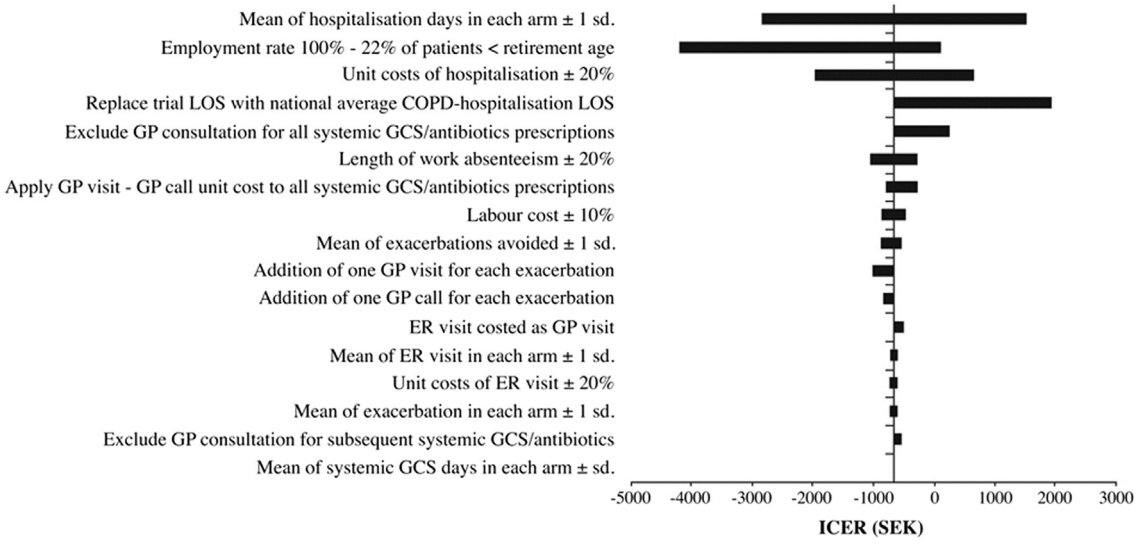


BUD/FORM: Budesonide/formoterol Turbuhaler®, TIO: Tiotropium Handihaler®, PBO: Placebo

Figure 2 Cost-effectiveness acceptability curves.

effectiveness percentages may be due to differences in healthcare systems and patient populations etc., and are provided purely as potential explanations for the different cost-effectiveness results.

Oostenbrink et al. (2004) [22] and Rutten-van Mölken et al. (2007) [23] estimated the cost effectiveness of monotherapies (ipratropium vs TIO and roflumilast vs PBO, respectively) and, as such, are not directly comparable to



SD: Standard deviation (based on bootstrapped distributions), LOS: Length of stay in hospital, GP: General practitioner, GCS: Glucocorticosteroid, ER: Emergency room.

Figure 3 One-way sensitivity analyses results for Sweden based on the societal perspective including antibiotics.

the present analysis. Oostenbrink et al. [22] found an incremental cost per exacerbation avoided of €667 from a Dutch healthcare perspective and reported probabilities of being cost effective using a WTP of €2000. Rutten-van Mölken et al. (2007) [23] found a cost per (severe or moderate) exacerbation avoided of €2356 from a UK societal perspective and of €1755 from the healthcare perspective and used WTP thresholds of €5000 and €50,000.

While cost-effectiveness results cannot easily be compared across studies because effectiveness, costs and definitions vary, it can be noted that the incremental costs per severe exacerbation avoided in the present analysis were all considerably smaller than those mentioned above. Also, the other studies used long time horizons compared with that of 3 months in the CLIMB study. Applying the lowest of the WTPs from the above-mentioned studies, €2000, to the results of the present analysis yielded probabilities of BUD/FORM being cost effective of 99–100% for the two perspectives across the four Nordic countries.

COPD is a chronic disease, so ideally economic evaluations of different treatments should have a lifetime perspective. Extrapolation of the results was not carried out beyond the 3-month clinical trial as this may lead to increased uncertainty in the estimates. One potential advantage of basing the analysis on a short trial is the low (and similar across treatments, 7.9% in BUD/FORM + TIO and 8.5% in PBO + TIO) discontinuation rate [20], which facilitates comparison and may reduce selection biases.

While some studies define severe exacerbations as hospitalisations only, the broader definition of a severe exacerbation used in this present analysis is indeed in line with many clinical studies performed to date, and was based on the CLIMB clinical trial parameters. In addition to the economic evaluations mentioned above, a number of examples of previous studies incorporating systemic GCS as part of the definition of exacerbations can be found in the published literature [56–58].

Economic evaluations often use quality-adjusted life years (QALYs) as an effectiveness measure to more precisely capture effects on the patient's health status. In the CLIMB trial, health status was assessed using St George's Respiratory Questionnaire – COPD (SGRQ-C), which, unlike the European Quality of Life – 5 Dimensions (EQ-5D), is not a utility measure. Therefore, it could not be used directly to calculate QALY values. Based on the UK's National Institute for Health and Clinical Excellence's (NICE) recommendation of not mapping SGRQ to EQ-5D [59], QALYs were not estimated for this present analysis even though a measure of health-related quality of life would have enhanced the comparability of these results with other studies in different disease areas. Note, that by purely estimating the cost per severe exacerbation avoided, the present analysis ignores the positive effects of adding BUD/FORM to TIO on health-related quality of life. In particular, the CLIMB trial showed that BUD/FORM + TIO, relative to PBO + TIO, improved SGRQ-C scores and led to rapid and sustained improvements in lung function, (overall and morning) symptoms and the ability to perform morning activities [20].

In the CLIMB trial, antibiotics were not included in the definition of exacerbation, but data, as well as the reasons stated by the investigator for the antibiotic use, were collected. Antibiotics are used in the management of exacerbations in not just Nordic and international guidelines [18,29–32], but also in CLIMB as 86% of the patients had been treated with antibiotics at their last exacerbation before entering the study. In the trial, the numbers of COPD-related prescriptions of antibiotics were 31 ($n = 27$) and 52 ($n = 48$) in the BUD/FORM + TIO and PBO + TIO groups, respectively [20]. Therefore, a sub-analysis of the CEA included antibiotics in the definition of exacerbation, which is not unheard of in clinical trials [60,61]. The effect of including antibiotics in the definition of an exacerbation on the results was not clear *ex ante*. It could be that including antibiotics would turn otherwise separate treatments into overlapping treatments, thereby reducing the number of exacerbations in either treatment arm while increasing costs. The analysis showed that the cost effectiveness of BUD/FORM + TIO was robust to including antibiotics in the definition of an exacerbation and even decreased ICERs by 8–15%.

Some limitations in conducting this present analysis should be highlighted in order to help with the interpretation of these results. Firstly, the CLIMB study was not designed to prospectively gather data on healthcare utilisation and sick-leave costs. As a result, costs associated with severe exacerbations were applied retrospectively in this analysis. As the CLIMB study was not powered to show national differences in severe exacerbations or healthcare utilisation, it was not possible to perform country-specific sub-analyses due to the small number of patients and severe exacerbations.

It should also be acknowledged within this present analysis that Sweden was the only country represented in terms of patients from actual research sites involved in the CLIMB trial. However, the main cost driver in COPD in general, and in this study in particular, was severe exacerbations. Given the similar genetic background and demographics of patients and similarities in healthcare systems within these four Nordic countries, it is likely that severe exacerbation rates would not differ much across the countries.

The present analysis included some data that were not collected as part of the CLIMB trial. No information on GP consultations was collected, and employment rates were based on the findings from an epidemiological study in Sweden [38] (36% of COPD patients aged <65 years in Sweden were in full- or part-time employment and 22% of patients with severe COPD were employed). However, the sensitivity analysis showed that results were robust to changes in the GP consultation assumptions. Assumptions regarding indirect costs (particularly sick leave due to COPD) were made to estimate results from a societal perspective. Sick leave was assumed to occur only on days when patients received treatment for severe exacerbations and patients were thus assumed to resume work immediately after ending treatment. As it was not recorded whether exacerbations occurred when patients would otherwise have been working, the cost per day was assumed to be the annual labour compensation divided by 365.25 instead of dividing by the number of annual workdays. Applying the cost per workday instead would have increased the indirect cost per day and would have made BUD/FORM + TIO even more cost effective, as indicated by

the one-way sensitivity analysis. Indirect costs arising from caregivers, productivity losses from early retirement and presenteeism (i.e. reduced work productivity) were not included in the analysis. Taken together, these limitations may mean that the true indirect costs were underestimated. In contrast, some argue that the HCA overestimates indirect costs as, for example, co-workers may be able to cover for sick colleagues. However difficult they are to estimate, there is no doubt that indirect costs are important and will be even more important given ageing populations and raising of retirement ages [62].

A degree of uncertainty exists as to the external validity of our results outside the setting of a clinical randomised trial. The close monitoring in randomised controlled trials itself might be considered part of a "treatment" strategy. Furthermore, other studies have suggested that both exacerbation rates and healthcare utilisation are higher in clinical trials, than in population-based studies. One suggested reason is that clinical trials often recruit patients from hospital clinics and that these patients are in worse condition than the average patient in the overall population. For example, Nielsen et al. (2011) [63] compared hospital-recruited patients with COPD patients in the general population and, although the authors adjusted for disease severity, education, gender, smoking habits, comorbidities and exacerbations, there was a noticeable difference in costs between these two groups. If this applied to the current study, the cost-effectiveness results would be different than those anticipated with a population-based study sample of COPD patients and the difference would be similar to the one-way sensitivity analyses relating to exacerbation rates. The same problem would, of course, apply to any other clinical study with a hospital-recruited setting.

As would be expected, there was a degree of variation in terms of unit costs between the four countries; for example, the cost of an ER visit (Table 4). Even though unit costs differed somewhat across countries, conclusions from the CEA were quite similar. Norway was the only country where treatment with BUD/FORM + TIO was the dominant option versus PBO + TIO under all scenarios. This can, to some degree, be explained by high hospitalisation costs relative to the acquisition cost of BUD/FORM. Finland was the only country in which treatment with BUD/FORM was not dominant from any perspective. This can partly be explained by the low relative cost of hospitalisation in Finland.

Conclusion

By utilising the clinical findings from the CLIMB trial, this analysis indicates that BUD/FORM + TIO represents a clinical benefit to patients and an economic benefit to healthcare providers and society for the treatment of COPD patients eligible for ICS/LABA combination therapy in Denmark, Finland, Norway and Sweden. In particular, BUD/FORM + TIO was the dominant treatment option in Denmark, Norway and Sweden, and had an incremental cost per severe exacerbation avoided of €174 in Finland from a societal perspective excluding antibiotics. Sensitivity analysis was performed and supported the robustness of the finding that, based on the CLIMB trial, BUD/FORM when added to TIO has a high probability of being cost effective in each of the four countries.

Conflicts of interest

Rune Nielsen has received research grants from Yara Praxair, Boehringer Ingelheim and GlaxoSmithKline; received fees for speaking from AstraZeneca, Pfizer and Boehringer Ingelheim; received travel expenses to the ATS conference from GlaxoSmithKline; received travel expenses to the ERS conference from GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim and Pfizer.

Hannu Kankaanranta has received fees for speaking from Almirall, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Leiras, Orion Pharma, Novartis, Pfizer and MSD and travel expenses to congresses have been provided by Boehringer Ingelheim, GlaxoSmithKline, Leiras, Mundipharma and Pfizer.

Leif Bjermer has during the last three years received honoraria for speaking and consulting and/or financial support for attending meetings from Almirall, AstraZeneca, Airsonett, André Pharma, Boehringer Ingelheim, GlaxoSmithKline, Merck, Mundipharma, Niigard Pharma, Novartis, Nycomed/Takeda and Orion Pharma.

Peter Lange has received research grants from Boehringer Ingelheim, GlaxoSmithKline and Pfizer; received fees for speaking from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Nycomed/Takeda and Pfizer; received fees for consulting from Almirall, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Mundipharma, Novartis, Nycomed/Takeda, and Pfizer.

Nicole Mittmann received travel funds from AstraZeneca to attend ERS 2010 and has received research funding from AstraZeneca and Boehringer Ingelheim.

Sofie Arnetorp, Morten Hedegaard and Anna Stenling were full-time employees and hold shares of AstraZeneca.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.rmed.2013.06.007.

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