The efficacy of extrafine beclomethasone dipropionate–formoterol fumarate in COPD patients who are not “frequent exacerbators”: a post hoc analysis of the FORWARD study

Dave Singh¹

Stefano Vezzoli²

Stefano Petruzzelli²

Alberto Papi³

¹Medicines Evaluation Unit, University of Manchester, Manchester, UK;

²Chiesi Farmaceutici SpA, Parma,

³Section of Respiratory Diseases, University of Ferrara, Ferrara, Italy

Abstract: The GOLD 2017 strategy document recommends that the pharmacological management of COPD patients be based on the risk of future exacerbations and the severity of symptoms. A threshold of two moderate exacerbations or one hospitalization is used to define high-risk patients. The FORWARD study was a randomized, double-blind, parallel-group trial that compared 48 weeks' treatment with extrafine beclomethasone dipropionate plus formoterol fumarate (BDP-FF) versus FF in severe COPD patients with a history of one or more exacerbations in the previous year. The new GOLD 2017 recommendations mean that many patients in the FORWARD study are now reclassified as GOLD B. We conducted a post hoc analysis of the FORWARD study, in order to investigate the effects of extrafine BDP/FF in patients with one exacerbation in the previous year, focusing on those categorized as group B using the GOLD 2017 definition. The analysis showed a 35% reduction in exacerbation rate with an inhaled corticosteroid (ICS) + long-acting β -agonist (LABA) versus LABA. We propose that ICS-LABA treatment is a therapeutic option for COPD patients with one exacerbation in the previous year.

Keywords: COPD, GOLD B, GOLD 2017, exacerbations, corticosteroid

Introduction

The GOLD 2017 strategy document recommends that the pharmacological management of COPD patients be based on the risk of future exacerbations and the severity of symptoms.¹ Forced expiratory volume in 1 second (FEV_1) has been removed as a criterion for identifying patients at high risk of exacerbation for pharmacological treatment decisions. A threshold of two exacerbations requiring antibiotics and/or corticosteroids or one hospitalization in the previous year is used as the sole criterion to identify patients at high risk of future exacerbations.

The ECLIPSE study showed that COPD patients with a history of one compared to zero exacerbations in the previous year were at increased risk of future exacerbations (OR 2.24, $P < 0.001$).² Other COPD cohorts have confirmed the increase in risk in patients with a history of one exacerbation in the previous year,³ supporting the case for treatment strategies to reduce future exacerbation risk in this subgroup of patients. However, GOLD has used two or more exacerbations, “frequent exacerbators”, as a threshold for preventive treatment, due to a greater level of risk (OR 5.72, $P < 0.001$ in the ECLIPSE study).²

Correspondence: Alberto Papi
Research Centre on Asthma and COPD,
Department of Medical Sciences,
University of Ferrara, 27 Via Rampari di
San Rocco, Ferrara 44121, Italy
Tel +39 0532 210 420
Fax +39 0532 210 297
Email ppa@unife.it

In line with the previous 2011 version, GOLD 2017 still recommends inhaled corticosteroid (ICS)–long acting β -agonist (LABA) combination inhalers for high-risk patients, ie, groups C and D,¹ but not for patients at lower risk (groups A and B). However, clinical trials investigating the effects of ICS-LABA combinations on exacerbation prevention have often used inclusion criteria of $FEV_1 < 50\%$ predicted and one or more exacerbations in the previous year.^{4–6} Under the GOLD 2011 recommendations, most enrolled in these studies were high-risk patients because of low FEV_1 , as only a minority had had two or more exacerbations in the previous year. However, the removal of FEV_1 from the risk assessment means that the patients enrolled in previous ICS/LABA clinical trials are a mixture of high- and low-risk patients using the GOLD 2017 definition.

The FORWARD study was a randomized, double-blind, parallel-group trial that compared 48 weeks' treatment with extrafine beclomethasone dipropionate (BDP) 100 μ g plus formoterol fumarate (FF) 6 μ g with pressurized metered-dose inhaler (two inhalations twice daily) versus FF 12 μ g with pressurized metered-dose inhaler (one inhalation twice daily).⁴ Severe COPD patients ($FEV_1 < 50\%$ predicted) with one or more exacerbations in the previous year were recruited. An important element of the design was that patients who had previously been taking the long-acting muscarinic antagonist (LAMA) tiotropium before screening were allowed to continue this treatment during the run-in period and after randomization to either BDP-FF or FF. This study demonstrated a significant and clinically relevant⁷ reduction in the rate of moderate–severe exacerbations (31% reduction using negative binomial model) and lung function improvement with BDP-FF compared to FF treatment. Moderate exacerbations were defined as events requiring treatment with oral CSs and/or antibiotics, while severe events required hospitalization.

The majority of patients in the FORWARD study did not meet the GOLD 2017 criteria for high exacerbation risk, as they had had one exacerbation in the previous year. While ICS-LABA treatments are not recommended by GOLD 2017 for such patients, the known increase in exacerbation risk in these patients indicates that treatments designed to prevent exacerbations should be considered. We conducted a post hoc analysis of the effects of extrafine BDP-FF in patients with one exacerbation in the previous year in the FORWARD study. We focused on patients with a higher level of symptoms who would be classified as GOLD B patients.

Materials and methods

The full design and results of the study have been published (registered at [ClinicalTrials.gov](https://clinicaltrials.gov), NCT00929851).⁴ The

study was approved by the ethics committee or institutional review board at each site (Tables S1–S3) and was done in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice (ICH/CPMP/135/95), and applicable local regulations. All patients provided written informed consent before any study-related procedure.

The COPD assessment test (CAT) and modified Medical Research Council (mMRC) scores were not collected at screening. We used the St George's Respiratory Questionnaire (SGRQ) to identify patients with greater symptoms using a threshold of ≥ 25 as previously described.⁸ This was called analysis 1. To provide confirmation of these results, we performed analysis 2, using items regarding breathlessness within the SGRQ that identify patients with dyspnea corresponding to mMRC scores ≥ 2 . The SGRQ questions were those about “what activities usually make subjects feel breathless” and those about “how activities may be affected by their breathing”. Answers indicating greater dyspnea than others of the same age or dyspnea while walking on level ground/need to rest were used to identify dyspnea corresponding to mMRC scores ≥ 2 .

Information on the number of exacerbations (requiring oral CSs and/or antibiotics) in the last year was available for each patient, but the specific number of these events resulting in hospitalization was not registered. A threshold of two exacerbations was used to define high-risk patients (GOLD C or D). Using the GOLD 2017 classification, 716 patients in analysis 1 (60.4% of 1,186 patients included in the intention-to-treat population) were categorized as GOLD B, with 87 (7.3%), 25 (2.1%), and 313 (26.4%) categorized as GOLD A, C, and D, respectively, while for 45 patients the category could not be assessed. There were similar proportions for analysis 2: 662 patients (55.8%) were GOLD B, with 160 (13.5%), 44 (3.7%), and 301 (25.4%) categorized as GOLD A, C, and D, respectively, while for 19 patients the category could not be assessed. In each GOLD group, the same approach for statistical analysis as originally used in the overall population was followed. The number of COPD exacerbations and predose morning FEV_1 were analyzed using a negative binomial model and a mixed model for repeated measures, respectively.⁴ Stratified analyses according to the concomitant use of tiotropium were additionally performed.

Results

For analysis 1, in GOLD B patients, adjusted exacerbation rates were 0.67 and 1.04 events/patient/year with BDP-FF and FF, respectively (Figure 1), with an adjusted RR of 0.65

Figure 1 Adjusted exacerbation rates (per patient/year) for analysis 1 in GOLD B and GOLD D patients.

Abbreviations: BDP-FF, beclomethasone dipropionate–formoterol fumarate; FF, formoterol fumarate.

($P<0.001$) in favor of BDP-FF (Table 1). Similar results were obtained for patients using tiotropium or no tiotropium (adjusted RR 0.54 and 0.76, respectively), although the latter was not statistically significant ($P=0.119$). Analysis 2 in GOLD B patients gave similar results: adjusted exacerbation rates were 0.71 and 1.09 events/patient/year with BDP-FF and FF, respectively (Figure 2), with an adjusted RR of 0.65 ($P<0.001$) in favor of BDP-FF. Effects of tiotropium versus no tiotropium use gave adjusted RRs of 0.58 and 0.7, respectively, with the latter again not reaching statistical significance ($P=0.054$).

For analyses 1 and 2, in GOLD B patients the adjusted mean difference in predose FEV₁ at week 12 was 69 mL ($P<0.001$) in favor of BDP-FF compared to FF. This significant difference between treatments was present in both analyses, irrespective of tiotropium use. Analyses for the overall population and GOLD D patients are shown in Table 1 and Figures 1 and 2. The number of exacerbations/patient/year was higher in GOLD D compared to GOLD B patients, but treatment effects were similar in these two groups for both FEV₁ changes and exacerbation rate reduction.

Discussion

This post hoc analysis focused on COPD patients with one exacerbation in the previous year and a high burden of symptoms. There was a 35% reduction in exacerbation rate with ICS-LABA compared to LABA. GOLD B consists of patients with no or one exacerbation in the previous year. The future exacerbation risk is higher in the subgroup with one event in the previous year,^{3,4} and we provide evidence for the efficacy of ICS-LABA over LABA alone in these patients.

It has been shown that some GOLD B patients are at high risk of rapid disease progression.⁹ The factors known to be associated with a greater decline in lung function include current smoking, emphysema, and exacerbations.¹⁰ GOLD B is clearly a heterogeneous patient group, and the data presented here support the use of ICS-LABA in a subset of GOLD B.

Table 1 COPD exacerbations and predose morning FEV₁ at week 12: BDP-FF versus FF overall in GOLD B and D patients (intention-to-treat population)

Group	n	COPD exacerbations: adjusted rate ratio*	Predose morning FEV ₁ (mL): adjusted mean difference*
Overall	1,186	0.69 (0.59–0.81; $P<0.001$)	69 (43–95; $P<0.001$)
Tiotropium	616 (51.9%)	0.68 (0.55–0.84; $P<0.001$)	48 (14–82; $P=0.006$)
No tiotropium	570 (48.1%)	0.70 (0.56–0.88; $P=0.003$)	90 (50–129; $P<0.001$)
Analysis 1			
GOLD B	716 (60.4%)	0.65 (0.52–0.81; $P<0.001$)	69 (36–103; $P<0.001$)
Tiotropium	370 (31.2%)	0.54 (0.41–0.72; $P<0.001$)	52 (8–96; $P=0.021$)
No tiotropium	346 (29.2%)	0.76 (0.54–1.07; $P=0.119$)	85 (35–136; $P=0.001$)
GOLD D	313 (26.4%)	0.75 (0.58–0.95; $P=0.017$)	79 (33–125; $P<0.001$)
Tiotropium	169 (14.2%)	0.87 (0.62–1.22; $P=0.419$)	66 (6–127; $P=0.033$)
No tiotropium	144 (12.1%)	0.62 (0.44–0.87; $P=0.006$)	90 (20–161; $P=0.013$)
Analysis 2			
GOLD B	662 (55.8%)	0.65 (0.52–0.82; $P<0.001$)	69 (36–102; $P<0.001$)
Tiotropium	359 (30.3%)	0.58 (0.43–0.78; $P<0.001$)	49 (6–92; $P=0.027$)
No tiotropium	303 (25.5%)	0.70 (0.49–1.01; $P=0.054$)	94 (42–145; $P<0.001$)
GOLD D	301 (25.4%)	0.74 (0.58–0.94; $P=0.012$)	83 (37–128; $P<0.001$)
Tiotropium	163 (13.7%)	0.85 (0.6–1.21; $P=0.366$)	61 (6–115; $P=0.030$)
No tiotropium	138 (11.6%)	0.63 (0.46–0.86; $P=0.004$)	101 (25–177; $P=0.010$)

Notes: *95% CI and P -value in parentheses. Number of COPD exacerbations and predose morning FEV₁ analyzed using a negative binomial model and MMRM, respectively. Analysis 1 used SGRQ score ≥ 25 to identify patients corresponding to GOLD B. Analysis 2 used dyspnea questions within the SGRQ to identify patients corresponding to GOLD B.

Abbreviations: FEV₁, forced expiratory volume in 1 second; BDP-FF, beclomethasone dipropionate–formoterol fumarate; FF, formoterol fumarate; SGRQ, St George's Respiratory Questionnaire.

Figure 2 Adjusted exacerbation rates (per patient/year) for analysis 2 in GOLD B and GOLD D patients.

Abbreviations: BDP-FF, beclomethasone dipropionate–formoterol fumarate; FF, formoterol fumarate.

We used the SGRQ to identify patients with a higher symptom burden and categorized these patients as GOLD B. The SGRQ threshold of 25 has been used previously for this purpose.⁸ We realize that this methodology does not strictly match the GOLD B definition based on CAT or mMRC scores, but it is a recognized way to identify patients with a greater level of symptoms. We performed an analysis using specific questions within the SGRQ to identify patients with greater breathlessness. The two different analyses provided very similar results.

Although we knew how many overall exacerbations occurred in the previous year, the number of these that required hospitalization was not known. It is thus likely that some patients categorized as GOLD B here were really GOLD D patients. These were likely to be only a small proportion of individuals, as hospitalizations occur in a minority of exacerbations. We suggest that this reclassification would not have altered the results, as the results in GOLD B and D were similar.

This post hoc analysis has limitations in terms of the definition of GOLD B patients. Furthermore, the smaller sample sizes of the subgroups analyzed results in a decrease in statistical power. Caution must thus be applied to the interpretation of these data. Nevertheless, these results provide a level of evidence to debate the place of ICS-LABA treatment for patients with a history of one exacerbation.

The FORWARD study was conducted in severe COPD patients being followed up, with approximately half taking tiotropium. A subanalysis of GOLD B patients according to concurrent tiotropium use showed efficacy for additional ICS therapy on exacerbations and lung function in both patients using a LABA alone and those using a LABA plus LAMA. Exacerbation rate reductions of 24% and 30% (analyses 1 and

2, respectively) due to ICS in patients not using tiotropium were not statistically significant ($P=0.119$ and $P=0.054$), and we suggest this was due to a relatively small sample size in a subgroup. Nevertheless, the overall pattern of results on exacerbations and FEV₁ in GOLD B patients with one exacerbation in the previous year support the addition of an ICS to either LABA monotherapy or LABA plus LAMA treatment. Indeed, the significant exacerbation reduction in both analyses for patients taking triple therapy (BDP-FF plus tiotropium) versus LABA-LAMA treatment (FF plus tiotropium) indicates the potential effectiveness of triple therapy in a subset of GOLD B patients.

GOLD recognizes that some of its recommendations lack evidence and may require refinement or alteration as new evidence becomes available.^{1,11} We provide some evidence to debate the current use of inhaled medicines in patients with a history of one exacerbation, particularly those corresponding to the definition of GOLD B. We propose ICS-LABA treatment is a therapeutic option in the subset of GOLD B patients with one exacerbation in the previous year.

Acknowledgments

We acknowledge Elisa Veratelli (University of Ferrara, Ferrara, Italy) for scientific editorial assistance in the preparation of the manuscript. This study received funding support from Chiesi Farmaceutici, Parma, Italy.

Disclosure

DS reports personal fees from Apellis, Cipla, and Peptinno-vate; and grants and personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Glenmark, Merck, Mundipharma, Novartis, Pfizer, Pulmatrix, Teva, Theravance, Verona, Genentech, and Skyepharma. SP and SV are employees of Chiesi Farmaceutici. AP reports grants and/or personal fees from Chiesi, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Merck Sharp and Menarini, Novartis, Zambon, Pfizer, Dohme, Takeda, Mundipharma, Teva, and Sanofi.

References

1. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 report: GOLD executive summary. *Am J Respir Crit Care Med*. 2017;195(5):557–582.
2. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010;363(12):1128–1138.
3. Keene JD, Jacobson S, Kechris K, et al. Biomarkers predictive of exacerbations in the SPIROMICS and COPDGen Cohorts. *Am J Respir Crit Care Med*. 2017;195(4):473–481.
4. Wedzicha JA, Singh D, Vestbo J, et al. Extrafine beclomethasone/formoterol in severe COPD patients with history of exacerbations. *Respir Med*. 2014;108(8):1153–1162.

5. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J*. 2003;22(6):912–919.
6. Sharafkhaneh A, Southard JG, Goldman M, Uryniak T, Martin UJ. Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study. *Respir Med*. 2012;106(2):257–268.
7. Calverley PM. Minimal clinically important difference: exacerbations of COPD. *COPD*. 2005;2(1):143–148.
8. Han MK, Muellerova H, Curran-Everett D, et al. GOLD 2011 disease severity classification in COPDGene: a prospective cohort study. *Lancet Respir Med*. 2013;1(1):43–50.
9. Lawrence PJ, Kolsum U, Gupta V, et al. Characteristics and longitudinal progression of chronic obstructive pulmonary disease in GOLD B patients. *BMC Pulm Med*. 2017;17(1):42.
10. Vestbo J, Edwards LD, Scanlon PD, et al. Changes in forced expiratory volume in 1 second over time in COPD. *N Engl J Med*. 2011;365(13):1184–1192.
11. Singh D. Pharmacological treatment for COPD: GOLD 2017 changes direction. *Br J Clin Pharmacol*. 2017;83(5):935–937.

Supplementary materials

Table S1 IECs/IRBs for recruitment wave 1

Country	Center, type	IEC/IRB name, address
Austria	CEC/LEC	Gesundheitsdienst der Stadt Wien Ethikkommission der Stadt Wien 8 Thomas-Klestil-Platz, Vienna 1030
	LEC Graz	Ethik-Kommission der Medizinischen Universität Graz 2 Auenbruggerplatz, Graz 8036
	LEC Linz	Ethikkommission am Krankenhaus der Elisabethinen 2 Fadingerstrasse, Linz 4010
Czech Republic	CEC/LEC	Etická Komise Fakultní Nemocnice v Motole 84 V Úvalu, 150 06 Prague 5
Germany	CEC/LEC Berlin	Landesamt für Gesundheit und Soziales Ethik-Kommission des Landes Berlin 1 Fehrbelliner Platz, Berlin 10707
	LEC Baden-Württemberg	Ethikkommission der Landesärztekammer Baden-Württemberg Körperschaft des öffentlichen Rechts 40 Jahnstrasse, Stuttgart 70597
	LEC Bayern	Ethikkommission der Landesärztekammer Bayern 16 Mühlbauerstrasse München 81677
UK	MREC	Professor Wellman Berkshire Research Ethics Committee Building L27, University of Reading, London Road, Reading RG1 5AQ
	MHRA	Information Processing Unit Area 6, Medicines & Healthcare Products Regulatory Agency, Market Towers, 1 Nine Elms Lane, London SW8 5NQ

Abbreviations: IECs, institutional ethics committees; IRBs, institutional review boards.

Table S2 IECs/IRBs for recruitment wave 2

Country	Center, type	IEC/IRB name, address, chair (if applicable)
Argentina	CEC	Comité Independiente de Ética para Ensayos en Farmacología Clínica – FEFYM 774 Pte JE Uriburu, 1 Piso – CABA (C1027AAP) Dr Luis Zieher
	320001	Comité de Docencia de Investigación French 2673, CABA, C1425AWC Clelia Haydee Magaril
	32002	NA
	32003	Comité de Docencia e Investigación (CDI) San Martín de Tours 2926 – CABA (1425) Dr Gustavo Badariotti
	32004 IRB	Servicio de Investigación de Patologías Alérgicas del Instituto ABC 2668 Salta, Rosario, Santa Fe (S2000JKR) Dr Alejandro García
	32005	NA
	36001 HREC	Southern Adelaide Clinical Human Research Ethics Committee The Flats, G5 – rooms 3 and 4 Flinders Drive, Flinders Medical Centre, Bedford Park, SA 5042 Professor Gordan
Australia	36002, 36003, 36004, 36005 HREC	BellBerry Human Research Ethics Committee 229 Greenhill Road, Dulwich, SA 5065 Brian Stoffell
	152001 152002 CEC	Comité Ético Científico Servicio de Salud Oriente 364 Avenida Salvador, Providencia, RM Dr Andres Stuardo
Chile		

(Continued)

Table S2 (Continued)

Country	Center, type	IEC/IRB name, address, chair (if applicable)
	152003 CEC	Comité Etico Científico Servicio de Salud Metropolitano Sur 3453 Avenida Santa Rosa, RM Veronica Rivera
	152006 CEC	Comité Etico Científico Servicio de Salud Coquimbo 795 Avenida Francisco Aguirre, La Serena Dr Buillermo Valdebenito
	152009 CEC	Comité Etico Científico del Servicio de Salud del Maule I Norte – 963, 2000 Edificio Centro, Piso Talca Dr Rafael Muñoz
New Zealand	All sites	Multi-region Ethics Committee Ministry of Health, 133 Molesworth Street, PO Box 5013, Wellington 6145 Richman Wee
South Africa	710001	University of Cape Town, Health Science Faculty Research Ethics Committee Room E52-24, Groote Schuur Hospital, Old Main Building Observatory, Cape Town 7925 Professor M Blockman
	710004	University of Stellenbosch, Faculty of Health Sciences Health Research Ethics Committee PO Box 19063, Tygerberg 7505 Dr J Meintjies
	All other sites	Pharma Ethics 123 Amcor Road, Lytelton Manor, Pretoria 0157 Dr C Duvenage

Abbreviations: IECs, institutional ethics committees; IRBs, institutional review boards.

Table S3 IECs/IRBs for recruitment wave 3

Country	Center, type	IEC/IRB name, address, chair (if applicable)
Bulgaria	MEC/CEC	Ethics Committee for Multicenter Clinical Trials 8 Damian Gruev Street; Sofia 1303 Dr Anastas Stoykov
Czech Republic	MEC	Multicentric Ethics committee 84 FN Motol V Úvalu, 150 06 Praue 5 Chair Vratislav Smeihaus
	203007 LEC	Regionální Etická Komise Nemocnice Tábor 2000 Kapitána Jaroše, Tábor 390 03 Ladislav Douda
	CEC	Comité de Protection des Personnes CPP Ile de France III, Hopital Tarnier-Cochin 89 rue d'Assas, Paris 75006 Professor Boris Christoforov
Germany	276001	Landesamt für Gesundheit und Soziales
	276016	Ethik-Kommission des Landes Berlin I Fehrbelliner Platz Berlin 10707 Dr Hans-Herbert Fulle
	276013	Ethikkommission der Landesärztekammer Sachsen
	276014	16 Schützenhöhe, Dresden 01099
	276015	Professor Habil R Haupt
	276005	Ethikkommission der Landesärztekammer Baden-Württemberg Körperschaft des öffentlichen Rechts 40 Jahnstrasse, Stuttgart 70597 Dr Georg Hook
	276016	Ethikkommission der Ärztekammer Niedersachsen 20 Berliner Allee, Hannover 30175 Dr Gisbert Voigt
	276012	Ethikkommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität 210–214 Gartenstrasse, Münster 48147 Professor Hans-Werner Bothe

(Continued)

Table S3 (Continued)

Country	Center, type	IEC/IRB name, address, chair (if applicable)
Hungary	All sites	Egeszsegugyi Tudomanyos Tanacs Klinikai Farmakologiai Etikai Bizottsaga 6–8 Ulitsa Arany Janos, Budapest 1051 Dr Zsussanna Furst
Italy	380001	Comitato per la Sperimentazione Clinica dei Medicinali dell'Azienda Ospedaliero Universitaria Pisana di Pisa 67 Via Roma, Pisa 56126
	380002	Comitato Etico per la Sperimentazione Clinica dei Medicinali dell'Azienda Ospedaliera Universitaria Integrata di Verona 1 Piazzale A Stefani, Verona 37126
	380003	Comitato Etico per la Sperimentazione Clinica dei Medicinali dell'Azienda Ospedaliero- Universitaria Careggi di Firenze 3 Largo Brambilla, Florence 50134
	380004	Comitato Etico Centrale Dell'Irccs Fondazione Salvatore Maugeri Di Pavia, 4 via Salvatore Maugeri, Pavia 27100
The Netherlands	528001	Medisch Ethische Toetsingscommissie Eindhoven Catharina-Ziekenhuis, Secretariaat METC 2 Michelangelolaan 2, Eindhoven 5623 MJH Stoffelen-Bruurs
	528002	Elkerliek Ziekenhuis, locatie Helmond METC, 25 Wesselmanlaan, Helmond 5707 Mr Corbeij
	528003	METC Noord-Holland Foreest Medical School 10 Nassauplein, Alkmaar 1815 B Blijham
	528004	Commissie WMO METC Noord-Holland, Foreest Medical School 10 Nassauplein, Alkmaar 1815
Poland	All sites	Komisja Bioetyczna Przy Okręgowej Izbie Lekarskiej w Warszawie 18 Ulitsa Puławska, Warsaw 02-512 Dr Marek Czarkowski
Romania	All sites	48 Aviator Sanatescu Street, Sector 1, Bucharest 011478 Professor Sava Dumitrescu
Spain	724002	Dr F Javier Abad Gimeno Secretario del Comité Ético de Investigación Servicio de Farmacia, planta 1. Avenida Ramón y Cajal, Puerto de Sagunto, Valencia 46520
	724003	Comité Etico de Investigación Clínica del Hospital General Universitario de Elche, Lorena Montolio Beltran 11 Camí de l'Almazara – 3, Planta del Edificio Anexo II, Elche, Alicante 03203
	724004	Paz Lavilla/Emma Fernández de Uzquiano Hospital General Planta, 261 Paseo de la Castellana, Madrid 28046
	724005	Hospital Clinic i Provincial–Comité Etico de Investigación Clínica/Villarreal, 170 Sótano – Escalera 6b, Barcelona 08036
Turkey	792-001	Mersin University Health Research and Practice Hospital Ihsaniye Mah, 4903 Sokak – 3 Necdet Unger Binası 3, Mersin 33079 Professor Bahar Tunctan
	MEC	Ministry of Health General Directorate of Pharmaceuticals and Pharmacy 2176 Söğütözü Mahallesi – 5 PK Çankaya, Ankara 06520 Hilal Ilbars
The UK	All sites	Berkshire Research Ethics Committee Building L27, University of Reading, London Road, Reading RG1 5AQ

Abbreviations: IECs, institutional ethics committees; IRBs, institutional review boards.

International Journal of COPD**Dovepress****Publish your work in this journal**

The International Journal of COPD is an international, peer-reviewed journal of therapeutics and pharmacology focusing on concise rapid reporting of clinical studies and reviews in COPD. Special focus is given to the pathophysiological processes underlying the disease, intervention programs, patient focused education, and self management protocols.

Submit your manuscript here: <http://www.dovepress.com/international-journal-of-chronic-obstructive-pulmonary-disease-journal>

This journal is indexed on PubMed Central, MedLine and CAS. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.