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

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. Forced expiratory volume in 1 second (FEV₁) 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). Other COPD cohorts have confirmed the increase in risk in patients with a history of one exacerbation in the previous year, 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).
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, 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\textsubscript{1} <50% predicted and one or more exacerbations in the previous year. Under the GOLD 2011 recommendations, most enrolled in these studies were high-risk patients because of low FEV\textsubscript{1}, as only a minority had had two or more exacerbations in the previous year. However, the removal of FEV\textsubscript{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 μg plus formoterol fumarate (FF) 6 μg with pressurized metered-dose inhaler (two inhalations twice daily) versus FF 12 μg with pressurized metered-dose inhaler (one inhalation twice daily). Severe COPD patients (FEV\textsubscript{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 relevant 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, NCT00929851). 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. 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 needing 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\textsubscript{1} were analyzed using a negative binomial model and a mixed model for repeated measures, respectively. 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.
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,
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. 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 FEV$_1$ 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. 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.

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Disclosure
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## 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      | Landesamt für Gesundheit und Soziales                      |
|                  | Berlin       | 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 Etica 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 Garcia                           |
|                  | 32005        | NA                                            |
| Australia        | 36001        | Southern Adelaide Clinical Human Research Ethics Committee |
|                  | HREC         | The Flats, G5 – rooms 3 and 4                   |
|                  |              | Flinders Drive, Flinders Medical Centre, Bedford Park, SA 5042 |
|                  |              | Professor Gordan                              |
|                  | 36002, 36003, | BellBerry Human Research Ethics Committee       |
|                  | 36004, 36005 | 229 Greenhill Road, Dulwich, SA 5065           |
|                  | HREC         | Brian Stoffell                                 |
| Chile            | 152001       | Comité Etico Cientifico Servicio de Salud Oriente |
|                  | 152002       | 364 Avenida Salvador, Providencia, RM          |
|                  | CEC          | Dr Andres Stuardo                              |

(Continued)
### Table S2 (Continued)

| Country                | Center, type | IEC/IRB name, address, chair (if applicable)                                                                 |
|------------------------|--------------|------------------------------------------------------------------------------------------------------------|
| 152003                 | CEC          | Comité Ético Científico Servicio de Salud Metropolitano Sur                                                   |
|                        |              | 3453 Avenida Santa Rosa, RM Verónica Rivera                                                             |
| 152006                 | CEC          | Comité Ético Científico Servicio de Salud Coquimbo                                                        |
|                        |              | 795 Avenida Francisco Aguirre, La Serena Dr Guillermo Valdebenito                                         |
| 152009                 | CEC          | Comité Ético Científico del Servicio de Salud del Maule                                                   |
|                        |              | 1 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 W.                        |
| 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 Meintjes                                                              |
| All other sites        | Pharma Ethics| 123 Amcor Road, Lytelson 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 Praha 5 Chair Vratislav Smelhaus                |
| France          | 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 1 Fehrwalliner Platz Berlin 10707 Dr Hans-Herbert Fulle              |
|                 | 276016       | Ethik-Kommission des Landes Berlin 1 Fehrwalliner Platz Berlin 10707 Dr Hans-Herbert Fulle                 |
|                 | 276013       | Ethikkommision der Landesärztekammer Sachsen 16 Schützenhöhe, Dresden 01099 Professor Habil R Haupt       |
|                 | 276014       | 16 Schützenhöhe, Dresden 01099 Professor Habil R Haupt                                                 |
|                 | 276015       | Ethikkommission der Landesärztekammer Baden-Württemberg Körperschaft des öffentlichen Rechts 40 Jahnstrasse, Stuttgart 70597 Dr Georg H. Dr Georg Hook |
|                 | 276005       | Ethikkommission der Landesärztekammer Baden-Württemberg Körperschaft des öffentlichen Rechts 40 Jahnstrasse, Stuttgart 70597 Dr Georg H. |
|                 | 276016       | Ethikkommision der Ärztekammer Niedersachsen 20 Berliner Allee, Hannover 30175 Dr Gisbert Voigt           |
|                 | 276012       | Ethikkommision der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität 210–214 Gartenstrasse, Münster 48147 Professor Hans-Werner Bothe |

(Continued)
| Country      | Center, type | IEC/IRB name, address, chair (if applicable) |
|-------------|-------------|-----------------------------------------------|
| Hungary     | All sites   | Egessegugyi Tudomanyos Tanacs                 |
|             |             | Klinikai Farmakologial Etkai Bizottsaga      |
|             |             | 6–8 Ullisa Arany János, Budapest 1051        |
|             |             | Dr Zsuzsanna 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’Ircs Fondazione Salvatore |
|             |             | Maegeri Di Pavia, 4 via Salvatore Maegeri, Pavia 27100 |
| The         | 528001      | Medisch Ethische Toetsingscommissie Eindhoven |
| Netherlands |             | Catharina-Ziekenhuis, Secretariaat METC      |
|             |             | 2 Michelangelolaan 2, Eindhoven 5623          |
|             |             | MJH Stoffelen-Bruurs                          |
|             | 528002      | Elkeriek Ziekenhuis, locatie Helmond         |
|             |             | METC, 25 Wesselsmanlaan, 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 Okregowej Izbie Lekarskiej w Warszawie  |
|             |             | 18 Ullisa 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 Ético de Investigación Clinica del Hospital General |
|             |             | Universitario de Elche, Lorena Montolito Beltran |
|             |             | 11 Cami 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 Proovicial–Comité Etico de Investigación Clinica/Villarroel, 170 Sótano – |
|             |             | Escalera 6b, Barcelona 08036                  |
| Turkey      | 792-001     | Mersin University Health Research and Practice Hospital |
|             |             | Ihsaniye Mah, 4903 Sokak – 3 Necdet Unger Binasi 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.
