**Additional File 1**

**Supplementary Table 1.** Analysis of sustained CID events by previous treatment with a LABA and / or LAMA (ITT population)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Prior LABA or LAMA** | **AB/FF 400/12 µg** | **AB 400 µg** | **FF 12 µg** | **Placebo** |
| Yes, n | 355 | 371 | 362 | 254 |
| HR vs placebo | 0.55\*\*\* | 0.48\*\*\* | 0.74\* | - |
| HR vs AB 400 µg | 1.16 | - | - | - |
| HR vs FF 12 µg | 0.75\* | 0.65\*\*\* | - | - |
| No, n | 365 | 349 | 353 | 271 |
| HR vs placebo | 0.48\*\*\* | 0.61\*\*\* | 0.58\*\*\* | - |
| HR vs AB 400 µg | 0.78 | - | - | - |
| HR vs FF 12 µg | 0.82 | 1.05 | - | - |

\*p<0.05, \*\*\*p<0.001
The risk of a sustained CID event was analyzed using a Cox-Proportional Hazard model including study, treatment group, and smoking status as covariates
AB, aclidinium bromide; CID, clinically important deterioration; FF, formoterol fumarate; HR, hazard ratio; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist

**Supplementary Table 2.** Analysis of sustained CID events by COPD severity at baseline (ITT population)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **COPD at baseline** | **AB/FF 400/12 µg** | **AB 400 µg** | **FF 12 µg** | **Placebo** |
| Moderatea, n | 418 | 411 | 436 | 293 |
| HR vs placebo | 0.57\*\*\* | 0.50\*\*\* | 0.61\*\*\* | - |
| HR vs AB 400 µg | 1.13 | - | - | - |
| HR vs FF 12 µg | 0.94 | 0.83 | - | - |
| Severeb, n | 301 | 306 | 278 | 231 |
| HR vs placebo | 0.44\*\*\* | 0.60\*\*\* | 0.77\* | - |
| HR vs AB 400 µg | 0.74\* | - | - | - |
| HR vs FF 12 µg | 0.58\*\*\* | 0.78 | - | - |

\*p<0.05, \*\*\*p<0.001
aPatients with ≥50% predicted post-bronchodilator FEV1; bPatients with <50%predicted post-bronchodilator FEV1
The risk of a sustained CID event was analyzed using a Cox-Proportional Hazard model including study, treatment group, and smoking status as covariates
AB, aclidinium bromide; CID, clinically important deterioration; COPD, chronic obstructive pulmonary disease; FF, formoterol fumarate; HR, hazard ratio; ITT population

**Supplementary Table 3.** Sensitivity analysis of the risk of first CID events for common visits over 24 weeks (ITT population)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **AB/FF400/12 µg(n = 720)** | **AB400 µg(n = 720)** | **FF12 µg(n = 715)** | **Placebo****(n = 525)** |
| Percentage of patients with ≥1 CID during the studya | 54.6 | 60.4 | 61.7 | 70.3 |
| HR vs placebo | 0.61\*\*\* | 0.71\*\*\* | 0.74\*\*\* | - |
| HR vs AB 400 µg  | 0.85\* | - | - | - |
| HR vs FF 12 µg | 0.82\*\* | 0.97 | - | - |

\*p<0.05, \*\*p<0.01, \*\*\*p<0.001

aWeeks 4, 12, and 24

The risk of a first CID event was analyzed using a Cox-Proportional Hazard model including study, treatment group, and smoking status as covariates

AB, aclidinium bromide; CID, clinically important deterioration; FF, formoterol fumarate; HR, hazard ratio; ITT, intent-to-treat

**Supplementary Table 4.** Sensitivity analysis of the risk of sustained CID events for common visits over 24 weeks (ITT population)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **AB/FF400/12 µg(n = 720)** | **AB400 µg(n = 720)** | **FF12 µg(n = 715)** | **Placebo****(n = 525)** |
| Percentage of patients with ≥1 sustained CID during the studya | 19.7 | 22.5 | 27.1 | 37.5 |
| HR vs placebo | 0.47\*\*\* | 0.54\*\*\* | 0.66\*\*\* | - |
| HR vs AB 400 µg  | 0.86 | - | - | - |
| HR vs FF 12 µg | 0.71\*\* | 0.82 | - | - |

\*\*p<0.01, \*\*\*p<0.001

aWeeks 4, 12, and 24

The risk of a sustained CID event was analyzed using a Cox-Proportional Hazard model including study, treatment group, and smoking status as covariates

AB, aclidinium bromide; CID, clinically important deterioration; FF, formoterol fumarate; HR, hazard ratio; ITT, intent-to-treat

**Supplementary Table 5.** Characterization of patients according to CID endpoints achieved (ITT population)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Number of CIDs, n (%)** | **AB/FF400/12 µg(n = 462)** | **AB400 µg(n = 511)** | **FF12 µg(n = 519)** | **Placebo(n = 444)** | **Total(n = 1936)** |
| 1a | 258 (55.8) | 281 (55.0) | 234 (45.1) | 170 (38.3) | 943 (48.7) |
| 2b | 138 (29.9) | 152 (29.7) | 202 (38.9) | 173 (39.0) | 665 (34.3) |
| 3c | 60 (13.0) | 67 (13.1) | 74 (14.3) | 87 (19.6) | 288 (14.9) |
| 4d | 6 (1.3) | 11 (2.2) | 9 (1.7) | 14 (3.2) | 40 (2.1) |

aDeterioration inany CID component of trough FEV1, TDI focal score, SGRQ total score, or exacerbation

bAny two CIDs of trough FEV1 + TDI focal score, trough FEV1 + SGRQ total score, trough FEV1 + exacerbation, TDI focal score + SGRQ total score, TDI focal score + exacerbation, or SGRQ total score + exacerbation

cAny three CIDs of trough FEV1 + TDI focal score + SGRQ total score, FEV1 + TDI focal score + exacerbation, trough FEV1 + SGRQ total score + exacerbation, TDI focal score + SGRQ total score + exacerbation

dAll four exacerbations, trough FEV1 + TDI focal score + SGRQ total score + exacerbation

AB, aclidinium bromide; CID, clinically important deterioration; FEV1, forced expiratory volume in 1 second; FF formoterol fumarate; ITT, intent-to-treat; SGRQ, St George’s Respiratory Questionnaire; TDI, Transition Dyspnea Index

**Supplementary Table 6.** List of ethics committees

|  |
| --- |
| Ethikkommission der Medizinischen, Universität Graz, Auenbruggerplatz 2, Graz, 8036, Austria |
| Ethisch Comité UZA, Wilrijkstraat 10, Edegem, 2650, Belgium |
| Ethics Committee for Multicenter Trials (ECMT), 5, ‘Sveta Nedelya’, Square 1000 Sofia, Bulgaria |
| Agency for Medicinal Product and Medical Devices of Croatia, Central Ethics Committee, Ksaverska cesta 4 Zagreb, 10000, Croatia |
| Multicentricka eticka komise Fakultni nemocnice u sv. Anny v Brne, Vystavni 17/19, Brno, 656 19, Czech Republic |
| De Videnskabsetiske Komitéer for Region Hovedstaden, Kongens Vænge 2, 3400, Hillerød, Denmark |
| Keski-Suomen sairaanhoitopiiri, Eettinen toimikunta, Sairaanhoitopiirin toimisto Rak. 6/2, Keskussairaalantie 19, 40620 Jyväskylä, Finland |
| Comité de Protection des Personnes Sud Ouest et Outre Mer III, Place Amélie Raba-Léon, Groupe Hospitalier Pellegrin – Service de Pharmacologie Clinique, Bât 1 A, Bordeaux Cedex, 33076, France |
| Landesärztekammer Rheinland-Pfalz, Place Amélie Raba-Léon, Groupe Hospitalier Pellegrin – Service de Pharmacologie Clinique, Bât 1 A, Bordeaux cedex, 33076, Germany |
| Egészségügyi Tudományos Tanács Klinikai Farmakológiai Etikai Bizottsága, Arany J. u. 6–8, Budapest, H-1051, Hungary |
| Comitato Etico Locale per la Sperim. Clin. dei Medicinali dell'Az. Osp.ra Univ.ria Senese di Siena, c/o Farmacia AOUS Viale Bracci, Siena, 53100, Italy |
| METC Catharina Ziekenhuis, Michelangelolaan 2, Eindhoven, 5623 EJ, Netherlands |
| Komisja Bioetyczna przy Instytucie Gruzlicy I Chorob Pluc, ul. Plocka 26, Warszawa, 01–138, Poland |
| Comisia Nationala de Etica, Str. Aviator Sanatescu Nr. 48, Bucuresti, Sector 1, 011478, Romania |
| Ethical Council at the MoH of RF, 3 Rakhmanovsky Pereulok, Moscow, 127994, Russia |
| Fakultná nemocnica s poliklinikou F.D. Roosevelta, Nám. L. Svobodu 1, 975 17 Banská Bystrica, Slovakia |
| CEIC Hospital Universitario Puerta de Hierro Majadahonda, Planta 1ª, Pasillo unidades, administrativas de servicios, c/ Manuel de Falla, 1, Majadahonda, 28222, Spain |
| Regionala Etikprövningsnämnden I Lund, Box 133, Östra Vallgatan 14/Östervångsvägen 1, Lund, 22100, Sweden |
| Central Ethics Commission of the Ministry of Health of Ukraine, 5, Narodnogo Opolchennya St., Kyiv, 03680, Ukraine |
| NRES Committee North, West-Greater Liverpool, Central, 3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, United Kingdom |

**Supplementary Figure legend**

**Supplementary Figure 1.** Analysis of the risk of CID events over 24 weeks, stratified by a) ICS use, b) previous treatment, c) symptoms defined by E-RS, and d) symptoms defined by BDI (ITT population)









\*p<0.05, \*\*p<0.01, \*\*\*p<0.001 HR vs placebo

aDefined as patients previously treated with LABAs and/or LAMAs, LABA/ICS combinations, or LABA/LAMA/ICS combinations or xanthines

bDefined as patients who were not previously treated with SABAs and/or SAMAs or with other medications (ICS, leukotriene antagonists, systemic corticosteroids, oxygen or influenza vaccine) not in accordance with GOLD guidelines [1].

Risk of first or sustained CID events and each individual component were analyzed using a Cox-Proportional Hazard model including study, treatment group, and smoking status as covariates

AB, aclidinium bromide; BDI, baseline dyspnea index; CID, clinically important deterioration; E-RS, Evaluating Respiratory Symptoms; FF, formoterol fumarate; GOLD, Global initiative for chronic Obstructive Lung Disease; HR, hazard ratio; ICS, inhaled corticosteroid; ITT, intent-to-treat; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β2-agonist; SAMA, short-acting muscarinic antagonist

**References**

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease2017. [[http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/]](http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/%5D). Accessed 1 Mar 2017.