OBSERVATIONAL STUDY REPORT SYNOPSIS

DETECT-Register

Docum**E**n**T**ation and **E**valuation of a **C**OPD Combination **T**herapy

Non-interventional Study for Documentation of the Therapeutic Efficacy, Use and Tolerance of the Fixed-Dose Combinations (FDC) Duaklir® Genuair® (Aclidinium/Formoterol), Ultibro® Breezhaler® (Glycopyrronium/Indacaterol) and Anoro® (Umeclidinium/Vilanterol) in the Treatment of COPD under Real Conditions in the Practices of Pneumologists, Internists, and General Practitioners.

Milestones:

Milestones	
Final version of study protocol	1.3 (16.08.2016)
Study initiation	October 2015
First patient first visit	06.03.2015 (retrospective)
Study enrolment of final patient	13.04.2017
Last patient last visit	31.01.2018
Final completion of electronic case report form (eCRF)	29.03.2018
Freezing of database	29.03.2018
Final result tables and evaluation of study data	12.07.2018
Draft medical report	27.04.2018
Completion of final medical report	20.07.2018

Phase of development: Not Applicable – Observational study

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This study was performed in compliance with Good Clinical Practice and Good Pharmacoepidemiology Practice, including the archiving of essential documents.

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Background/Rationale: LABA/LAMA combination preparations are indicated as bronchodilating maintenance therapy and for symptomatic relief in adults with chronic-obstructive pulmonary disease (COPD). Nevertheless, the types of patient groups for which LABA/LAMA combination therapy is the agent of choice had never been accurately described.

Objectives: The primary goal of this non-interventional study was to describe the patient group/patient characteristic, which was selected specifically for LABA/LAMA combination therapy under real conditions in the practices of pneumologists, internists, and general practitioners. The secondary goal of the non-interventional study was to document the therapeutic efficacy, inhaler use, and tolerance of the combination preparations in the treatment of COPD under real conditions in the practices of pneumologists, internists, and general practitioners. The focus was on a patient-oriented evaluation of the therapy.

Study design: The present study was a non-interventional study as defined in § 4, (23), Sentence 3, of the AMG. A prospective, multi-centre, non-interventional study was the most suitable way to investigate the above-cited goals in a sufficiently large number of patients.

It is important to note that the treatment of the patients included in the non-interventional study were chosen exclusively based on the judgement of the physician under consideration of the medical benefit and need. The use of the medication was not determined in advance by the observation plan; on the contrary, it was clearly separated from participation in the non-interventional study.

The planning, execution, and evaluation of the non-interventional study were based not only on the regulations of the AMG but also on the corresponding recommendations of the BfArM and PEI and on the guidelines of the FSA Codex.

Data source: The plan called for the recruitment of 600 medical practices (pneumologists, internists, and specialized general practitioners) to obtain a representative documentary result. Main emphasis was stressed on pneumologists, but general practitioners with a special interest in pulmonology were also contacted. The centres were distributed throughout Germany. Each physician could recruit up to 15 patients for the study. The goal was to acquire documentation on the therapy experience of 6600 patients with COPD.

The data were managed based on the "Guidelines and Recommendations on Ensuring Good Epidemiological Practice (GEP)". The study database, including the automatic plausibility check, were designed before the study physician or his representative entered the data.

Data was collected within all but two and a half calendar years, beginning in October 2015 and ending in January 2018. In part, data had been collected retrospectively.

Physicians' entered the data into an electronic case report form (eCRF) created especially for the project. The Internet Usage Handbook contained relevant information on entering data. After entering the data, the physician was asked to confirm that the data were correct and complete.

The eCRF generated automatic emails as soon as adverse events (AE) were entered into the database and thus initiated the further processing of events. Furthermore, the data in the eCRF were checked for suspicious, i.e. possible adverse events. AE were monitored centrally by the commissioned research institute ANFOMED GmbH und forwarded to AstraZeneca drug safety. The consistency of the AE data were ensured by reconciling the study database with AstraZeneca safety database. Discrepancies were corrected by mutual agreement.

Study population: The patients to be included in the study were those who had been diagnosed with COPD, who had been changed over within the last three months to a fixed-dose combination (FCD) or for whom such a changeover was intended, and whose lung function parameters and CAT score from the time prior to the changeover were available (within the last 6 months) or were determined at the time of the 1st visit, if this was planned as part of the routine treatment.

Inclusion criteria: Patients who were accepted into the study had to fulfil the following criteria:

- The patient (female/male) was at least 40 years of age.
- The patient had been diagnosed with COPD.
- The patient was changed over within the last 3 months to a fixed-dose combination (FDC) (Aclidinium/Formoterol, Glycopyrronium/Indacaterol or Umeclidinium/Vilanterol), or there is already the intent to change the patient over to a fixed-dose combination (Aclidinium/Formoterol, Glycopyrronium/Indacaterol or Umeclidinium/Vilanterol).
- Lung function parameters and CAT score from the time prior to the changeover to an FDC were on record (within the last 6 months in the case of patients who had already been changed over) or were determined at the 1st visit (in the case of patients who had not yet been changed over but for whom such a changeover was intended).
- The signed declaration of consent was on file.

The decision to prescribe a FDC was made by the physician independently of the possible participation of the patient in the study.

Exclusion criteria: Patients in whom at least one of the following criteria was present were not allowed to be included in the study:

- The prescribing information for the fixed-dose combinations (Duaklir® Genuair®, Ultibro® Breezhaler® or Anoro®) listed contraindications for the patient.

- The patient was pregnant, planned to become pregnant, or was nursing during the therapy period.
- The patient suffered from hypersensitivity to one of the active ingredients of the fixed-dose combinations.
- The patient was participating in a clinical trial.

Statistical methods: In accordance with the goals of the non-interventional study, the focus of the statistical evaluation was on a summarizing and detailed description of the acquired data. Descriptive methods and possibly graphics reproduce and illustrate the information contained in the data.

The statistical analysis was conducted based on the Intention to Treat (ITT) sample. The ITT sample consisting of all patients who had received at least one dose of one of the study medications.

For nominal and ordinal features, absolute and relative frequencies (percentage values) were determined. For the quantitative variables, the values to be determined were mean value, standard deviation, minimum, lower quartile, median, upper quartile, and maximum. These statistics are shown in tables for each point in time.

For variables that had been documented once in the course of the study, missing values were not replaced. For variables that had been noted several times in the course of the investigation, an analysis according to the last observation carried forward method (LOCF) was performed, i.e. that missing values in the course of the study were replaced by the last actual observation. Condition for the application of this method was the existence of a baseline value and a value after baseline.

No statistical hypotheses were formulated in the observational plan. To the extent that statistical tests were calculated, they were exploratory in character and were not used for the confirmatory testing of hypotheses formulated prior to the study. All hypotheses were subjected to a two-sided test. No alpha-adjustment was made.
Adverse events/adverse drug reactions were coded according to MedDRA, Version 20.1. All cases were listed in frequency tables based on preferred terms and system organ classes. A line listing of all events was prepared.

Data processing and statistical analysis were carried out with the SAS™ program system. ANFOMED GmbH performed the statistical evaluation.

Results: In total, 254 observation centres enrolled 3653 patients. Data of all planned visits (V1-V5) were available for 2369 patients (64.85% of all patients). Mean duration of observation was 11.03 (±4.13, median 11.97) months with a minimum of 0.13 months and a maximum of 30.89 months.

More than half of the patients (2121 patients, 58.06%) were treated with Duaklir® Genuair®, followed by Ultibro® Breezhaler® (1056 patients, 28.91%) and Anoro® (476 patients, 13.03%) therapy.

Concerning patient demographics, no appreciable difference of sex and age was detected between the three treatment groups. 1205 Duaklir® Genuair® patients (56.81%) were male and 916 patients (43.19%) were female, with a mean age of 65.50 years. Almost similar numbers

were obtained for Ultibro® Breezhaler® and Anoro®: 650 male patients (61.55%), 406 female patients (38.45%), mean age 65.69 years; 251 male patients (52.73%), 225 female patients (47.27%), mean age 65.44 years. The majority of patients were either smokers at enrolment into the study (Duaklir® Genuair®, 47.85%; Ultibro® Breezhaler®, 49.15%; Anoro®, 49.58%) or had been smokers in the past (Duaklir® Genuair®, 38.65%; Ultibro® Breezhaler®, 37.59%; Anoro®, 38.03%).

37.62% of patients treated with Duaklir® Genuair® suffered from concomitant disease. Most commonly documented preferred term was hypertension (65.29% of patients with concomitant disease), coronary artery disease (15.41%) and diabetes mellitus (12.16%). 32.58% of patients who received Ultibro® Breezhaler® treatment had an accompanying disease. Similar to Duaklir® Genuair®-treated patients, hypertension (63.37%), coronary artery disease (16.28%) and diabetes mellitus (11.63%) was most often documented. Moreover, 38.03% of patients under Anoro® therapy were affected by concomitant disease. Hypertension (67.96%), coronary artery disease (13.81%) and hypercholesterolaemia (12.15%) were mentioned most frequently.

Patients who were treated with Duaklir® Genuair® within this study had on average 0.75 exacerbations within 24 months prior to study. Patients under therapy with Ultibro® Breezhaler® experienced a mean number of 0.57, while patients who received Anoro® had on average 0.71 exacerbations within the last 24 months. Regarding the occurrence of exacerbations during the observational period, an almost similar percentage of patients with exacerbations was found with Duaklir® Genuair®, Ultibro® Breezhaler® and Anoro® (7.02%, 6.45%, 8.15%), whereas the great majority of patients remained free of exacerbations. Furthermore, the mean number of exacerbations was comparable: 0.10, Duaklir® Genuair®; 0.08, Ultibro® Breezhaler®; 0.12, Anoro®.

The data collected in this study indicated an improvement of pulmonary function with Duaklir® Genuair®, Ultibro® Breezhaler® and Anoro®, demonstrated by an increase of FEV1 (Forced Expiratory Volume) and FVC (Forced Vital Capacity) values during the NIS.

Prior to medication switch, FEV1 values were 1.68, 1.72 and 1.59 litres (Duaklir® Genuair®, Ultibro® Breezhaler® and Anoro®). During the underlying study, they increased by 0.09 in Duaklir® Genuair® patients, by 0.06 in Ultibro® Breezhaler® treated patients and by 0.12 litres in patients under Anoro® therapy. Furthermore, FEV1 in percent of target showed higher values at the end of the NIS (increase by 3.23%, Duaklir® Genuair®; by 1.85%, Ultibro® Breezhaler®; by 3.42%, Anoro®). FVC values were enhanced by 0.10, 0.05 and 0.10 litres (Duaklir® Genuair®, Ultibro® Breezhaler®, Anoro®) and FVC values in percent of target were higher than 75% in all treatment groups at the final documentation (increase by 3.22%, 1.24% and 3.12%). Moreover, the Tiffeneau-Pinelli index improved during the observational period regardless which of the three fixed-dose combinations was taken. Interestingly, highest increase was noticed in patients treated with Anoro® (1.53% versus 0.39%, Duaklir® Genuair®, and 0.61%, Ultibro® Breezhaler®).

All three fixed-dose COPD medications led to a decrease of night-time as well as morning COPD symptoms. Overall severity at night was significantly reduced by 0.35 during the treatment with Duaklir® Genuair®, by 0.30 under Ultibro® Breezhaler® therapy and by 0.31 scores when patients were treated with Anoro®. In addition, the number of puffs of rescue medication that needed to be taken at night was lower at the end of the NIS: reduction by 0.23,

Duaklir® Genuair®; by 0.22, Ultibro® Breezhaler® and by 0.13, Anoro®. Concerning overall early morning COPD symptoms, an improvement by a score of 0.42 in Duaklir® Genuair® patients, of 0.36 in Ultibro® Breezhaler® patients and of 0.31 in patients treated with Anoro® was noted, indicating better symptom control when compared to baseline values.

The number of rescue puffs could be reduced during treatment with all three fixed dose medications. Reduction by 0.24 puffs was achieved in patients treated with Duaklir® Genuair®. This value was slightly higher than obtained for Ultibro® Breezhaler® (reduction 0.19 puffs) and Anoro® patients (reduction 0.16 puffs).

Evaluation of COPD Assessment Test (CAT) showed a comparable and continuous reduction of CAT score in all treatment groups. Each of the eight CAT-questions showed a significantly reduced mean score at the final visit. The CAT score was reduced from 19.88 (prior to switch) to 15.71 (reduction 4.17) points after about 15 months Duaklir® Genuair®, from 18.92 to 15.26 (reduction 3.66) points with Ultibro® Breezhaler®, and from 19.33 to 15.27 (reduction 4.06) points with Anoro®-treatment.

At the end of the study, patients mainly rated handiness, comfort, easy understanding of handling, grip, usability, easy preparation of dose, and control mechanism of correct inhalation of Duaklir® Genuair®, Ultibro® Breezhaler® and Anoro® as very good to good.

Overall, a comparable percentage of AE and ADR were noticed in enrolled patients no matter which of the three LABA/LAMA study medication was taken. In total, AE were reported in 283 patients (13.25%) treated with Duaklir® Genuair®, in 142 patients (13.16%) under Ultibro® Breezhaler® therapy and in 63 patients (12.73%) who received Anoro®. Concerning ADR, the following numbers of affected patients were reported: 87 patients, 4.07%; 38 patients, 3.52%; and 18 patients, 3.64%.

Most frequently reported ADR in patients treated with Duaklir® Genuair® were dyspnoea (16 events in 15 patients, 0.70%), tremor (10 events in 9 patients, 0.42%), tachycardia (8 events in 8 patients, 0.37%), ineffective drug (7 events in 7 patients, 0.33%), and cough (6 events in 6 patients, 0.28%). ADR noted in patients under Ultibro® Breezhaler® therapy included most often cough (12 events in 12 patients, 1.11%), dyspnoea (3 events in 3 patients, 0.28%), abdominal pain, drug ineffective, dysphagia, productive cough, and tremor (2 events in 2 patients each, 0.19%). Most frequently reported ADR in Anoro® patients were ineffective drug (3 events in 3 patients, 0.61%), chronic obstructive pulmonary disease, cough, dyspnoea, productive cough, and stomatitis (2 events in 2 patients each, 0.40%).

Conclusion: Altogether, the data collected in this study with Duaklir® Genuair®, Ultibro® Breezhaler® and Anoro® showed an improvement of lung function and indicated better symptom control in patients suffering from COPD. The CAT test, which combines eight questions concerning multiple symptoms of COPD, such as shortness of breath, phlegm and quality of sleep, showed a significant score reduction during the study.

Tolerability and safety analysis of the study indicated good general drug tolerability, but under-reporting of events by health-care professionals in contrast to previously performed clinical trials cannot be excluded in this practical-use study setting. Handiness, comfort, easy understanding of handling, grip, usability, easy preparation of dose and control mechanism of correct inhalation were rated as very good to good by most of the patients.

In conclusion, results of the non-interventional study presented here strongly support the effectiveness of Duaklir® Genuair®, Ultibro® Breezhaler® and Anoro® in the treatment of COPD. The analysed patient cohort was considered representative regarding age, gender, smoking, concomitant disease and co-medication. Treatments with Aclidinium/Formoterol (Duaklir® Genuair®), Glycopyrronium/Indacaterol (Ultibro® Breezhaler®) and Umeclidinium/ Vilanterol (Anoro®) were effective and well tolerated under routine medical practice conditions in a characteristic clientele of patients.

Publications: planned

AMENDMENT HISTORY

No changes to the protocol were made after formal review was conducted and signatures were obtained for approval.

No major/substantial amendments were added to the statistical plan.