Boehringer Ingelheim

# Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

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| **Name of company:** Boehringer Ingelheim | | **Tabulated Trial Report** | Boehringer Ingelheim |
| **Name of finished product:** Fluticasone propionate HFA-MDI | | **EudraCT No.:** 2007-002522-29 | |
| **Name of active ingredient:** Fluticasone propionate | | **Page:** 1 of 9 | **Synopsis No.:** |
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| **Title of trial:** | A randomised, double-blind, active-controlled study to evaluate the impact of stepwise withdrawal of inhaled corticosteroid treatment in patients with severe to very severe chronic obstructive pulmonary disease (COPD) on optimised bronchodilator therapy |
| **Coordinating Investigator:** | [redacted] |
| **Trial sites:** | Multinational trial at 205 sites in 23 countries in continents Africa, Asia, Australia, Europe, and South America |
| **Publication (reference):** | Magnussen H, Watz H, Kirsten A, et al. Respir Med 2014;108(4):593-599<br>Magnussen H, Disse B, Rodriguez-Roisin R, et al. N Engl J Med 2014;371(14): 1285-94 |
| **Clinical phase:** | IV |
| **Objectives:** | To clarify the need for continuous inhaled corticosteroid (iCS) use in patients with severe to very severe COPD (GOLD stage III to IV) on otherwise optimised therapy (according to guidelines), and to describe the effect of stepwise withdrawal of iCS in these patients |
| **Methodology:** | Randomised, active-controlled, double-blind, parallel-group study of 2 treatment groups over a period of 52 weeks |
| **No. of patients:** | |
| **planned:** | to be entered: 2456 |
| **actual:** | enrolled: 3426<br>entered: 2488<br>Treatment iCS withdrawal:<br>entered: 1244 treated: 1242 analysed (for primary endpoint): 1242<br>Treatment iCS:<br>entered: 1244 treated: 1243 analysed (for primary endpoint): 1243 |
| **Diagnosis and main criteria for inclusion:** | Outpatients of either sex, aged ≥ 40 years with a diagnosis of COPD (GOLD Stage III to IV; post-bronchodilator $FEV_1$ < 50% of predicted [ECCS criteria] and $FEV_1/FVC$ < 70%) and a documented history of exacerbations |

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| **Test product:** | Fluticasone propionate HFA-MDI (Flixotide®) |
| **dose:** | 1000 µg (2 inhalations of 250 µg, twice daily) |
| **mode of admin.:** | Oral inhalation |
| **batch no.:** | Multiple batches of fluticasone propionate were employed, a list of the batch numbers is provided in Appendix 16.1.6 of the clinical trial report |
| **Reference therapy:** | Tiotropium bromide capsule (Spiriva®) |
| **dose:** | 18 µg |
| **mode of admin.:** | Oral inhalation via the HandiHaler® |
| **batch no.:** | Multiple batches of tiotropium bromide were employed, a list of the batch numbers is provided in Appendix 16.1.6 of the clinical trial report |
| **Reference therapy:** | Salmeterol xinafoate HFA-MDI (Serevent®) |
| **dose:** | 100 µg (2 inhalations of 25 µg, twice daily) |
| **mode of admin.:** | Oral inhalation |
| **batch no.:** | Multiple batches of salmeterol xinafoate were employed, a list of the batch numbers is provided in Appendix 16.1.6 of the clinical trial report |
| **Reference therapy:** | Fluticasone propionate HFA-MDI (Flixotide®) |
| **dose:** | 500 µg (2 inhalations of 125 µg, twice daily) |
| **mode of admin.:** | Oral inhalation |
| **batch no.:** | Multiple batches of fluticasone propionate were employed, a list of the batch numbers is provided in Appendix 16.1.6 of the clinical trial report |
| **Reference therapy:** | Fluticasone propionate HFA-MDI (Flixotide®) |
| **dose:** | 200 µg (2 inhalations of 50 µg, twice daily) |
| **mode of admin.:** | Oral inhalation |
| **batch no.:** | Multiple batches of fluticasone propionate were employed, a list of the batch numbers is provided in Appendix 16.1.6 of the clinical trial report |

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| **Reference therapy:** | Placebo for fluticasone propionate HFA-MDI |
| **dose:** | Not applicable |
| **mode of admin.:** | Oral inhalation |
| **batch no.:** | Multiple batches of placebo were employed, a list of the batch numbers is provided in Appendix 16.1.6 of the clinical trial report |
| **Duration of treatment:** | Open-label run-in period: free combination of 18 µg tiotropium + 100 µg salmeterol + 1000 µg fluticasone for 6 weeks<br>Double-blind randomised-treatment period (2 arms: iCS or iCS withdrawal): iCS arm: free combination of 18 µg tiotropium + 100 µg salmeterol + 1000 µg fluticasone for 52 weeks<br>iCS withdrawal arm (3 steps): free combination of 18 µg tiotropium + 100 µg salmeterol + 500 µg fluticasone for 6 weeks, followed by 18 µg tiotropium + 100 µg salmeterol + 200 µg fluticasone for 6 weeks, followed by 18 µg tiotropium + 100 µg salmeterol + placebo for 40 weeks |
| **Criteria for evaluation:** | |
| **Efficacy:** | Primary endpoint: time in days to first moderate or severe on-treatment COPD exacerbation during the randomised-treatment period<br>Secondary endpoints: number of moderate or severe on-treatment COPD exacerbations; proportion of patients with ≥1 moderate or severe on-treatment COPD exacerbation; time to first severe on-treatment COPD exacerbation; number of severe on-treatment COPD exacerbations; proportion of patients with ≥1 severe on-treatment COPD exacerbation; time to first on-treatment COPD exacerbation of any severity; number of on-treatment COPD exacerbations of any severity; proportion of patients with ≥1 on-treatment COPD exacerbation of any severity; severity of on-treatment COPD exacerbations; change from baseline to Weeks 6, 12, 18, and 52 in on-treatment trough forced expiratory volume in 1 second ($FEV_1$). There were further secondary endpoints in the trial, which are not listed in the synopsis; these are described in the body of the clinical trial report. |
| **Safety:** | Measurement of safety and tolerability was based on the incidence and intensity of adverse events (AEs), changes in vital signs, changes in physical examination reported as AEs, incidence of pneumonia, vital status information, incidence of |

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| **Safety (cont.):** | major adverse cardiovascular events (MACE), incidence of fatal MACE, incidence of stroke |
| **Statistical methods:** | Primary endpoint: Cox's proportional hazards regression model including terms for baseline $FEV_1$ and treatment group. An upper confidence limit of the hazard ratio <1.2 indicates the non-inferiority of iCS withdrawal in comparison to continued treatment with iCS. If non-inferiority was shown, the p-value from Wald's chi-square test was calculated to test the superiority of continued iCS treatment over iCS withdrawal. A Kaplan-Meier plot was also produced along with the corresponding log-rank test.<br><br>Secondary endpoints: Cox's proportional hazards model with Kaplan-Meier plot and corresponding log-rank test for 'time to first exacerbation' endpoints; negative binomial analysis with log treatment exposure as offset and log link function for 'number of exacerbations' endpoints; Fisher's exact test for 'proportion of patients with exacerbations' endpoints; restricted maximum likelihood-based repeated measures approach for analyses of changes from baseline; descriptive statistics for the severity of on-treatment exacerbations. |

**SUMMARY – CONCLUSIONS:**

**Efficacy results:**

A total of 2488 patients were randomised in a 1:1 ratio to the 2 treatment groups in this trial (iCS or iCS withdrawal); the treated set (TS) included 2485 patients (iCS: 1243 patients; iCS withdrawal: 1242 patients). Of the treated patients, 2027 patients (81.6%) completed the trial and 458 patients (18.4%) discontinued trial medication prematurely (iCS: 18.3%; iCS withdrawal: 18.6%); AEs were the most frequent reason for discontinuation (iCS: 8.7%; iCS withdrawal: 8.1%). Overall, the demographic profile of the study population was well balanced between the 2 treatment groups. The trial population contained more male patients (82.5%) than female patients (17.5%), and the majority of patients were White (81.4%). The mean age was 63.8 years (SD: 8.5) and the mean BMI was 25.214 $kg/m^2$. All participating patients were either ex-smokers (66.6%) or current smokers (33.4%) with a mean smoking history of 45.02 pack-years. The mean duration of COPD in the study population was 7.87 years, and 61.2% of the patients were classified as GOLD stage III, while 38.1% of the patients were classified as GOLD stage IV. In general, the baseline disease characteristics were as expected for a population of patients with severe to very severe COPD; the mean $FEV_1$ (post bronchodilator) was 0.933 L, 32.75% of predicted normal.

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**Efficacy results (cont.):**

*Primary endpoint*

Non-inferiority of iCS withdrawal was demonstrated for the primary endpoint, time to first moderate or severe on-treatment COPD exacerbation during the 12-month randomised-treatment period: the hazard ratio for iCS withdrawal versus iCS was found to be 1.058 (95% CI 0.941, 1.189). Furthermore, the superiority of iCS over iCS withdrawal was not shown, p = 0.3497. The Kaplan-Meier estimate for the time by which ≥25% of patients had a first moderate or severe on-treatment COPD exacerbation was similar for both treatment groups (iCS: 107.0 days [95% CI 94.0, 124.0]; iCS withdrawal: 110.0 days [95% CI 99.0, 120.0]).

The primary analysis was supported by a sensitivity analysis that included post-treatment exacerbations: the hazard ratio for iCS withdrawal versus iCS was found to be 1.061 (95% CI 0.945, 1.191); the upper 95% CI limit needed to be <1.2 in order to demonstrate non-inferiority.

No significant differences between the treatment groups were observed in any of the subgroups analysed for the primary endpoint (geographical region, age group, gender, smoking status, baseline BMI, and baseline 6-minute walking test).

*Secondary endpoints*

In general, the secondary endpoints exploring COPD exacerbations supported the findings of the primary endpoint.

The total number of moderate or severe on-treatment COPD exacerbations was similar in each treatment group (iCS: 953 events, with adjusted event rate per patient year = 0.91; iCS withdrawal: 972 events, with adjusted event rate per patient year = 0.95). The mean rate ratio (iCS withdrawal/iCS) of moderate or severe exacerbations was 1.05 (SE: 0.06; p = 0.4441).

There was no difference in the proportion of patients that experienced ≥1 moderate or severe on-treatment COPD exacerbation between treatment groups (iCS: 44.2%; iCS withdrawal: 46.7%), p = 0.2269.

For time to first severe on-treatment COPD exacerbation, the hazard ratio for iCS withdrawal versus iCS was found to be 1.202 (95% CI 0.975, 1.481). Although non-inferiority of iCS withdrawal was not supported by this result, superiority of iCS was not demonstrated (p = 0.0849).

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**Efficacy results (cont.):**

The total number of severe on-treatment COPD exacerbations was numerically higher in the iCS withdrawal group (iCS: 205 events, with adjusted event rate per patient year = 0.20; iCS withdrawal: 230 events, with adjusted event rate per patient year = 0.23); however, the mean rate ratio (iCS withdrawal/iCS) of severe exacerbations was 1.15 (SE: 0.13; p = 0.2291).

There was no difference in the proportion of patients that experienced ≥1 severe on-treatment COPD exacerbation between treatment groups (iCS: 13.4%; iCS withdrawal: 15.2%), p = 0.2083.

In terms of time to first on-treatment COPD exacerbation of any severity, the hazard ratio for iCS withdrawal versus iCS was found to be 1.035 (95% CI 0.923, 1.160).

The total number of on-treatment COPD exacerbations of any severity was similar in each treatment group (iCS: 1078 events, with adjusted event rate per patient year = 1.03; iCS withdrawal: 1097 events, with adjusted event rate per patient year = 1.08). The mean rate ratio (iCS withdrawal/iCS) of exacerbations of any severity was 1.05 (SE: 0.06; p = 0.4342).

There was no difference in the proportion of patients that experienced ≥1 on-treatment COPD exacerbation of any severity between treatment groups (iCS: 46.9%; iCS withdrawal: 49.0%), p = 0.3155.

The severity of COPD exacerbation reported for each patient was similar in each of the 2 treatment groups; most patients were reported with a moderate exacerbation (iCS: 30.8%; iCS withdrawal: 31.5%).

No difference in the change from baseline in on-treatment $FEV_1$ measured in clinic was seen between the iCS and iCS withdrawal groups at Weeks 6 and 12; however, a statistically significant treatment difference in favour of iCS was observed at Week 18 (–0.038 L [95% CI –0.056, –0.020]) and also at Week 52 (–0.043 L [95% CI –0.069, –0.017]).

The remaining secondary endpoints are described in the body of the clinical trial report.

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**Safety results:**

Mean exposure was similar for each treatment group (iCS: 320.0 days; iCS withdrawal: 317.5 days). During the randomised-treatment period, the overall incidence of AEs was comparable between treatment groups (iCS: 70.8%; iCS withdrawal: 71.7%). The most frequently reported treatment-emergent AEs were COPD (iCS: 45.4%; iCS withdrawal: 47.7%), followed by nasopharyngitis (iCS: 7.5%; iCS withdrawal: 6.4%); all other AEs were reported at a frequency of <5% in either treatment group. In total, 528 patients (21.2%) were reported with AEs of severe intensity (iCS: 20.9%; iCS withdrawal: 21.6%). AEs assessed by the investigator as being drug related were reported for a similar proportion of patients in each treatment group (iCS: 6.2%; iCS withdrawal: 5.0%). There were 27 drug-related AEs of severe intensity, reported for 25 patients during the randomised-treatment period. All but 2 patients (both in the iCS group) had recovered by the end of the trial. For 1 patient, the follow up was sufficient. The other patient was reported with a severe case of COPD which required hospitalisation (but did not lead to discontinuation), and a fatal case of aspergillosis. While most of the drug-related AEs of severe intensity required hospitalisation (iCS: 10 patients; iCS withdrawal: 8 patients), 2 were immediately life-threatening (1 patient reported with severe COPD in each treatment group), and 6 were considered not to be serious (3 patients in each treatment group). Drug-related AEs of severe intensity led to the premature discontinuation of trial medication for 11 patients (iCS: 7 patients; iCS withdrawal: 4 patients); a further 3 patients (iCS: 2 patients; iCS withdrawal: 1 patient) were reintroduced following an interruption to their treatment, e.g. during hospitalisation.

AEs leading to discontinuation were reported for 9.3% of iCS patients and 10.2% of iCS withdrawal patients. Other significant AEs (according to ICH E3), defined as those non-serious and non-significant AEs that led to discontinuation or dose reduction of the trial medication, were reported for 4.7% of iCS patients and 5.0% of iCS withdrawal patients.

The proportion of patients reported with SAEs during the randomised-treatment period was comparable between groups (iCS: 23.5%; iCS withdrawal: 24.2%). The investigator assessed 24 of the SAEs as drug-related; this included SAEs reported for 12 patients (1.0%) in the iCS group and 10 patients (0.8%) in the iCS withdrawal group. All but 1 patient had recovered by the end of the trial.

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**Safety results (cont.):**

The patient that did not recover was reported with 2 drug-related SAEs of severe intensity and was already described above. While most of the drug-related SAEs required hospitalisation (iCS: 11 patients; iCS withdrawal: 8 patients), 2 were immediately life-threatening (1 patient reported with COPD in each treatment group), and 1 was considered by the investigator to be serious for 'other' reasons (1 patient reported with stomatitis in the iCS withdrawal group). Drug-related SAEs led to the premature discontinuation of 12 patients (iCS: 7 patients; iCS withdrawal: 5 patients), while a further 2 patients were reintroduced following an interruption to their treatment with trial medication (1 patient in each treatment group).

In total, 81 patients (3.3%) died during the conduct of this trial (iCS: 38 patients, 3.1%; iCS withdrawal: 43 patients, 3.5%). AEs assigned to the randomised-treatment period that led to death were reported for a total of 74 patients (3.0%) in this trial (iCS: 34 patients, 2.7%; iCS withdrawal: 40 patients, 3.2%). The most frequently reported AEs leading to death were COPD (iCS: 5 patients, 0.4%; iCS withdrawal: 8 patients, 0.6%), pneumonia (iCS: 4 patients, 0.3%; iCS withdrawal: 4 patients, 0.3%), and cardiac arrest (iCS: 2 patients, 0.2%; iCS withdrawal: 4 patients, 0.3%). There was a difference of >1 death between treatment groups for the following AEs: COPD (iCS: 5 patients; iCS withdrawal: 8 patients), cardiac arrest (iCS: 2 patients; iCS withdrawal: 4 patients), acute myocardial infarction (iCS: 2 patients; iCS withdrawal: 0 patients), hypertensive heart disease (iCS: 0 patients; iCS withdrawal: 2 patients), sudden death (iCS: 1 patient; iCS withdrawal: 3 patients), sudden cardiac death (iCS: 1 patient; iCS withdrawal: 3 patients), and death (iCS: 0 patients; iCS withdrawal: 2 patients). Only 1 SAE that led to death was assessed by the investigator as drug related: 1 severe incidence of aspergillosis in the iCS group.

For this trial, pneumonia, MACE, fatal MACE, and stroke were defined as AEs of special interest. AEs that triggered the aggregated pharmacovigilance term 'pneumonia #PV' were reported for 5.8% of iCS patients compared with 5.5% of iCS withdrawal patients. MACE endpoints were reported for 2.0% of iCS patients and 2.2% of iCS withdrawal patients, while fatal MACE endpoints were reported for 1.1% of iCS patients and 1.5% of iCS withdrawal patients. AEs that triggered the aggregated pharmacovigilance term 'stroke #PV' were reported for 0.7% of iCS patients compared with 0.5% of iCS withdrawal patients.

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| **Safety results (cont.):** | Of the 191 patients in the iCS group who discontinued the study prematurely but who gave their permission to be contacted regarding vital status, 155 patients (76.7%) were reported as alive, while 13 patients (6.4%) were lost to follow up. Of the 197 patients in the iCS withdrawal group who discontinued the study prematurely but who gave their permission to be contacted regarding vital status, 159 patients (74.3%) were reported as alive, while 12 patients (5.6%) were lost to follow-up.<br><br>The mean SBP, DBP, and pulse rate was comparable between treatment groups at baseline, and also throughout the 52 weeks of the randomised-treatment period of the trial. Any changes in SBP, DBP, or pulse rate were numerically very small and were not considered to be of clinical relevance.<br><br>There were no pregnancies reported during the course of this trial. |
| **Conclusions:** | In a population of adult patients with severe to very severe COPD on optimised bronchodilator therapy (according to guidelines), non-inferiority was demonstrated for the stepwise withdrawal of iCS treatment in terms of time to first on-treatment moderate or severe COPD exacerbation. While this was generally supported by the exploratory analyses of other exacerbation endpoints, the exploratory analyses of spirometry endpoints including $FEV_1$ suggested that the complete withdrawal of iCS treatment was associated with a greater decline in lung function compared with continued iCS therapy. Following the initial drop in lung function on complete withdrawal of iCS, no further decline was visible thereafter. The safety profile of iCS withdrawal was similar to that of continued iCS treatment. |