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**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: NA		**EudraCT No.:** 2007-003169-42	
Name of active ingredient: Ciclesonide + tiotropium bromide + salmeterol xinafoate Fluticasone propionate		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 03 APR 2009	**Trial No. / U No.:** 1249.1 / U09-1288-02	**Date of trial:** 04 DEC 2007 – 30 SEP 2008	**Date of revision :** 03 SEP 2009

Title of trial:	A Randomised, Phase II, Double-Blind, Double-Dummy, four-period Crossover Efficacy and Safety Comparison of 4-Week Treatment Periods of Blinded Fluticasone (500 mcg bid, MDI), Ciclesonide (400 mcg qd, MDI), Ciclesonide (800 mcg qd, MDI) or placebo in Free Combination with Open-Label Tiotropium (18 mcg qd, HandiHaler) and Salmeterol (50 mcg bid, Diskus) in Patients with COPD
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study cf. Appendix 16.1.4
Publication (reference):	Data of this study has not been published
Clinical phase:	II
Objectives:	The objective of this trial was to evaluate the lung function response to the free combinations of open-label tiotropium (18 µg once daily) plus open-label salmeterol (50 µg twice daily) combined with either blinded a. Fluticasone (500 µg twice daily ex valve) b. Ciclesonide (400 µg once daily ex actuator) c. Ciclesonide (800 µg once daily ex actuator) d. Placebo at the end of 4-week treatment periods in patients with COPD. The primary objective of this cross-over study was to evaluate and compare the effect on lung function parameters of the four different combinations mentioned above at the end of 4-week periods of randomised treatment.
Methodology:	Double-blind, double-dummy, placebo-controlled, 4-period cross-over, 2-week washout
No. of subjects:	Enrolled: 130
planned:	Entered: 100

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: NA		**EudraCT No.:** 2007-003169-42	
Name of active ingredient: Ciclesonide + tiotropium bromide + salmeterol xinafoate Fluticasone propionate		**Page:** 2 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 03 APR 2009	**Trial No. / U No.:** 1249.1 / U09-1288-02	**Date of trial:** 04 DEC 2007 – 30 SEP 2008	**Date of revision :** 03 SEP 2009

actual:	Enrolled: 130 Entered: 103 Placebo: entered: 96 treated: 96 analysed (per protocol): 96 (85) Ciclesonide 400µg: entered: 97 treated: 97 analysed (per protocol): 97 (91) Ciclesonide 800µg: entered: 96 treated: 96 analysed (per protocol): 96 (90) Fluticasone 1000 µg: entered: 98 treated: 98 analysed (per protocol): 98 (90)
Diagnosis and main criteria for inclusion:	Outpatients of either sex, aged ≥ 40 years. COPD [post bronchodilator 30%≤ FEV1<80% of predicted (ECSC criteria). FEV1/FVC <70%]
Test product:	Open label Tiotropium powder capsule + open label salmeterol Diskus® combined with either blinded a. Flutide Forte (fluticasone) b. Alvesco 80 Inhaler (ciclesonide) c. Alvesco 160 Inhaler (ciclesonide) d. Placebo
dose:	Tiotropium powder capsule 18 µg qd (morning) + salmeterol Diskus® 1 puff of 50 µg bid (morning and evening) a. 500 µg bid (2 puffs of 250 µg morning and evening) b. 400 µg qd (5 puffs of 80 µg morning) c. 800 µg qd (5 puffs of 160 µg morning) d. Placebo
mode of admin.:	Oral inhalation via the HandiHaler®, Diskus® or metered dose inhalers (MDI)
batch no.:	B071002653, B071002795 and PR07/10242
Reference therapy:	Open-label Tiotropium capsule + open-label salmeterol Diskus®
dose:	Tiotropium powder capsule 18 µg qd (morning) + salmeterol Diskus® 1 puff of 50 µg bid (morning and evening)
mode of admin.:	Oral inhalation via the HandiHaler® (tiotropium) and Diskus® (salmeterol)
batch no.:	B071002653 and B071002795

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: NA		**EudraCT No.:** 2007-003169-42	
Name of active ingredient: Ciclesonide + tiotropium bromide + salmeterol xinafoate Fluticasone propionate		**Page:** 3 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 03 APR 2009	**Trial No. / U No.:** 1249.1 / U09-1288-02	**Date of trial:** 04 DEC 2007 – 30 SEP 2008	**Date of revision :** 03 SEP 2009

Duration of treatment:	A 4-week run-in period followed by four 4-week treatment periods separated by 2-week wash out periods and a 2-week follow-up period (a total of 28 weeks)
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Primary: FEV_1 (primary endpoint: trough FEV_1) Secondary: FVC, VC, IC, PEF, dyspnoea (Mahler BDI/TDI), rescue medication use, DL_{CO}, FE_{NO}
Safety:	Adverse events and vital signs
Statistical methods:	ANCOVA with terms for centre, patient within centre, treatment, and period; descriptive statistics

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

One hundred and thirty patients were enrolled in the trial and 103 patients were randomized. The baseline demographic and disease characteristics are comparable to other COPD studies performed.

The primary endpoint was not met: Neither of the inhaled steroids demonstrated a statistically significant difference from placebo (all given on top of maintenance tiotropium and salmeterol) in the primary efficacy endpoint, mean trough FEV_1 response at Day 28. This was the case both for the FAS and the PP set.

Secondary endpoints: The observed peak (0-3h) in FEV_1 response were similar at both Day 1 and Day 28 ranging from 0.201 L to 0.250 L. On Day 28 fluticasone 1000 µg, but not the two ciclesonide doses, showed a statistically significant increase in FEV_1 peak (0-3h) compared to placebo (0.044 L). FEV_1 AUC (0-3h) revealed similar results. After 4 weeks of treatment a decrease in FVC was shown for all the inhaled steroids, reaching nominal statistical significance for ciclesonide 800 µg only.

The trial was not powered for all the secondary endpoints. However, an advantage of fluticasone 1000 µg could be observed compared to ciclesonide

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: NA		**EudraCT No.:** 2007-003169-42	
Name of active ingredient: Ciclesonide + tiotropium bromide + salmeterol xinafoate Fluticasone propionate		**Page:** 4 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 03 APR 2009	**Trial No. / U No.:** 1249.1 / U09-1288-02	**Date of trial:** 04 DEC 2007 – 30 SEP 2008	**Date of revision :** 03 SEP 2009

Efficacy / clinical pharmacology results cont.:	and placebo. The two ciclesonide doses do not clearly separate from each other or from placebo in terms of efficacy. Inspiratory capacity revealed no statistically significant differences between treatments Using the Mahler Transition Dyspnoea Index (TDI) patients' dyspnoea at Day 28 was rated better than at Day 1 for all treatments except placebo. The difference of active treatments to placebo ranged between 0.34 to 0.78 scoring points, however, neither of the active treatments nor placebo achieved a change in the focal score of >1, which is considered to be the minimal clinically important difference (MCID). Additional subgroup analyses (first period only, current smokers vs. ex-smokers,, severity at baseline [FEV1 <= 50% vs. > 50% of predicted normal], salbutamol responders vs. non-responders, DLCO, IgE, CRP and eosinophiles [lower vs. higher than the median at baseline for the latter four parameters]), were performed on the primary efficacy variable FEV1, but none of these gave a different conclusion of the result.
Safety results:	Evaluation of all of the safety data collected from this trial did not reveal any unexpected safety findings for any of the treatments. There were more AEs during treatment with the two ciclesonide doses (32-33%) compared to fluticasone (24.5%) and placebo (28.1%). Two patients on ciclesonide 400µg and three patients on ciclesonide 800µg had a severe event, while there were none during treatment with placebo and fluticasone. In contrast, a higher percentage of the AEs were treatment related while patients were on fluticasone (7.1%) compared to all other treatments (2.1% on placebo, 5.2% on ciclesonide 400 µg and 4.2% on ciclesonide 800 µg). COPD exacerbation was the most common AE during any treatment phase. It is worth noting that 10.4% of the patients had a COPD exacerbation while on

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: NA		**EudraCT No.:** 2007-003169-42	
Name of active ingredient: Ciclesonide + tiotropium bromide + salmeterol xinafoate Fluticasone propionate		**Page:** 5 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 03 APR 2009	**Trial No. / U No.:** 1249.1 / U09-1288-02	**Date of trial:** 04 DEC 2007 – 30 SEP 2008	**Date of revision :** 03 SEP 2009

Safety cont.	placebo, whereas it was only 5.2% on ciclesonide 400 µg and 1.0% on ciclesonide 800µg and 2.0% on fluticasone. Seven patients had a COPD exacerbation in a wash-out or follow-up period. None of the five SAEs reported were considered drug related. Two patients had a SAE during treatment with ciclesonide 800µg, two while on ciclesonide 400µg period and one in a wash-out period. All these patients required hospitalization which triggered classification as SAE. There was no unblinding of medication. The only AEs reported as drug related in more than one patient was dysphonia with 2.0% of patients experiencing this AE during treatment with ciclesonide 400µg and fluticasone, and pharyngeal erythema with an incidence of 2.0% during treatment with ciclesonide 400µg. One patient in each treatment period and five patients in a wash-out or follow-up period were withdrawn from the study due to an AE - of these only three were considered drug related. The most common AE leading to withdrawal from the study was worsening of COPD, which was the reason for withdrawal of five patients.
Conclusions:	The primary endpoint was not met in this clinical trial; i.e. no statistically significant difference in trough FEV1 response could be shown for ciclesonide 400µg, ciclesonide 800µg or fluticasone 1000µg in comparison to placebo (all given on top of maintenance tiotropium and salmeterol). In almost all endpoints results were slightly in favour of fluticasone 1000 µg compared to the other treatments. Some of these differences were statistically significant. The two ciclesonide doses did not clearly separate from each other or from placebo in terms of efficacy. The safety evaluation did not reveal any unique safety issues for ciclesonide 400µg or 800 µg or fluticasone 1000µg. The adverse event profiles were typical for a trial of this size, duration and patient population. Imbalances across treatment groups are difficult to interpret due to the small patient numbers, low incidence of each particular event and lack of a consistent pattern of relationship across the treatments. Ciclesonide appears to have a similar adverse event profile in COPD to fluticasone.