Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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: Not applicable		**EudraCT No.:** 2009-014551-80	
Name of active ingredient: BI 671800 ED		**Page:** 1 of 6	**Synopsis No.:**
Module: na		**Volume: na**	
Report date: 31 MAR 2015	**Trial No. / Doc No.:** 1268.16 / U13-1187-01 / c01694730-02	**Date of trial:** 20-04-2010 to 09-08-2011	**Date of revision:** Not applicable

Title of trial:	Randomised, double-blind, double-dummy, placebo-controlled, parallel group study to assess the efficacy and safety of 6 weeks of oral BI 671800 ED 400 mg b.i.d., Montelukast 10 mg q.d., or placebo in symptomatic asthma patients on fluticasone propionate MDI
Coordinating Investigator:	[redacted] Nottingham University Hospitals NHS Trust Dept of Therapeutics & Molecular Medicine Queens Medical Centre Derby Road Nottingham, NG7 2UH [redacted]
Trial sites:	Multi-centre, multi-national, [redacted]
Publication (reference):	P12 - 12342
Clinical phase:	IIa
Objectives:	To investigate the efficacy, safety and tolerability of BI 671800 ED 400 mg b.i.d. compared to placebo or montelukast 10 mg q.d., given for 6 weeks as add-on therapy to fluticasone propionate MDI (50 µg 2 puffs bid) in symptomatic asthmatic patients.
Methodology:	Randomised, double-blind, placebo-controlled, double dummy, parallel group design.
No. of subjects:	
planned:	Entered/randomised:225 (75 in each treatment arm)
actual:	enrolled: 647; entered/randomised: 243; treated 243 Placebo: entered: 95; treated: 95; analysed (for primary endpoint): 87 BI 671800 ED 400 mg b.i.d.: entered: 81; treated: 81; analysed (for primary endpoint): 77 Montelukast 10 mg q.d.: entered: 67; treated: 67;analysed (for primary endpoint): 66

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Diagnosis and main criteria for inclusion:	Male or female (adequate contraception or not of child bearing potential), non-smoker or ex-smoker (smoking history of < 10 pack-years), 18 to 65 years old, ≥ 3 month history of physician diagnosed asthma, documented FEV1 reversibility to salbutamol ≥ 12% and ≥ 200 mL (at any visit before randomisation), pre-bronchodilator FEV_1 60 to 85% predicted and ACQ ≥ 1.5 at randomisation. Stable asthma controller medication prior to screening Visit 2.
Test product:	BI 671800 ED
dose:	400 mg twice daily (b.i.d.)
mode of admin.:	Oral capsules
batch no.:	B093000591
Reference therapy:	Montelukast
dose:	10 mg once daily (q.d.)
mode of admin.:	Oral tablets
batch no.:	B093000593, B101000544, B101005007
Reference therapy:	BI 671800 ED placebo
dose:	Not applicable
mode of admin.:	Oral capsules
batch no.:	B093000586, B093000587
Reference therapy:	Montelukast placebo
dose:	Not applicable
mode of admin.:	Oral tablets
batch no.:	B093000585
Duration of treatment:	6 weeks

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Criteria for evaluation:

Efficacy / clinical pharmacology:	Efficacy parameters: Morning trough forced expiratory volume in one second (FEV_1) % predicted, asthma control questionnaire (ACQ),FEV_1, forced vital capacity (FVC), Forced expiratory flow $(FEF)_{25-75\%}$, Peak FEV_1, Peak FVC, FEV_1 area under the curve $(AUC)_{0-3h}$, FVC AUC_{0-3h}, standardised asthma quality of life questionnaire (AQLQ(S)), daily symptom scores (am and pm), weekly means of daily puffs of rescue medication usage, peak expiratory flow (PEF) and FEV_1, asthma symptom-free days, asthma controlled weeks, asthma exacerbations, fractional exhaled Nitric Oxide (FeNO), total IgE and eosinophilic cationic protein (ECP). Pharmacokinetic (PK) parameters: Population PK from plasma concentrations of BI 671800 sampled during the treatment period (total of two samples/patient).
Safety:	Adverse events (AEs), routine laboratory, physical examinations, 12 lead electrocardiogram (ECG), vital signs
Statistical methods:	Restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). Descriptive statistics.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:	The trial met its primary endpoint for BI 671800 ED 400 mg b.i.d. vs. placebo in symptomatic asthmatic patients receiving low dose iCS, with a statistically significantly superior effect size of approximately 4% predicted FEV_1 vs. placebo (equivalent to an increase in FEV_1 of approximately 140 mL). For the primary endpoint, trough FEV_1 % predicted change from baseline (Week 0) after 6 weeks of treatment, the adjusted mean treatment differences (and SE) compared to placebo were 3.87% (1.49%) and 2.37% (1.57%) for BI 671800 ED 400 mg b.i.d. and montelukast 10 mg q.d., respectively. The difference was statistically significant at the one-sided 2.5% level for BI 671800 ED 400 mg b.i.d. but not for montelukast 10 mg q.d.. Compared with montelukast 10 mg q.d., the adjusted mean treatment difference (and SE) after 6 weeks for BI 671800 ED 400 mg b.i.d. was 1.50% (1.60%). This difference was not statistically significant at the one-sided 2.5% level.

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For the secondary endpoint, change from baseline in ACQ, the adjusted mean treatment differences (and SE) compared to placebo were -0.280 (0.118) and -0.180 (0.124) for BI 671800 ED 400 mg b.i.d. and montelukast 10 mg q.d. respectively. The difference from placebo was statistically significant at the one-sided 2.5% level for BI 671800 ED 400 mg b.i.d. but not for montelukast 10 mg q.d..

For the exploratory efficacy endpoints, with the exception of trough FVC, the in-clinic spirometry assessments consistently showed BI 671800 ED 400 mg b.i.d. to be statistically significantly superior to placebo at Week 6. This was replicated in home e-diary spirometry assessments for morning FEV_1 but not evening FEV_1 or PEF, the asthma control assessments (asthma symptoms and well controlled weeks) or in the assessment of quality of life (AQLQ).

BI 671800 ED 400 mg b.i.d. demonstrated a clear improvement in FEV_1 trough % predicted which was supported by an improvement in the secondary endpoint and several exploratory endpoints.

Safety Results:

BI 671800 ED at a daily dose of 400 mg b.i.d. administered for 6 weeks, in symptomatic asthmatic patients receiving low-dose iCS, was safe and generally well tolerated.

The percentage of patients who experienced at least one AE during the treatment phase of the trial was lower on BI 671800 ED 400 mg b.i.d. (34.6%) than on placebo (45.3%) and montelukast 10 mg q.d. (43.3%). In decreasing order of overall frequency, the most common treatment-emergent AEs (reported in at least three patients in any of the treatment groups) were nasopharyngitis, headache, asthma, nausea, influenza, hypertension and rash. The majority of all AEs reported during the trial were considered mild or moderate in intensity; severe AEs were reported by six patients (of 243). Five severe AEs were reported by four patients in the placebo treatment group, two severe AEs were reported by one patient in the BI 671800 ED 400 mg b.i.d. treatment group and one severe AE was reported in the montelukast 10 mg q.d. treatment group. There were no deaths reported during the trial. One patient in the BI 671800 ED 400 mg b.i.d. treatment group experienced one SAE; toxic hepatitis, considered by the investigator to be drug related, which was reported on the last day of planned treatment for the patient so did not lead to discontinuation of study medication.

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Sixteen patients experienced a total of 25 treatment-emergent AEs that led to discontinuation from trial medication. Of the 16 patients who discontinued trial medication due to an AE, seven patients were in the placebo treatment group, five patients were in the BI 671800 ED 400 mg b.i.d. treatment group and four patients were in the montelukast 10 mg q.d. treatment group.

Seven of the 25 AEs that led to discontinuation of trial medication were considered by the investigator to be drug-related; three of these seven AEs occurred in the BI 671800 ED 400 mg b.i.d. treatment group (three separate patients), while the other four AEs occurred in one montelukast 10 mg q.d. patient. None of the AEs that led to discontinuation of trial medication was considered serious.

Changes in laboratory safety assessment parameters were seen for a small proportion of patients in all treatment groups. With the exception of mean increases in AST and ALT observed in the BI 671800 ED 400 mg b.i.d. treatment group, there were no clinically relevant changes from baseline in mean values for any haematology, blood chemistry, or urinalysis parameter during the treatment phase of the trial.

No changes >3 × ULN were observed in any haematology parameters and possibly clinically significant elevations in haematology parameters were uncommon with no AEs related to changes in haematology laboratory parameters reported.

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For blood chemistry parameters, elevations >3 × ULN were seen in AST for three patients receiving BI 671800 ED 400 mg b.i.d. (including one patient with elevation >5 x ULN and one patient with elevation > 8 x ULN), in ALT for four patients receiving BI 671800 ED 400 mg b.i.d. (including two patients with elevation >5 x ULN and one patient with elevation > 8 x ULN), in creatine kinase for one patient receiving placebo (elevation >5 x ULN) and two patients receiving montelukast 10 mg q.d., (including one patient with elevation >5 x ULN) and in C-reactive protein for five patients receiving placebo (including two patients with elevation >8 x ULN), three patients receiving BI 671800 ED 400 mg b.i.d. (including one patient with elevation >5 x ULN and one patient with elevation > 8 x ULN) and two patients receiving montelukast 10 mg q.d. (including one patient with elevation >5 x ULN). Possibly clinically significant changes were few, although hepatic transaminase changes were seen in BI 671800 ED 400 mg (three patients with possibly clinically significant elevations in both AST and ALT, and a fourth patient with a possibly clinically significant elevation in ALT only). These changes were reflected in liver-related AEs toxic hepatitis, hepatic steatosis, increased ALT and increased AST. No possibly clinically significant abnormalities in bilirubin were seen in any treatment group.

No relevant findings were seen in the analysis of vital signs (blood pressure and heart rate).

Conclusions:

The study met the primary endpoint demonstrating clinically and statistically significant improvements in trough FEV_1 for BI 671800 400 mg b.i.d. compared to placebo. This provides evidence for clinical activity and proof of concept for this mechanism of action following treatment of symptomatic asthma patients receiving fluticasone propionate 100 µg b.i.d. with BI 671800 ED 400 mg b.i.d., for 6 weeks.

With the exception of elevated hepatic transaminases in four patients, treatment with BI 671800 ED 400 mg b.i.d. for 6 weeks was safe and well tolerated.

Exposure of BI 671800 and its BI 600957 metabolite was as expected based on previous clinical data.b.i.d.