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: Not applicable		**EudraCT No.:** 2010-023326-20	
Name of active ingredient: BI 671800 ED		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 01 DEC 2015	**Trial No. / U No.:** 1268.17 / **c01694824-02**	**Date of trial:** 18 March 2010 – 26 May 2011	**Date of revision:** Not applicable

Title of trial:	A randomized, double blind, placebo and active controlled, parallel group study to evaluate the safety and efficacy of 6-week treatment with oral doses of 50 mg bid, 200 mg bid, and 400 mg bid BI 671800 ED in steroid-naïve patients with persistent asthma
Co-ordinating Investigator:	[redacted], MD
Trial sites :	Multi-centre, multi-national, cf. Appendix 16.1.4
Publication (reference):	R15-1932
Clinical phase:	IIa
Objectives:	To investigate the efficacy, safety and tolerability of BI 671800 ED (50 mg bid / 200 mg bid / 400 mg bid) compared to fluticasone propionate 110 mcg 2 puffs bid and placebo in symptomatic steroid-naïve asthma patients.
Methodology:	Randomised, double-blind, placebo-controlled, parallel group, double dummy design (5 treatment arms)
No. of subjects:	
planned:	Entered (randomized): 390 (78 each treatment arm)
actual:	Enrolled: 1045; entered: 389; treated: 388
	Placebo: treated: 78; analyzed (for primary endpoint): 72
	BI 671800 ED 50 mg bid: treated: 77; analyzed (for primary endpoint): 75
	BI 671800 ED 200 mg bid: treated: 83; analyzed (for primary endpoint): 82
	BI 671800 ED 400 mg bid: treated: 79; analyzed (for primary endpoint): 76
	Fluticasone 220 mcg bid: treated: 71; analyzed (for primary endpoint): 68

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2010-023326-20	
Name of active ingredient: BI 671800 ED		**Page:** 2 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 01 DEC 2015	**Trial No. / U No.:** 1268.17 / **c01694824-02**	**Date of trial:** 18 March 2010 – 26 May 2011	**Date of revision:** Not applicable

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 inclusive; ≥3 month history of physician diagnosed asthma; pre-bronchodilator forced expiratory volume in 1 second (FEV_1) 60 to 85% predicted FEV_1 reversibility ≥12% and ≥200 mL after 400 mcg albuterol/salbutamol, Asthma Control Questionnaire ACQ ≥1.5 at randomization, on albuterol/salbutamol therapy as needed only therapy
Test product:	BI 671800 ED
dose:	50 mg bid capsules 200 mg bid capsules 400 mg bid capsules
mode of admin. :	Oral capsules
batch no.:	50 mg: B093000590, 200 mg and 400 mg: B093000591, B093000592
Reference therapy:	Fluticasone propionate MDI
dose:	110 mcg, 2 puffs bid
mode of admin. :	Oral inhalation
batch no.:	B093000767, B102000014, B102000182
Reference therapy:	Placebo capsules
dose:	Not applicable
mode of admin. :	Oral capsules
batch no:	B093000586, B093000587
Reference therapy:	Placebo MDI
dose:	Not applicable
mode of admin. :	Oral inhalation
batch no:	B093000766, B102000197

Name of company: Boehringer Ingelheim		Tabulated Trial Report	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2010-023326-20	**Synopsis No.:**
Name of active ingredient: BI 671800 ED		**Page:** 3 of 5	
Module:		**Volume:**	
Report date: 01 DEC 2015	**Trial No. / U No.:** 1268.17 / **c01694824-02**	**Date of trial:** 18 March 2010 – 26 May 2011	**Date of revision:** Not applicable

Duration of treatment:	6 weeks
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Primary endpoint: Trough FEV_1 % predicted Secondary endpoints: Asthma Control Questionnaire (ACQ); Other endpoints: PEF a.m. / p.m. (as assessed by an electronic peak flow meter); FEV_1 % predicted AUC_{0-3h}; FEV_1; FVC; FEV_1 AUC_{0-3h}; FVC AUC_{0-3h}, Exhaled FeNO (selected sites only); IgE, Asthma Quality of Life Questionnaire (AQLQ); daytime and nocturnal symptoms (a.m. / p.m.) as assessed by an electronic diary; asthma control weeks; asthma worsening and exacerbations; rescue medication use
Criteria for pharmacokinetics:	Population pharmacokinetics from plasma concentrations of BI 671800 ED sampled throughout the treatment period (total of four samples per patient at select sites)
Safety:	Adverse events, 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 at 200 and 400 mg bid vs. placebo in symptomatic controller-naïve asthma patients. Maximum efficacy was achieved at 400 mg bid (approximately 4% predicted FEV1 vs. placebo).

For the primary endpoint, the 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 3.083% (1.650%), 3.589% (1.600%), 3.977% (1.640%), and 8.619 (1.684%) for BI 671800 ED 50 mg bid, BI 671800 ED 200 mg bid, BI 671800 ED 400 mg bid, and fluticasone 220 mcg bid, respectively. These differences were statistically significant at the one-sided 2.5% level in trough FEV_1 % predicted change from baseline between placebo and active treatment for all treatment groups with the exception of the BI 671800 ED 50 mg bid group..

	For the secondary endpoint, change from baseline in ACQ, the adjusted mean treatment differences (and SE) compared to placebo were: -0.0073 (0.113), -0.080 (0.110), -0.061 (0.113), and -0.333 (0.116), for BI 671800 ED 50 mg bid, BI 671800 ED 200 mg bid, BI 671800 ED 400 mg bid, and fluticasone 220 mcg bid, respectively. Although all treatment groups showed an adjusted mean improvement in mean ACQ score of at least 0.5 from baseline, only the fluticasone group was statistically significantly superior to placebo. Statistically significant effect was seen in FEV_1 trough % predicted change from baseline at the highest dose levels of BI 671800 ED. Although not replicated with the secondary endpoint (ACQ), a number of the exploratory endpoints provided supportive results, namely FEV_1% predicted AUC_{0-3h}, trough FEV_1[L], FEV_1 [L] AUC_{0-3h}, trough FEF [L/sec], morning PEF [L/min] and time to asthma worsening.
Safety results:	BI 671800 ED at daily doses of 50 mg bid, 200 mg bid, and 400 mg bid administered for 6 weeks, in symptomatic steroid-naïve asthma patients, was safe and well tolerated. There were no deaths reported during the trial. Two patients experienced SAEs, one in the placebo treatment group (blurry vision, headache, lightheadedness and nausea) and one in the BI 671800 ED 400 mg bid treatment group (acute respiratory failure, decompensated heart failure and pneumonia) which was considered not drug related. Twenty-five patients experienced a total of 33 treatment-emergent AEs that led to discontinuation from trial medication. Of the 25 patients who discontinued trial medication due to an AE, 10 patients were in the placebo group, 6 patients in the BI 671800 ED 50 mg bid group, 1 patient in the BI 671800 ED 200 mg group, 5 patients in the BI 671800 ED 400 mg bid group, and 3 patients in the Fluticasone group Eight of the 33 AEs that led to discontinuation of trial medication were considered by the investigator to be drug-related; seven of these eight were in the placebo group and one was in the fluticasone group. Seven of the AEs that led to discontinuation of trial medication were considered serious: four in the placebo group and three in the BI 671800 ED 400 mg bid group.

Overall, no adverse trends were noted for safety laboratory parameters. An increase in frequency in liver related tests (> 3x ULN) was noted for BI 671800 200 and 400 mg bid. There were no corresponding changes in liver function or associated clinical findings. No relevant findings were seen in the analysis of vital signs (blood pressure and heart rate).

The percentage of patients who experienced at least one AE during the treatment phase of the trial was similar during treatment with BI 671800 ED at any dose and fluticasone (48.1%, 42.2%, 46.8% and 45.1% of patients during treatment with BI 671800 ED 50g bid, 200 mg bid, 400 mg bid and fluticasone respectively) and with placebo (41.0%). The most common treatment-emergent AEs (reported in at least 3 patients in any of the 5 treatment groups) were asthma, upper respiratory tract infection (URTI), diarrhea, nausea, nasopharyngitis, myalgia, increased appetite, and headache. The majority of all AEs reported during the trial were considered mild or moderate in intensity; severe AEs were reported by five patients out of 388). Two severe AEs were reported in the placebo treatment group, one in the BI 671800 ED 200 mg bid treatment group and two in the BI 671800 400 ED mg bid treatment group.

Conclusions:

Treatment with BI 671800 ED 200 mg bid and 400 mg bid, for 6 weeks, in symptomatic controller-naïve asthma patients, met the primary endpoint for this trial demonstrating statistically and clinically significant improvements in trough FEV_1 in symptomatic controller-naïve asthmatic patients.

Treatment with BI 671800 ED for 6 weeks was safe and well tolerated at all doses evaluated in this study.