Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		Tabulated Trial Report	Boehringer Ingelheim
Name of finished product: BI 54903 ethanolic solution for inhalation (EIS)		**EudraCT No.:** 2010-023167-17 (1248.5), 2010-023168-41 (1248.6), 2010-023169-23 (1248.7).	**Synopsis No.:**
Name of active ingredient: BI 54903		**Page:** 1 of 5	
Module:		**Volume:** {hyperlink }	
Report date: 27 AUG 2012	**Trial No. / U No.:** 1248.5-7 / U12-1955-01	**Date of trial:** 21 JUL 2011 – 23 DEC 2011	**Date of revision:** Not applicable

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Title of trial:	Randomised, double-blind, double-dummy, placebo- (1248.5-6) or active-controlled (1248.7), parallel group studies to assess and compare efficacy and safety of an 8-week treatment with BI 54903 (dose range of 22.7 µg to 363.6 µg b.i.d.) administered via Respimat® inhaler and fluticasone propionate HFA MDI in patients with asthma.
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre, multinational studies.
Publication (reference):	Not applicable.
Clinical phase:	II
Objectives:	To assess and compare efficacy and safety of BI 54903, fluticasone propionate HFA MDI and placebo (1248.5-6) or a low dose fluticasone propionate (1248.7) over an 8-week treatment period in asthmatic patients inadequately controlled on iCS (1248.6-7) or on-demand SABA therapy only (1248.5).
Methodology:	
No. of subjects:	
planned:	entered: 755 evaluable patients per trial.
actual:	Study 1248.5: treated: 29 analysed (for primary endpoint): not applicable Study 1248.6: treated: 29 analysed (for primary endpoint): not applicable Study 1248.7: treated: 9 analysed (for primary endpoint): not applicable

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Diagnosis and main criteria for inclusion:	- Outpatients of either sex, 12-65 years old, - Never-smokers or ex-smokers (for at least 1 year) with a smoking history of < 10 pack-years, - Diagnosis of asthma stable for the past 6 weeks on medium-dose iCS without LABA or on low-dose iCS with/without LABA (1248.5), high-dose iCS without LABA or medium-dose with LABA (1248.6), or high-dose iCS with LABA (1248.7), - An a.m. pre-bronchodilator FEV_1 ≥ 60-90% predicted and an ACQ-6 score < 1.5 at the pre-screening Visits 1 and 2. - Improvement in FEV_1 of ≥ 12% and an absolute change of at least 200 mL within 15 to 30 min post 400 µg salbutamol/albuterol HFA MDI as demonstrated at pre-screening Visit 1 or during one of the visits during the run-in period. After the initial pre-screening visit, patients continued on their pre-trial asthma medication for a 2-week pre-screening period, followed by a up to 4-week run-in period on placebo (1248.5) or fluticasone propionate HFA MDI [1248.6: 88 µg b.i.d. (ex actuator); 1248.7: 220 µg b.i.d. (ex actuator)] and salbutamol/albuterol HFA MDI p r n. as the only asthma medication. Patients were randomised if all eligibility criteria of the pre-screening period were fulfilled as well as the following criteria during the run-in period: - showing a decrease in a m. FEV_1 ≥ 10% and ≤ 25% from pre-screening baseline (for patients demonstrating a drop in a m. FEV_1 > 25%, it was the investigator's clinical judgement whether it was clinically safe to randomise the patient or to withdraw the patient from the study and to re-start pre-trial controller medication and/or an oral steroid treatment), - An ACQ-6 score ≥ 1.5.
Test product:	BI 54903 ethanolic solution for inhalation.

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dose:	1248.5: 2 puffs of 11.4 µg b.i.d. (22.7 µg b.i.d. / ex actuator); 2 puffs of 22.7 µg b.i.d. (45.5 µg b.i.d. / ex actuator); 2 puffs of 45.5 µg b.i.d. (90.9 µg b.i.d. / ex actuator). 1248.6: 2 puffs of 22.7 µg b.i.d. (45.5 µg b.i.d. / ex actuator); 2 puffs of 45.5 µg b.i.d. (90.9 µg b.i.d. / ex actuator); 2 puffs of 90.9 µg b.i.d. (181.8 µg b.i.d. / ex actuator). 1248.7: 2 puffs of 45.5 µg b.i.d. (90.9 µg b.i.d. / ex actuator); 2 puffs of 90.9 µg b.i.d. (181.8 µg b.i.d. / ex actuator); 2 puffs of 181.8 µg b.i.d. (363.6 µg b.i.d. / ex actuator).
mode of admin.:	Oral inhalation via Respimat® inhaler (combined with placebo HFA MDI, 2 puffs b.i.d.).
batch no.:	11.4 µg: B102000161; 22.7 µg: B102000073; 45.5 µg: B102000078; 90.9 µg: B102000079; 181.8 µg: B102000108. Respimat® inhaler: B102000151, B082000195. Placebo MDI HFA: 906475A
Reference therapy:	1248.5: placebo HFA MDI and fluticasone propionate HFA MDI (Flovent®). 1248.6: placebo HFA MDI and fluticasone propionate HFA MDI (Flovent®). 1248.7: 2 doses of fluticasone propionate via HFA MDI (Flovent®).
dose:	1248.5: placebo; 2 puffs of 44 µg b.i.d. (88 µg b.i.d. / ex actuator). 1248.6: placebo; 2 puffs of 110 µg b.i.d. (220 µg b.i.d. / ex actuator). 1248.7: 2 puffs of 44 µg b.i.d. (88 µg b.i.d. / ex actuator); 2 puffs of 220 µg b.i.d. (440 µg b.i.d. / ex actuator).
mode of admin.:	Oral inhalation from HFA-MDI (combined with placebo Respimat® inhaler).
batch no.:	44 µg: F0672, F0731, F0727, F0542-2; 110 µg: F0414, F0466; 220 µg: F0240, F0265A.; placebo MDI HFA: 906475A. Placebo ethanolic solution: B102000035; Respimat® inhaler: B102000151, B082000195.
Duration of treatment:	Up to 4-week run-in period followed by an 8-week treatment period with investigational drug and, subsequently, a 2-week follow-up period

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Criteria for evaluation: **Efficacy / clinical pharmacology:**	Following a critical evaluation of unexpected regulatory authority feedback Boehringer Ingelheim decided to discontinue the three ongoing BI 54903 dose finding studies 1248.5-7. This decision was not based on or related to any safety or efficacy issue. It became clear that the requirements for registering a new formulation of a marketed compound as mono-treatment had been raised to an extent that it was concluded that the ongoing clinical program would not lead to registration. In consequence, the ongoing studies had become futile. On 21 July 2011 the first patient was enrolled. The decision to terminate the 8-week trials 1248.5-7 was made on 11 November 2011, i.e. relatively shortly after initiation of the trials, meaning that not only a limited number of patients had been randomised to study drug but also that only a few patients had completed the 8-week double-blind treatment period and, therefore, a primary endpoint analysis as originally defined (refer to Section 9.7 of this abbreviated report) had become futile. On 23 December 2011 the last patient terminated the study. The primary endpoint in the studies was defined as the mean change from randomisation baseline to the end of the 8-week treatment period in trough FEV_1 (i.e. morning pre-dose and pre-rescue bronchodilator). For this reason it was decided to prepare an abbreviated report including the three studies 1248.5-7. Note: Section 9 is based on the text included in the three individual study protocols. The analyses on available data (refer to Sections 10, 11 and 12) were changed and are detailed in Section 9.8 of this abbreviated report.
Criteria for safety:	Adverse events, routine laboratory, vital signs (BP, PR), 12-lead ECG.
Criteria for pharmacokinetics (only in 1248.7):	As only a limited number of samples were available at the time of termination, no samples were analysed and, therefore, no pharmacokinetic data are available.
Other assessments (only in 1248.7):	As only a limited number of urine samples were available for cortisol analyses at the time of termination, no samples were analysed and, therefore, no cortisol data are available.
Statistical methods:	The analysis of the primary endpoint was planned using a restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). The primary comparison was between test treatments and placebo (1248.5-6) or between test treatments and low dose fluticasone propionate (88 µg b.i.d.) (1248.7) at week 8.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results: No efficacy analyses were performed due to the low number of patients per treatment arm at the time the three dose finding studies were terminated.

Safety results: In addition to a low number of patients per treatment group, also the mean extent of exposure was short and ranged between 16.1 – 45.8 days across the three studies. As a consequence, the frequency of reported AEs was low and no meaningful conclusion could be drawn.

Conclusions: Data collected in the three dose finding studies 1248.5-1248.7 was limited due to the early study termination by the sponsor.

As the number of patients completing the 8-week treatment period was extremely low, no analyses of primary and secondary efficacy endpoints were conducted.

Similarly, due to limited data and low mean extent of exposure no conclusions could be drawn in terms of the safety profile of the new formulation of ciclesonide using the propellant-free Respimat® inhaler (BI 54903).