Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
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Name of active ingredient: BI 671800		**Page:** 1 of 12	**Synopsis No.:**
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Title of trial:	Randomised, double-blind, triple-dummy, partial crossover (each active treatment with placebo) study using an Environmental Challenge Chamber (ECC) to assess the safety and efficacy of 2 weeks of oral BI 671800 ED 50, 200 or 400 mg b.i.d., compared to montelukast 10 mg q.d., fluticasone propionate nasal spray 200 µg q.d. (2 nasal actuations to each nostril of 50 µg) versus placebo in seasonal allergic rhinitis patients out-of-season, sensitive to *Dactylis glomerata*
Principal Investigator:	[redacted], Fraunhofer Institute of Toxicology and Experimental Medicine, Hannover, Germany
Trial site:	Single-centre study at the Fraunhofer Institute of Toxicology and Experimental Medicine (ITEM), Hannover, Germany
Publication (reference):	Data of this study have not been published
Clinical phase:	IIa
Objectives:	The primary objective of the trial was to investigate the efficacy, safety, and tolerability of BI 671800 ED at 3 dose levels (50 mg, 200 mg, and 400 mg) compared with fluticasone propionate (200 µg, 2 actuations per nostril of 50 µg) or montelukast (10 mg) given for 2 weeks, in patients with seasonal allergic rhinitis known to be sensitive to the aeroallergen *Dactylis glomerata* who were exposed to allergen out-of-season in the ECC.
Methodology:	This was a randomised, placebo-controlled, double-blind, triple-dummy, partial crossover design, exploratory efficacy and safety trial. The trial compared 2 weeks of active treatment with BI 671800 ED at 50 mg b.i.d., 200 mg b.i.d., or 400 mg b.i.d. with montelukast 10 mg q.d., fluticasone propionate nasal 200 µg q.d., and placebo. BI 671800 ED was administered morning and evening and the comparator agents were administered in the morning; allergen challenge was conducted in the morning. The overall duration of the trial was about 10 weeks, comprising: 1 week of screening, 2 weeks of baseline assessment, two 2-week treatment periods (patients received an active treatment in one treatment period and placebo in the other) separated by a 2 to 4-week washout period, and with 1 week of follow up.

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No. of patients:	
planned:	screened: 300 patients randomised: 150 patients, with 150 patients in the placebo group and 30 patients in each active treatment group completing: 120 patients
actual:	screened: 301 entered/randomised: 146
	BI 671800 ED 400 mg: entered: 28 treated: 28 analysed (for primary endpoint): 25
	BI 671800 ED 200 mg: entered: 30 treated: 28 analysed (for primary endpoint): 27
	BI 671800 ED 50 mg: entered: 28 treated: 26 analysed (for primary endpoint): 22
	Montelukast 10 mg: entered: 29 treated: 29 analysed (for primary endpoint): 25
	Fluticasone propionate 200 µg: entered: 31 treated: 30 analysed (for primary endpoint): 29
	Placebo: entered: 146 treated: 143 analysed (for primary endpoint): 123
Diagnosis and main criteria for inclusion:	Male and female patients aged 18 to 65 years, with a history of seasonal allergic rhinitis and with a positive skin prick test to *Dactylus glomerata* within the previous 12 months were screened for entry into the trial. To be randomised to receive study treatment, patients were required to have a total nasal symptom score (TNSS) of ≤2 prior to allergen exposure at the baseline visit and a TNSS of >5 at least once during the 2 hour baseline ECC after allergen exposure. To undergo each allergen exposure in the ECC the patient's post-bronchodilator forced expiratory volume over 1 second (FEV_1) was to be ≥80% of their personal best.

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Test product:	BI 671800 ED, capsule
dose:	50 mg, 200 mg, and 400 mg twice daily
mode of admin.:	Oral
batch nos.:	25 mg: B093000590 100 mg: B093000591
Reference therapies:	
therapy:	Montelukast, capsule
dose:	10 mg per day
mode of admin.:	Oral
batch no.:	B093000593
therapy:	Fluticasone propionate, nasal spray
dose:	200 µg per day
mode of admin.:	Nasal puffs
batch no.:	957184A
therapy:	BI 671800 matching placebo, capsule
dose:	Not applicable
mode of admin.:	Oral
batch no.:	B093000586
therapy:	Montelukast matching placebo, capsule
dose:	Not applicable
mode of admin.:	Oral
batch no.:	B093000585

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therapy:	Fluticasone propionate matching placebo, nasal spray
dose:	Not applicable
mode of admin.:	Nasal puffs
batch no.:	4000151A
Duration of treatment:	2 weeks of active treatment and 2 weeks of placebo treatment
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Efficacy was assessed in terms of the primary efficacy variable of TNSS assessed as the area under the curve (AUC) of values obtained every 20 minutes over 0 to 6 hours. Secondary endpoints comprised: the AUCs for TNSS, total ocular symptom score (TOSS), and total symptom score (TSSc) while in the ECC (every 20 minutes over 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 2 to 6 hours, 0 to 6 hours, 0 hour to t_{max}, t_{max} to 6 hours, and hourly); the AUCs for nasal and ocular subscores (single symptoms) while in the ECC (every 20 minutes over 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 2 to 6 hours, 0 to 6 hours, 0 hour to t_{max}, t_{max} to 6 hours, and hourly); the AUCs of nasal flow rate based on rhinomanometry while in the ECC (at 2, 4, and 6 hours). An exploratory endpoint assessed descriptively during the study comprised the change in paper tissue weight while in the ECC (over 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, and 0 to 6 hours). Blood BI 671800 levels were used to model pharmacokinetic (PK) behaviour over time using a population-based approach. Exploratory pharmacodynamic endpoints assessed descriptively during the study comprised: eosinophil shape change (ESC), change in biomarker levels in non-fibrous nasal pledgets, and change in inflammatory cells from nasal lavage fluid over time per treatment period.
Safety:	Safety was assessed in terms of the incidence and intensity of adverse events (AEs), vital signs (pulse rate and blood pressure), laboratory safety parameters with C-telopeptide of type 1 collagen (CTX-1) as a marker of bone metabolism, 12-lead resting ECG, and physical examination.

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Statistical methods:	Three hypotheses for testing superiority of the active treatments with BI 671800 versus placebo were defined. The hypotheses were to be tested based on adjusted means of TNSS $AUC_{0\text{-}6h}$ using a mixed-effects model with repeated measures. This model included effects accounting for the sources of variation of: treatment and period as fixed effects and patient as a random effect. The SAS procedure MIXED was used, involving the restricted maximum likelihood estimation and the Kenward-Roger approximation of denominator degrees of freedom. This model was used to analyse all continuous endpoints (primary and secondary). Exploratory analyses considered nasal secretion (paper tissue) weight, ESC, biomarker levels, and inflammatory cell levels in a descriptive manner. PK and safety parameters were assessed using descriptive statistics.

SUMMARY – CONCLUSIONS:

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Efficacy results:

Overall, 93 male patients (63.7%) and 53 female patients (36.3%) were randomised into the treatment phases of the trial; most of those randomised were white (143 patients; 97.9%) and their mean age was 36.1 years. All 146 patients (100.0%) treated during the study were allergic to *Dactylus glomerata* pollen. Most patients experienced allergic rhinitis symptoms of itching eyes (113 patients; 77.4%), rhinorrhea (105 patients; 71.9%), nasal congestion (80 patients; 54.8%), and sneezing (73 patients; 50.0%).

The numbers of patients randomised to treatment, treated and completing treatment is presented in Table 1 below.

Table 1

	Placebo n (%)	BI 671800 50 mg n (%)	BI 671800 200 mg n (%)	BI 671800 400 mg n (%)	Montelukast 10 mg n (%)	Fluticasone 200 µg n (%)
Randomised	146	28	30	28	29	31
Treated	143	26	28	28	29	30
Completed treatment	138 (96.5)	26 (100.0)	28 (100.0)	28 (100.0)	26 (89.7)	30 (100.0)
Discontinued	5 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.3)	0 (0.0)
AE	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.9)	0 (0.0)
Other AE	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.9)	0 (0.0)
Refusal	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other reasons	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)

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Efficacy results (continued):

Four patients (2 patients each in the placebo and montelukast groups) discontinued a treatment period due to other AEs as they were unable to enter the ECC due to nasopharyngitis or gastroenteritis; other patients discontinued a treatment period for other reasons (3 patients) or refused to continue with the study medication (1 patient).

All of the study treatments assessed showed a numerically lower adjusted mean TNSS AUC_{0-6h} than placebo. BI 671800 200 mg b.i.d., montelukast and fluticasone propionate showed a statistically significant reduction in adjusted mean TNSS AUC_{0-6h} when compared with placebo, as shown in Table 2 below.

Table 2

	N	TNSS AUC_{0-6h} adjusted mean (SE)	Comparison vs. placebo		
			Adjusted mean of the difference (SE)	95% CI	p-value
Placebo	123	5.02 (0.148)			
BI 671800 50 mg	22	4.62 (0.309)	-0.40 (0.306)	-1.01, 0.20	0.1917
BI 671800 200 mg	27	4.16 (0.281)	-0.85 (0.279)	-1.40, -0.30	0.0026
BI 671800 400 mg	25	4.50 (0.293)	-0.51 (0.293)	-1.09, 0.06	0.0810
Montelukast 10 mg	25	4.28 (0.292)	-0.74 (0.290)	-1.31, -0.17	0.0115
Fluticasone 200 µg	29	3.37 (0.273)	-1.64 (0.271)	-2.18, -1.11	0.0000

The results demonstrated clinical proof-of-concept to support the use of BI 671800 200 mg b.i.d. administered twice daily as a treatment for allergic rhinitis. Comparison of the absolute and percentage difference in TNSS from placebo showed that the effect of BI 671800 200 mg (-0.85, -17%) was greater than with montelukast (-0.74, -15%) but less than with fluticasone propionate (-1.64, -33%). However the pre-specified hierarchical testing failed, as BI 671800 400 mg b.i.d. did not show a statistically significant difference versus placebo.

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Efficacy results (continued):

The TNSS profiles assessed over 0 to 2, 2 to 4, 4 to 6, 2 to 6 hours, and hourly for the different study treatments were broadly consistent with those seen for the primary endpoint. A numerical reduction in individual ocular symptom $AUC_{0\text{-}6h}$ scores was seen for most active treatments, though none achieved statistical significance. The assessment of TSSc $AUC_{0\text{-}6h}$ showed similar findings to the primary analysis, with a statistically significant difference in the adjusted mean as compared with placebo for BI 671800 200 mg (absolute and percentage difference -1.01, -17%; p = 0.0046), montelukast (difference -0.87, -15%; p = 0.0182), and fluticasone propionate (difference -1.89, -32%; p = 0.000); the TSSc profiles assessed over 0 to 2, 2 to 4, 4 to 6, 2 to 6 hours, and hourly were broadly consistent with these findings.

The individual nasal symptom $AUC_{0\text{-}6h}$ scores for the different treatments indicated efficacy: for BI 671800 200 mg against rhinorrhea (difference -0.29; p = 0.0010), itching (difference -0.24; p = 0.0057), and sneezing (difference -0.19; p = 0.0232); for fluticasone propionate against congestion (difference -0.39; p = 0.0001), rhinorrhea (difference -0.50; p = 0.0000), itching (difference -0.38; p = 0.0000), and sneezing (difference -0.37; p = 0.0000); and for montelukast against congestion (difference -0.28; p = 0.0065) and rhinorrhea (difference -0.19; p = 0.0305). The individual ocular symptom scores did not show a significant difference versus placebo for any of the study treatments.

Assessment of nasal airflow rate by rhinomanometry was associated with a high degree of variability. Only fluticasone showed a statistically significant increase in flow rate versus placebo over 0 to 6 hours (difference 52.62 mL/s; p = 0.0381). All study treatments reduced tissue weight (as an estimate of nasal secretion weight) compared with placebo when assessed over the 6 hours the patients spent in the ECC. A 54.6% reduction in tissue weight from placebo was seen with fluticasone, a 24.5% reduction was seen with BI 671800 200 mg, a 22.9% reduction was seen with BI 671800 400 mg, a 13.8% reduction was seen with montelukast, and an 11.5% reduction was seen with BI 671800 50 mg.

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Clinical pharmacology results:

Plasma BI 671800 C_{max} and AUC_{0-tz} exposure increased with dose. Geometric mean plasma exposures appeared to increase in a greater than linear fashion, as shown in the summary of PK parameters presented in Table 3 below.

Table 3

	Geometric mean (geometric CV)	
	AUC_{0-tz} (ng•h/mL)	C_{max} (ng/mL)
50 mg BI 671800	4690 (51)	1000 (55)
200 mg BI 671800	8740 (61)	1910 (65)
400 mg BI 671800	23500 (72)	4780 (81)

However, variability in AUC_{0-tz} and C_{max} values was high and a definitive conclusion on linearity could not be made.

After BI 671800 administration the area under the effect curve below baseline ($AUEC_{below}$) for ESC increased from the corresponding placebo values to a greater extent as the dose level increased, as shown in Table 4 below; minimum observed effect (E_{min}) values for ESC decreased with increasing dose. This reflected greater inhibition of shape change with BI 671800 dose. There was little change versus placebo following montelukast and fluticasone dosing.

Table 4

	Mean (%CV)			
	$AUEC_{below}$ [%•h]	% change	E_{min}[%]	% change
BI 671800 ED 50 mg	46.0 (54.3)	283.3%	3.61 (63.9)	-52.4%
Placebo for BI 671800 ED 50 mg	12.0 (102)		7.58 (52.0)	
BI 671800 ED 200 mg	56.7 (61.8)	247.9%	2.09 (109)	-75.5%
Placebo for BI 671800 ED 200 mg	16.3 (111)		8.52 (46.5)	
BI 671800 ED 400 mg	68.8 (53.4)	352.6%	0.852 (248)	-89.1%
Placebo for BI 671800 ED 400 mg	15.2 (101)		7.82 (49.0)	
Montelukast 10 mg	9.12 (192)	-24.6%	7.30 (46.3)	1.5%
Placebo for montelukast	12.1 (101)		7.19 (49.8)	
Fluticasone 100 µg to each nostril	11.4 (104)	-24.0%	8.81 (36.9)	-3.1%
Placebo for fluticasone	15.0 (117)		9.09 (35.6)	

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Clinical pharmacology results (continued):	BI 671800 exerted a moderate inhibitory effect on IL-5 and IL-13 nasal pledget concentrations and pharmacodynamic parameters when administered at 200 mg. The 50 mg dose generally showed little effect. The inhibitory effect on IL-5 and IL-13 levels was generally of smaller magnitude when BI 671800 was administered at 400 mg, so inhibition appeared to not be dose-related. Fluticasone reduced IL-5 and IL-13 nasal pledget levels to a greater extent than BI 671800 at the 200 mg b.i.d. dose, whereas montelukast had little effect. Although the effects were more modest for eosinophil counts, IL-4 and eotaxin, the inhibition of the rise in levels of these biomarkers on allergen exposure followed a similar pattern; fluticasone showed the greatest inhibition and montelukast showed negligible effect; BI 671800 50 mg showed little or no effect whereas BI 671800 200 mg showed moderate inhibition which was less than seen with fluticasone but greater than with montelukast. Inhibition by BI 671800 ED 400 mg was generally less than seen at 200 mg, implying that the biomarkers did not show a BI 671800 dose-response.
Safety results:	Of the 146 patients treated in the study: 14 patients (48.3%) reported AEs during montelukast treatment, 13 patients (43.3%) reported AEs during fluticasone propionate treatment, 54 patients (37.8%) reported AEs during placebo dosing, 10 patients (35.7%) reported AEs during BI 671800 200 mg treatment, 9 patients (34.6%) reported AEs during BI 671800 50 mg treatment, and 9 patients (32.1%) reported AEs during BI 671800 400 mg treatment. The most common AE seen during the study was headache, which occurred in 24.1% of patients in the montelukast group, 23.3% of patients in the fluticasone propionate group, 14.3% of patients in the BI 671800 200 mg group, 12.6% of patients in the placebo group, and 10.7% of patients in the BI 671800 400 mg group. Other AEs seen in at least 5% of patients in a treatment group comprised: urinary tract infection which occurred in 10.3% of patients receiving montelukast, 3.6% receiving BI 671800 200 mg, and 1.4% receiving placebo; nasopharyngitis which occurred in 10.0% of patients receiving fluticasone propionate, 9.1% receiving placebo, 7.7% receiving BI 671800 50 mg, 7.1% receiving BI 671800 400 mg, and 6.9% receiving montelukast; epistaxis which occurred in 10.0% of patients receiving fluticasone propionate, in 7.1% receiving BI 671800 200 mg, and in 2.8% receiving placebo; and lip swelling which occurred in 7.1% of patients receiving BI 671800 200 mg and 3.6% receiving BI 671800 400 mg.

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Safety results (continued):

Most AEs seen during the study were mild or moderate in intensity, and the incidence of severe AEs was comparable when considering the different treatment periods.

AEs considered related to study medication were reported for: 8 patients (26.7%) during fluticasone propionate treatment, 5 patients (17.9%) during BI 671800 200 mg treatment, 2 patients (7.7%) during BI 671800 50 mg treatment, 2 patients (6.9%) during montelukast treatment, and 9 patients (6.3%) during placebo dosing.

The most common drug-related, or potentially procedure-related, AEs were headache and epistaxis. Drug-related headache occurred in 13.3% of patients during treatment with fluticasone propionate, 3.6% of patients during treatment with BI 671800 200 mg, 3.4% of patients during treatment with montelukast, and 2.1% of patients during placebo dosing. Drug-related epistaxis occurred in 10.0% of patients during treatment with fluticasone propionate, 3.6% of patients during treatment with BI 671800 200 mg, and 1.4% of patients during placebo dosing. Headache and epistaxis are known to occur during exposure to allergen in the ECC.

No patient treated with BI 671800 experienced other significant AEs, SAEs, death, or AEs leading to discontinuation of the trial.

Changes in laboratory safety assessment parameters were seen for a small proportion of patients in all treatment groups. No clinically significant change in laboratory values related to BI 671800 treatment; overall there was no indication that BI 671800 had adverse effects on liver function parameters or creatine kinase levels. No relevant findings were seen in the analysis of vital signs (blood pressure and heart rate) or ECG parameters recorded 6 hours after allergen exposure. At the highest BI 671800 dose (400 mg) a slightly higher proportion of patients experienced an increase of >30 ms in QTcB interval (17.9% versus 5.0% with placebo and 7.4% with montelukast); however in the lower BI 671800 dose groups and the fluticasone group the incidence of QTcB prolongation was notably lower (3.8% with BI 671800 50 mg, 3.6% with BI 671800 200 mg, and 3.3% with fluticasone). No patient experienced a new-onset increase in QT or QTcB interval of > 500 ms or >60 ms.

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Conclusions:

The BI 671800 200 mg b.i.d. dose demonstrated efficacy when treating allergic rhinitis symptoms induced by allergen exposure in the ECC, particularly in terms of the nasal symptoms of rhinorrhea, nasal itching, and sneezing. The statistically significant benefit in terms of TNSS over 0 to 6 hours of allergen exposure was supported by lower TSSc, lower individual rhonorrhea, sneezing and nasal itching scores, and reduced nasal secretion as assessed by paper tissue weights. These results established proof-of-concept of BI 671800 200 mg b.i.d. clinical activity against allergic rhinitis symptoms.

Pharmacokinetic data from the study indicated that $AUC_{0\text{-}tz}$ and C_{max} exposure increased with BI 671800 dose although, due to the variability and sparseness of the data, dose linearity could not be established. BI 671800 administration resulted in a dose-related inhibition of ex vivo PGD_2-induced eosinophil shape change and non-dose related reductions in the nasal inflammatory cytokines IL-5, IL-13 and eotaxin, and a reduction in nasal eosinophil levels.

BI 671800 treatment over 14 days was well tolerated at doses up to 400 mg b.i.d., with the 200 mg b.i.d. dose being considered optimal.