ABSTRACT

Introduction
Allergic rhinitis is a Th2 driven inflammatory disorder in which prostaglandin D2 (PGD2), is a key inflammatory component. PGD2 is released primarily by mast cells with Th2 cells, dendritic cells, and macrophages being secondary sources. PGD2 binds to its receptor (CRTH2) on basophils, mast cells, eosinophils, and TH2 cells driving chemokine/ inflammatory mediators. Targeting the CRTH2 receptor is a promising new therapy to reduce the allergic inflammation.

Objective
To assess the efficacy, safety, and tolerability of BI 671800 ED, an oral CRTH2 antagonist, at 3 dose levels (50 mg, 200 mg, and 400 mg) administered bid, compared with fluticasone propionate (2 actuations 671800 ED, an oral CRTH2 antagonist, at 3 dose levels (50 mg, 200 mg, and 400 mg) administered bid, compared with fluticasone propionate (2 actuations bid) and montelukast (10 mg) q.d. in the morning given for 2 weeks, in patients with seasonal allergic rhinitis known to be sensitive to the aeroallergen Dactylus glomerata, which were treated out-of-season using an ECC.

Methods
Patients 146 grass sensitive SAR patients (24% had mild intermittent asthma treated with SABA only) were included. Patients 146 who were treated out-of-season using an ECC. The geometric mean or median data appeared to increase in a manner that was greater than dose proportional with high variability

RESULTS

TABLE 1: Demographic and baseline disease characteristics

Statistics: Mixed effects model with repeated measures (MIMM) with treatment and period as fixed effects and patient as random effect.

Allergen challenge: Subjects at screening underwent an initial test for responsiveness to Dactylus glomerata by means of a 2 hour (maximum duration) Fraunhofer exposure to Dactylus glomerata. At the end of each 2-week treatment period, patients were exposed to Dactylus glomerata in the ECC for 6 hours and evaluated for treatment efficacy. The treatment periods were separated by 2 to 4 weeks.

Outcome Measures: Total nasal (TNSS = rhinorrhea, nasal obstruction, sneezing, nasal itching) and ocular (TOSS=tearing and itching eyes) symptom scores were obtained every 20 min. Nasal flow (rhinomometry) and nasal secretions were measured every 120 min during challenge. FEV1 was measured every 60 min and during or just after a symptom. Nasal lavage/ non-fibrous nasal pledget assessment (IL-4, IL-5, IL-13, IL-8, IL-9, and eotaxin) was obtained at the end of ECC (6 hrs). Eosinophil shape change (ESC) and pharamcokinetics were assessed during the challenge and at defined timepoints, at the end of ECC (6 hrs), and out to 9 hrs.

Primary Endpoint: Nasal symptoms (TNSS). Other key endpoints included PGD2 induced eosinophil shape change (ESC), cytokines and eosinophils in nasal secretion and lavage. The geometric mean or median data appeared to increase in a manner that was greater than dose proportional with high variability. Pharmacokinetics: Pharmacokinetic data from the study indicated that AUC0-tz and Cmax exposure increased with BI 671800 dose.

CONCLUSIONS

• BI 671800 at a dose of 200 mg twice a day reduced TNSS versus placebo over a 6 hour allergen challenge period; and at the end of the 6 hours showed a reduction in Th2 inflammatory cytokines as well as a reduction in the number and % of nasal eosinophils compared to placebo.

CONTACT

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CRTH2 ANTAGONIST, BI 671800 (BI), REDUCES NASAL SYMPTOMS AND INHIBITS NASAL CYTOKINES AND EOSINOPHILS IN SAR PATIENTS EXPOSED TO GRASS POLLEN IN AN ENVIRONMENTAL CHALLENGE (ECC)

Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM) - Hannover/DE, Boehringer Ingelheim - Biberach/DE, Boehringer Ingelheim - Ridgefield, CT/USA

ECC (6hr)
BI671800 50mg bid
BI671800 400mg bid
Montelukast
by means of a 2 hour (maximum duration) Fraunhofer
an initial test for responsiveness to
Allergen challenge:
Study design:
who were treated out-of-season using an ECC.
TARGETING THE CRTH2 RECEPTOR IS A PROMISING NEW
biological response modifiers (anti-IgE, anti-IL5, anti-IL9, and anti-eotaxin) for the treatment of asthma.
ECC exposure to Dactylus glomerata. At the end of each
visit 1
visit 2
visit 3
visit 4
visit 5
visit 6
visit 7
FIGURE 1: Total Nasal Symptom Score (TNSS)

FIGURE 3: Eosinophil and cytokines

FIGURE 4: Eosinophil Shape Change