# Synopsis of OX914-001 clinical study report

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| **Study code:** OX914-001 | **EudraCT No:** 2008-001179-30 |

**Title of study:**

A double-blind, randomized, placebo-controlled, cross-over, allergen challenge study to evaluate the efficacy, safety and tolerability of BLX-028914 in subjects with allergic rhinitis

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**Publication (reference):** No current publication.

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| **Study period**<br>First subject screened: 1 Sep 2008<br>Last subject completed: 18 Dec 2008 | **Phase of development:** II |

**Objectives**

Primary objective:

- To demonstrate superiority of BLX-028914 50 mg/day to placebo regarding the efficacy on total nasal symptoms ten minutes after allergen challenge on treatment days 11-13

Secondary objectives:

- To evaluate the efficacy of BLX-028914 50 and 15 mg/day on nasal symptoms, treatment days 11-13 compared to placebo
- To evaluate the efficacy of BLX-028914 50 and 15 mg/day on peak nasal inspiratory flow (PNIF), treatment days 11-13 compared to placebo
- To evaluate the effects of BLX-028914, 50 and 15 mg/day on nasal mucosal inflammatory response treatment day 14, compared to placebo (as assessed by $\alpha_2$-macroglobulin, eosinophil cationic protein and tryptase levels in nasal lavage)
- To evaluate the safety and tolerability of treatment with BLX-028914

**Methodology:** Single center, double-blind, placebo controlled, randomized, three-way cross-over study in subjects with seasonal allergic rhinitis. The study was conducted outside the pollen season and consisted of three treatment periods of 14 days with daily morning and evening ratings of nasal symptoms score (assessments of congestion, rhinorrhea and itching/sneezing on a scale from 0-3) and measurements of peak nasal inspiratory flow (PNIF).

On treatment days 7-13, an artificial pollen season was created by spraying a dose of the allergen into each nostril. The allergen dose was set by a titration procedure at screening, where the lowest allergen dose causing a definite degree of rhinitis symptoms was chosen. Nasal symptoms and PNIF were rated ten minutes after the allergen challenges.

Nasal lavages (saline only and with addition of histamine, 400 µg/ml) were collected prior to the first treatment and on treatment day 14 of each treatment period.

A blood sample for plasma concentration measurement was taken on day 14 of each treatment for evaluation of compliance.

Blood samples for safety evaluations were taken prior to first treatment and on day 14 of each treatment period. Adverse events were collected by open questioning and in a patient diary until one week after completion of the last treatment period.

**Number of subjects:** 36 subjects were planned for randomization. 36 subjects were randomized and 30 subjects completed all treatment periods of the study.

**Diagnosis and main criteria for inclusion:** Male or female subjects with a history of seasonal allergic rhinitis, 18-50 years old, sensitized to timothy or birch tree pollen but otherwise healthy.

**Investigational Medicinal Products (IMPs):**

**Test products, dose and mode of administration, batch numbers:**
BLX-028914, 50 mg (treatment A): Two BLX-028914 oral capsules, 25 mg (batch no. F08-E007) and one Placebo oral capsule (batch no. F08-E005) daily in the morning.

BLX-028914, 15 mg (treatment B): Three BLX-028914 oral capsules, 5 mg (batch no. F08-E006) daily in the morning.

**Reference therapy, dose and mode of administration, batch number:**
Placebo (treatment C): Three Placebo oral capsules (batch no. F08-E005) daily in the morning.

**Duration of treatment:**
Three treatment periods of 14 days, one with each treatment, separated by a washout period of at least 7 days.

**Criteria for evaluation:**

Efficacy:
Nasal symptoms: The total nasal symptoms score (TNSS) was calculated as the sum of the three individual nasal symptoms scores for congestion, rhinorrhea and itching/sneezing. The mean of the ten minutes post allergen challenge TNSS for treatment days 11-13 was the primary efficacy variable. The mean of the morning TNSS treatment days 12-14 and evening TNSS treatment days 11-13 as well as the mean of each individual ten minutes post challenge nasal symptoms score, day 11-13, were also evaluated.

PNIF: The mean of ten minutes post allergen challenge and evening PNIFs day 11-13 and morning PNIFs day 12-14 were evaluated.

Nasal lavages: Levels of $\alpha_2$-macroglobulin, eosinophil cationic protein (ECP) and tryptase were evaluated in saline and histamine nasal lavages on day 14.

Safety:
Safety evaluations were based on adverse events (AEs) collected continuously during the study, laboratory safety measurements and vital signs collected prior to first treatment and on the last day of each treatment period and reasons for withdrawals.

**Statistical methods:**

Efficacy analyses:
The efficacy variables (as described above) were compared between treatments (A-C, B-C and A-B) using a mixed linear regression model adjusted for treatment and period as fixed effects and subject as random effect. Treatment sequence was dropped from the model, since it did not have a significant effect on the primary analysis.

The primary analysis was the comparison of the mean of post allergen challenge TNSS ratings treatment days 11-13 between 50 mg and placebo.

The main analyses were performed on the intention to treat (ITT) analysis set, including all subjects receiving at least one capsule of IMP, and confirmatory analyses were performed on the per-protocol (PP) analysis set, including all subjects receiving IMP without any major protocol deviations.

Safety analyses:
Safety endpoints were presented with descriptive statistics. The safety analysis set included all subjects receiving IMP.

## RESULTS AND CONCLUSIONS

**Efficacy results:**

**Primary objective – efficacy analysis:**

- No statistically significant difference in mean total nasal symptoms score (TNSS) ten minutes post allergen challenge on treatment days 11-13 was seen between BLX-028914, 50 mg/day and placebo (p=0.731).

### Mean ten minutes post allergen challenge TNSS day 11-13, BLX-028914 50 mg and placebo (primary efficacy endpoint)

| | | 50 mg/day (N=34) | Placebo (N=33) |
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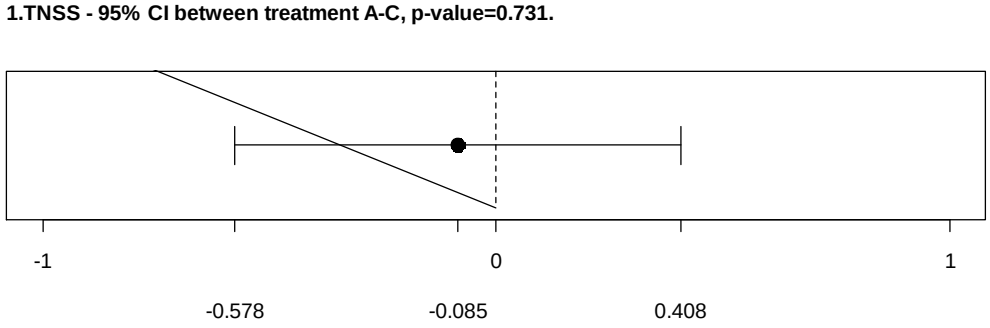
| **10 min. after challenge mean TNSS (day 11-13)** | | | |
| | **Mean (SD)** | 5.31 (1.77) | 5.63 (1.84) |
| | **Median** | 5.33 | 5.67 |
| | **Range** | 1.67 to 8.67 | 2.00 to 9.00 |
| | **n** | 32 | 33 |

### Difference in primary efficacy endpoint between BLX-028914, 50 mg/day (A) and Placebo (C), including 95% CI – ITT population




**Secondary objectives – efficacy analyses:**

Nasal symptoms

- No statistically significant differences between BLX-028914 50 mg/day or 15 mg/day and placebo, or between 50 mg/day and 15 mg/day were found in any of the following allergic nasal symptoms endpoints (p>0.05 for all comparisons):
  - Ten minutes post allergen challenge TNSS on treatment days 11-13 (comparing 15 mg/day to placebo and 50 mg/day to 15 mg/day)
  - Morning TNSS on treatment days 12-14
  - Evening TNSS on treatment days 11-13
  - Ten minutes post allergen challenge nasal congestion score on treatment days 11-13
  - Ten minutes post allergen challenge rhinorrhea score on treatment days 11-13
  - Ten minutes post allergen challenge itchy nose/sneezing score on treatment days 11-13

PNIF

- No statistically significant differences between BLX-028914 50 mg/day or 15 mg/day and placebo, or between 50 mg/day and 15 mg/day were found in any of the following peak nasal inspiratory flow (PNIF) endpoints ($p>0.05$ for all comparisons):
  - 10 minutes post allergen challenge PNIF on treatment days 11-13
  - Morning PNIF on treatment days 12-14
  - Evening PNIF on treatment days 11-13

Nasal mucosal inflammatory response

- No statistically significant differences between BLX-028914 50 mg/day or 15 mg/day and placebo, or between 50 mg/day and 15 mg/day were found in any of the following allergic rhinitis inflammatory markers in nasal lavages collected on treatment day 14 ($p>0.05$ for all comparisons):
  - $\alpha_2$-macroglobulin levels in saline lavage
  - $\alpha_2$-macroglobulin levels in 400 µg/ml histamine lavage
  - ECP levels in saline lavage
  - ECP levels in 400 µg/ml histamine lavage
  - Tryptase levels in 400 µg/ml histamine lavage

  In saline lavages, tryptase levels after treatment with 15 mg/day was statistically significant higher than after placebo treatment ($p=0.019$). Due to the implausible result (with a negative treatment effect), a lack of robustness in the results and that there were no correction for multiplicity in the study, this is not interpreted as a significant effect.

**Safety results:**

There were more gastrointestinal AEs during active treatment compared to placebo (seven subject during treatment with 50 mg compared to three during placebo treatment). Diarrhea, which occurred in a total of four subjects during active treatment, was the most common gastrointestinal AE. Diarrheas were mild in intensity and lasted for 1-3 days. One case of myelitis, occurring a few days after end of study, was reported as a serious adverse event (SAE). A connection to the IMP was assessed as unlikely by both the investigator and the sponsor.

There were no clinically significant abnormalities in safety laboratory values or vital signs during the study, nor could any significant trends of change in these parameters be detected. One withdrawal was due to an AE with a possible relationship to BLX-028914 (insomnia).

**Conclusions**

Efficacy

No statistically significant difference in the primary efficacy endpoint, mean total nasal symptoms score ten minutes after allergen challenges on treatment days 11-13, was seen between BLX-028914, 50 mg/day and placebo. Thus, superiority of BLX-028914 50 mg/day to placebo could not be demonstrated.

No significant differences in efficacy on nasal symptoms, PNIF or nasal mucosal inflammatory response were found between BLX-028914 (50 and 15 mg/day) and placebo (secondary objectives).

Safety

Treatment with up to 50 mg BLX-028914 per day for 14 days was safe and tolerable in this study. There was no SAE during the study. There was one withdrawal due to moderate insomnia. Other adverse events were mild to moderate in intensity and there were no clinically significant laboratory findings or changes in vital signs.