# Clinical Trial Results Disclosure Synopsis

**Name of Sponsor:**

Nycomed: Ein Unternehmen der Takeda-Gruppe
Nycomed Pharma AG
Wallisellenstrasse 55
CH-8600 Dübendorf
Switzerland

**Title of Study:** Ciclesonide For The Treatment Of Airway Hyper-Responsiveness: The Mannitol Asthma Ciclesonide Study (Macs) A Double-Blind, Randomized, Parallel Group Study

**Phase of Development:** Phase 4

**Name of Active Ingredient:** Ciclesonide

**Name of Finished Product:** Ciclesonide

**Investigator:** 1 principal investigator enrolled subjects**.**

**Study Site:** Subjects were enrolled at 1 site in one site in Switzerland

**Publication Based on the Study (Citation) at Time of Study Completion:** Not applicable

**Study Period:**

**Date first subject signed informed consent form:** 09 Sep 2008
**Date of last subject's last visit/contact (from the Clinical database):** 29 Jul 2010

**Objectives:**

The study objective was to investigate in a placebo-controlled, double-blind manner the effect of inhaled corticosteroid (ciclesonide) on airway hyper-responsiveness measured as a provocative dose causing a 15% fall in forced expiratory volume over 1 second ($PD_{15}FEV_1$).

**Methodology:**

This was a double-blind, randomized, parallel group study in patients who had symptoms of suspected asthma. Eligible patients who had given informed consent, received 320 µg (2 x 160 µg) ciclesonide (or matching placebo), administered by a metered-dose inhaler, once daily for 4 weeks. Safety and pharmacodynamic assessments were performed prior to receipt of any investigational medicinal product at visit T0, and after 4 weeks of treatment, at visit T4.

**Number of Subjects:**

Planned: It was planned to include 24 mannitol positive patients and 46 mannitol negative patients.
Enrolled: 72 subjects
Analyzed: Safety set: 70 subjects, Intention-to-treat (ITT): 70 subjects, Per-protocol (PP): 61 subjects

**Diagnosis and Main Criteria for Inclusion:**

Male and female patients aged 18 to 70 years, who had been referred to the pulmonology department because of suspected asthma, and had asthma symptoms partly controlled according to Global Initiative for Asthma (GINA) with a forced expiratory volume over 1 second ($FEV_1$) ≥ 70% predicted were enrolled in the study.

**Duration of Treatment:** Approximately 4 weeks

**Test Product, Dose and Mode of Administration, and Lot Number:**

| Study Medication | Product Dose Strength and Form | Study Dosage | Mode of Administration | Drug Product Lot Number |
|---|---|---|---|---|
| Ciclesonide | 160 µg / puff ex mouth piece (200 µg ex valve), metered dose inhaler (MDI) | two puffs per occasion | Inhaled | 0000002122 [4BGA009] |

**Reference Therapy, Dose and Mode of Administration, and Lot Number:**

| Study Medication | Product Dose Strength | Study Dosage | Mode of Administration | Drug Product Lot Number |
|---|---|---|---|---|
| Matching placebo | Metered dose inhaler (MDI) | N/A | Inhaled | 0000002022 [0BGA005] |

**Criteria for Evaluation:**

Efficacy:

- Medical history including demographic/ anthropometric data
- Blood pressure and heart rate
- Clinical safety laboratory assessments
- Pulmonary function test : $FEV_1$, forced vital capacity (FVC), peak expiratory flow (PEF)
- Level of exhaled nitric oxide (eNO)
- Challenge tests: mannitol, methacholine
- Asthma quality of life questionnaire (AQLQ), asthma control questionnaire (ACQ)

Safety:

- Adverse events

**Statistical Methods:**

The primary statistical analysis was performed in the patients who demonstrated to be mannitol positive at baseline.

Primary Endpoint/Variables:

Change of hyper-responsiveness to mannitol assessed by $PD_{15}FEV_1$ after 4 weeks of treatment with ciclesonide vs. Placebo in the patients with demonstrated airway hyperresponsiveness to an inhaled mannitol challenge (mannitol positive) at baseline, measured on the basis of the proportion of responder patients.

A responder is defined as patient for whom the $PD_{15}FEV_1$ fulfills the following condition:

$$\frac{(PD_{15}FEV_1)_{T4} - (PD_{15}FEV_1)_{T0}}{DD} \geq 1.5$$

where DD represents the doubling dose at baseline.

For the primary variable the following hypothesis was tested:

$H_0$: the odds ratio ciclesonide vs. Placebo $\leq 1$

$H_1$: the odds ratio ciclesonide vs. Placebo $> 1$

The test was made one-sided at a level of $\alpha=0.025$.

If $H_0$ could be rejected, it was concluded that ciclesonide is superior to Placebo.

Secondary variables:

*Mannitol test based*

1) Change of hyper-responsiveness to mannitol after 4 weeks of treatment with ciclesonide vs Placebo in the mannitol positive patients at baseline as assessed by the numerical value of $PD_{15}FEV_1$ at 4 weeks minus $PD_{15}FEV_1$ at baseline.
2) Change of hyper-responsiveness to mannitol after 4 weeks of treatment with ciclesonide vs Placebo in all patients included in the study as assessed by the proportion of responder patients.
3) Change of hyper-responsiveness to mannitol after 4 weeks of treatment with ciclesonide vs Placebo in all patients included in the study as assessed by the numerical value of $PD_{15}FEV_1$ at 4 weeks minus $PD_{15}FEV_1$ at baseline.

4) RDR mannitol (response-dose-ratio = %fall in $FEV_1$ after the last administered dose of mannitol / cumulative provocation dose given). It will be separately performed for mannitol positive, mannitol negative and all study patients.

*Methacholine test based*

5) Responsiveness to methacholine ($PD_{20}FEV_1$) after 4 weeks of treatment as measured by the change in the $PD_{20}FEV_1$ value at week 4 as compared to baseline. It will be separately performed for mannitol positive, mannitol negative and all study patients.

6) Responsiveness to methacholine ($PD_{20}FEV_1$) after 4 weeks of treatment as measured by the proportion of responder patients. A responder is defined as a patient fulfilling the following condition: ($PD_{20}FEV_1$) at 4 weeks minus ($PD_{20}FEV_1$) at baseline divided by the doubling dose should be greater or equal than 1.5. It will be separately performed for mannitol positive, mannitol negative and all study patients.

7) RDR methacholine (response-dose-ratio = %fall in $FEV_1$ after the last administered dose of methacholine / cumulative provocation dose given). It will be separately performed for mannitol positive, mannitol negative and all study patients.

*Expired nitric oxide based*

8) Level of exhaled nitric oxide after 4 weeks of treatment.

9) Change from baseline in the level of exhaled nitric oxide after 4 weeks of treatment.

*Combined asthma control endpoints*

10) Proportions of patients meeting a combined endpoint (main lung function improvement combined endpoint) based in the following 3 criteria

    1. Improvement of $FEV_1$ of at least 200 ml and 12% after 4 weeks of treatment
    2. Improvement of AQLQ by at least 0.5 after 4 weeks of treatment
    3. Change of the asthma control questionnaire ACQ (Juniper) of less than or equal to -0.5 after 4 weeks of treatment

Responders will be evaluated using 2 different definitions: patients fulfilling all 3 criteria and patients fulfilling at least one criterion.

This analysis will be separately performed for mannitol positive, mannitol negative and all study patients.

11) Proportions of patients meeting a combined endpoint (secondary lung function improvement combined endpoint) based in the following 3 criteria

    1. Improvement of $FEV_1$ of at least >200ml and >12% after 4 weeks of treatment
    2. Improvement of PEF of at least 12% after 4 weeks of treatment

3. Decrease of the asthma control questionnaire ACQ (Juniper) score of at least 1.5 after 4 weeks of treatment

Responders will be evaluated using 2 different definitions: patients fulfilling all 3 criteria and patients fulfilling at least one criterion.

This analysis will be separately performed for mannitol positive, mannitol negative and all study patients.

*Endpoints based in diaries and clinical evaluation*

12) Mean change of ACQ after 4 weeks of treatment

13) Mean change of AQLQ after 4 weeks of treatment

14) Mean change of symptoms, rescue medication use, nocturnal awakening according to GINA after 4 weeks of treatment

15) Exacerbation rates during the 4 weeks of treatment

For secondary variables the p-values of the statistical tests are interpreted only in an exploratory sense.

**SUMMARY OF RESULTS:**

**Baseline Demographics and Other Relevant Characteristics:**

| | **Placebo (N = 36)** | **320 µg Ciclesonide (N = 34)** |
|---|---|---|
| Gender: Male | 12 (33.3%) | 9 (26.5%) |
| Female | 24 (66.7%) | 25 (73.5%) |
| Origin: Asian | 1 (2.8%) | 1 (2.9%) |
| White | 35 (97.2%) | 31 (91.2%) |
| Other | 35 (97.2%) | 2 (5.9%) |
| Age (years) | 39.7 (15.1) | 40.9 (12.4) |
| BMI ($kg/m^2$) | 23.84 (3.43) | 24.75 (3.56) |
| Body mass index - BMI, N = number of patients. Number (percentage) of patients are presented for gender and origin, mean (standard deviation) values are presented for age and BMI | | |

**Subject Disposition:**

Seventy-two patients were enrolled in the study, 36 randomized to ciclesonide and 36 to placebo.

Sixty-eight patients completed the study, 32 from ciclesonide and 36 from placebo group. Two patients withdrew due to an adverse event, and 2 patients withdrew consent prior to receiving any study medication. For each treatment (ciclesonide or placebo) 24 patients were mannitol negative, and 12 patients were mannitol positive.

**Efficacy Results:**

The primary study efficacy endpoint, proportion of mannitol positive patients who fulfilled the prospective responder definition based in a specific threshold decrease (at least 1.5 doubling doses) in mannitol elicited airway hyperresponsiveness from baseline to week 4, was higher in the ciclesonide treated patients both in the ITT (63.6% on active; 41.7% on placebo) and in the PP analysis set (70.0% on active; 44.4% on placebo), but these differences did not reach statistical significance (lowest one sided Fisher's exact test p value 0.2632 in the ITT analysis; 0.2549 in the PP analysis). No significant predictors for the main study endpoint were found by logistic regression analysis.

The analysis of the different secondary efficacy variables, showed no statistically significant differences between ciclesonide and placebo.

A non-significant statistical trend (p=0.0687) towards a higher decrease in the fraction of nitric oxide in expired air (arithmetic mean (95% CL) change in FeNO -16.41 (-43.98 - 11.15) % on active; 6.24 (-9.34 - 21.82) % on placebo) from the start to the end of the treatment period was observed in ciclesonide treated mannitol-positive patients.

Geometric mean FeNO baseline values were lower in the ciclesonide mannitol-positive treated group (geometric mean (95% CL) baseline FeNO 30.39 (17.14 - 53.88) ppb on active; 41.93 (22.58 - 77.86) ppb on placebo), but the 95% confidence limits widely overlap.

The logistic regression analyses did not find any significant predictors for the different study outcomes in the mannitol positive population.

In mannitol negative patients at baseline, the analysis of the secondary efficacy variables, showed no statistically significant differences between both study treatments.

The only significant predictor identified by the logistic regression analyses for a study outcome in the mannitol negative population was gender as a predictor for fulfilling at least one of the criteria included in the main combined lung function endpoint. The odds ratio for a female patient as compared to a male patient to meet this improvement definition was 7.000 (1.319 - 37.154).

In the pooled mannitol positive and mannitol negative patient population, the analysis of the secondary efficacy variables showed no statistically significant differences and no trends (p values between 0.05 and 0.10) towards a statistically significant difference between ciclesonide and placebo.

Significant predictors identified by the logistic regression analyses for a study outcome in the full patient population included:

- Gender and baseline methacholine challenge test $PD_{20}FEV_1$ for improvement of methacholine $PD_{20}FEV_1$ by 1.5 doubling units from baseline. Female patients showed a lower likelihood of improvement in methacholine test (odds ratio 0.183 (0.034 - 0.993); p=0.0490) and the likelihood of improvement increased with the baseline methacholine $PD_{20}FEV_1$ value (odds ratio 3.090 (1.139 - 8.830; p=0.0267). This result is consistent with the evaluation of methacholine $PD_{20}FEV_1$ and methacholine RDR at week 4 using analysis of covariance, where their baseline value was in both cases a highly significant (p<0.0001) predictor, and gender was a significant predictor (p=0.0158 for $PD_{20}FEV_1$; p=0.0233 for RDR).
- FeNO at baseline for the likelihood for fulfilling at least one criterion of the main combined lung function improvement endpoint evaluated in the intention to treat patient set. The odds ratio was 1.022 (1.003 - 1.041; p=0.0262), meaning that patients with a higher baseline FeNO were more likely to meet at least one criterion of the main combined lung function improvement endpoint.

A separate logistic regression analysis with generation of ROC curves based evaluation of potential predictors for therapeutic response to inhaled ciclesonide was also performed. No significant statistically baseline predictors or patient covariates (age and sex were evaluated) for response to ciclesonide defined using several different criteria were identified. A statistical trend (p=0.0930) was found for FeNO at baseline below 50 ppb in the ITT set as a predictor of not reaching at least a criterion of the main combined lung function endpoint. The observation of a FeNO at baseline below 50 ppb met the criterion for entry in the multivariate analysis (p=0.1045 for the ITT set; p=0.1281 in the PP set) as a predictor of reaching at least a criterion of the main combined lung function endpoint.

In the pooled mannitol positive and mannitol negative patients per protocol analysis set, a trend was found in univariate analysis for FeNO at baseline below 50 ppb (p=0.0757) as a predictor for not reaching at least a criterion of the secondary combined lung function endpoint. Female sex reached the criterion to be evaluated in multivariate analysis (p=0.1380, female subjects less likely to reach at least a criterion of the secondary combined lung function endpoint). Multivariate analysis including both variables was performed, and neither baseline FeNO below 50 ppb nor patient's sex were significant predictors.

**Safety Results:**

Regarding the safety evaluation, treatment courses of up to 40 days (scheduled 28 days) of once daily 320 µg ciclesonide, administered by MDI, was safe and well tolerated by men and women with symptoms of asthma. There were no drug-related adverse events, and no clinically significant and potentially IMP related findings in clinical laboratory tests or vital signs.

**CONCLUSIONS**

- The primary study efficacy endpoint, proportion of mannitol positive patients meeting the responder definition based in the change of mannitol elicited airway hyperresponsiveness from baseline to week 4, was met by a higher proportion of active treated patients both in the ITT (63.6% on active; 41.7% on placebo) and in the PP analysis set (70.0% on active; 44.4% on placebo). However, the differences were not statistically significant.
- An unexpectedly high placebo response rate (ITT analysis set 41.7%, PP analysis set 44.4%) as compared to a value of 20% used for the study design would provide an explanation of why the study became underpowered for its main efficacy endpoint.
- The differences between active and placebo for the main efficacy endpoint may be clinically relevant, but the study does not allow evaluating them. A study including a higher number of mannitol positive patients would be needed for its proper evaluation.
- No statistically significant differences were found in neither of the patient populations for any of the secondary efficacy endpoints. A single isolated statistical trend was found for a different endpoint associated to hints for a potential effect of baseline imbalances in the mannitol positive population, thus being of doubtful interpretation. No clear predictors for changes in airway hyper-reactivity or for ciclesonide treatment response were identified.
- Treatment courses of up to 40 days (scheduled 28 days) of once daily 320 µg ciclesonide, administered by MDI, was safe and well tolerated by men and women with symptoms of asthma. There were no drug-related adverse events, and no clinically significant and potentially drug related findings in clinical laboratory tests or vital signs.

**Study ID Number:**

BY9010/CH101

**Other Study ID Number(s):**

NCT00826969 [NCT Number]

U1111-1137-3949 [UTN Number]

**DATE OF DISCLOSURE SYNOPSIS:** 29 October 2012