2. SYNOPSIS

Name of Company: Mundipharma AB	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: **MAnnitol Challenge Test – Aridol™ /Osmohaler™**	Referring to Part … of the Dossier	
Name of Active Ingredient:	Volume: Page:	

Title of the Study:

An open-label single site single dose pilot study using mannitol challenge test with the purpose to explore treatment with fixed dose combinations in adult subjects with asthma in primary care in Sweden

Investigator: This study was carried out at one site in Sweden.

Publication (Reference): None

Study Dates:	**Study Status:**	**Phase of Development:**
05-Sep-2011 to 17-Apr-2012	Completed	Phase 4

Objectives: The primary objective was to identify if asthma patients prescribed fixed dose combinations (FDC)(budesonide/formoterol (Symbicort®), salmeterol/fluticasone (Seretide®) beclometasone/formoterol (Innovair®)) are optimally treated, as determined by the mannitol challenge test and the reversibility test.

Methodology: An open-label, single site, single dose pilot study using Aridol™/Osmohale™ (mannitol inhalation powder) as a bronchial challenge test, in subjects who were using FDC for the treatment of asthma.

At the first visit subjects were given information about the study and signed informed consent. They continued with their asthma and allergy medication as usual until the day of the second visit/challenge test. On the day of the second visit they were not allowed to take any medication for asthma or allergy in the morning, but prior to that could medicate as usual. This included all different types of medication such as FDC, short-acting β2-agonist, antihistamines and montelukast.

At the second visit the subjects begun by completing an Asthma Control Test (ACT) to establish whether the patient was “well-treated” or “symptomatic”. An evaluation of the Investigator evaluated the subject regarding their asthma control (Asthma Score). All subjects would then perform the mannitol challenge test.

Number of Subjects: Planned:100 subjects. Entered: 98 subjects. Completed: 98 subjects.

Indication and Criteria for Inclusion: Males and females with asthma who were being treated with a FDC treatment for at least 3 months, who had a baseline FEV_1 of ≥70% of the predicted value, who had no other respiratory disease, infection or exacerbation and had not been treated with oral corticosteroid within 28 days of the challenge test.

Test Treatment, Dose, and Mode of Administration: Oral mannitol inhalation powder (0 mg, 5 mg, 10 mg, 20 mg, 40 mg, 80 mg, 160 mg) for use consecutively in the challenge test.

Duration of Treatment: 2 Days. Visit 2 was to occur within 4 weeks of Visit 1.

Treatment Schedule: The challenge test was undertaken once per subject.

Criteria for Evaluation:

Efficacy: The test result of the mannitol challenge test could be either be positive or negative. The test result was considered as positive if: >= 15% fall in FEV_1 from baseline (using the post 0 mg FEV_1 as comparator). >= 10% incremental fall in FEV_1 (between consecutive mannitol doses). After the mannitol challenge test, all Subjects (both those with a positive and a negative outcome) performed a reversibility test with a short-acting β_2-agonist. A Subject was also classified as positive if they obtained a reversibility of ≥15%.

Statistical Methods: Dichotomous variables and categorical variables were given as number and percentage. Continuous variables as well as changes and differences in continuous variables were presented as mean, standard deviation (SD), median, min and max.
For proportions regarding the primary and secondary dichotomous variables 95% two-sided confidence intervals (CI) were given. All significance was two-sided and conducted at the 5% significance level.
Changes of FEV_1 values over time were analysed with the Wilcoxon Signed Rank test.
For the prediction of a positive outcome from the mannitol test, univariable and multivariable logistic regression were used. The odds ratio (OR) with 95% CI, area under the receiver operating characteristics (ROC) curve was presented for descriptive purposes. The associated p-values were presented.
The analysis of the relationship between the continuous variables and the ordered categorical variables was investigated using the Jonckheere-Terpstra test.
Safety parameters were analysed using descriptive statistics.

Intent-To-Treat Population: The Intention-to-Treat (ITT) Population was all enrolled subjects with at least one measured value on the primary or secondary efficacy variables.

Per Protocol Population: The Per Protocol (PP) Population was all subjects in the ITT Population without major protocol violations.

Safety Population: The Safety Population consisted of all subjects that had taken at least one dose of study medication.

Results: There were more females than males in this study (62.2% versus 37.8% respectively). Aside from asthma, the most common current medical condition was allergic conjunctivitis (74 events in 74 subjects). The most frequently used concomitant medications at Visit 2 were corticosteroids, potent group III (9 subjects) and proton pump inhibitors (9 subjects).

For the ITT Population, 64 (65.3%, 95% exact CI 55.0%-74.6%) subjects showed a positive outcome with the mannitol challenge test + short-acting β2-agonist. The corresponding value for the positive outcome of the mannitol challenge test alone was 60 (61.2%, 95% exact CI 50.8%-70.9%), and was 49 (50.0%, 95% exact CI 39.7%-60.3%) for the positive outcome of the reversibility test with a short-acting β2-agonist alone.

The subject-rated mean ACT was 21.4, resulting in 74 (76%) subjects being rated as well-treated (ACT 20-25). The subject's normal physician prescribed most of the patients (99%) moderate/severe asthma medication and the Investigator rated the subjects' severity of symptoms as follows: no symptoms for 34% patients, symptoms 1-2 days weekly for 50% patients, symptoms 3-6 days weekly for 14% patients. Only 2 subjects were rated as having daily symptoms.

The FEV_1 values during the mannitol challenge test decreased over time, with the greatest decrease occurring between dose 6 (155 mg cumulative dose) and dose 8 (475 mg cum. dose). The FEV_1 value increased from the last mannitol test to the reversibility test with a relative change of 116%.

Exploratory analyses show that FEV_1% and FEV_1% of predicted, were the best statistically significant predictive variables for a positive outcome of the mannitol challenge test. The mean PD15 within the subjects with a positive outcome was 376 mg. Most of them had mild (PD15 > 155 mg) bronchial hyperresponsiveness (67%) and only 6% had severe (PD15 ≤ 35 mg) bronchial hyperresponsiveness.

No statistically significant relationship between ACT and bronchial hyperresponsiveness could be shown.

Thirteen (13%) subjects experienced 16 adverse events. The most common AE was no therapeutic response in 9 (9%) subjects. As well as these 9 events, which were considered treatment related, there was one other treatment-related event of a cough. Only 2 (2%) subjects had 2 AEs (a wound and a cough) that were of moderate severity.

There were no occurrences of deaths, other SAEs, severe AEs or AEs that led to discontinuation.

Conclusions:

- 64 (65.3%, 95% CI, 55.0%-74.6%) subjects showed a positive outcome with the mannitol challenge test + short-acting β2-agonist.
- 60 (61.2%, 95% CI, 50.8%-70.9%), subjects showed a positive outcome to the mannitol challenge test alone.
- 49 (50.0%, 95% CI, 39.7%-60.3%) subjects had a positive outcome for the reversibility test with a short-acting β2-agonist alone.
- 74 (76%) subjects were rated as well-controlled (ACT 20-25) on their current medication. The mean ACT was 21.4.
- The subjects' normal physician prescribed moderate/severe asthma medication for most of the subjects (99%). 50% of subjects were rated as having symptoms 1-2 days weekly by the Investigator.
- The FEV_1 values during the mannitol challenge test decreased over time, with the greatest decrease occurring between dose 6 (155 mg cumulative dose) and dose 8 (475 mg cumulative dose). The FEV_1 value increased from the last mannitol test to the reversibility test with a relative change of 116%.
- Exploratory analyses showed that FEV_1 % and FEV_1 % of predicted were the best statistically significant predictive variables for a positive outcome of the mannitol challenge test.
- No statistically significant relationship between ACT and bronchial hyperresponsiveness could be shown.
- There were no occurrences of deaths, other SAEs, or severe AEs and no AEs that led to discontinuation.
- Thirteen (13%) subjects experienced 16 AEs. The most common AE was no therapeutic response in 9 (9%) subjects.
- All 'no therapeutic response' events were considered to be treatment-related, the only other treatment-related AE was a cough. All AEs were mild with the exception of a wound and a cough which were of moderate severity.

Overall this study showed that not all asthma patients currently receiving a FDC treatment for their asthma were optimally treated on the therapies currently available.

Date of the Report: 17 July 2012