1. TITLE PAGE

J. URIACH Y COMPAÑÍA, S.A.

Grupo Uriach
Uriach Pharma

Polígon Industrial Riera de Caldes, Avinguda Camí Reial 51-57, 08184 Palau-solità i Plegamans (Barcelona, Spain)

CLINICAL STUDY REPORT

Title:	Efficacy and safety of rupatadine in persistent allegic rhinitis and health-related quality of life in children age 6-11 years: A randomized, double blind, placebo-controlled clinical trial.
Clinical Phase:	III
Author(s):	Dr. Iñaki Izquierdo (J. Uriach y Compañía, S.A. +34 902 47 15 11) Dr. Carlos M. Hortelano (AAIPharma, +34 91 372 60 00)
Principal/Coord. Investigator:	There was no global principal coordinator.

Dates of Trial:

First patient enrolled: 31 March 2009

Last patient completed: 10 February 2010

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Volume I of III Pages 1 to 523
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Volume III of III Pages 1028 to 1321

The study was conducted in compliance with the applicable regulations regarding the Informed Consent, Good Clinical Practices and the Declaration of Helsinki.

SIGNATURE PAGE

HEAD CLINICAL DEVELOPMENT
J. URIACH Y COMPAÑÍA, S.A.

29 Jul. 2010
DATE

DR. IÑAKI IZQUIERDO

CLINICAL TEAM LEADER
AAIPHARMA

28 JUL 2010
DATE

SANTIAGO ZAS

MEDICAL DIRECTOR
AAIPHARMA

28-JUL-2010
DATE

DR. CARLOS M. HORTELANO

2. SYNOPSIS

Name of Sponsor: J. Uriach y Compañía, S.A.	**Individual Study Table Referring to Part of the Dossier** **Volume:** TBD	(For National Authority Use only)
Name of finished product: Not yet marketed in any country		
Name of active ingredient: Rupatadine fumarate	**Page:** TBD	

Title of study:	Efficacy and safety of rupatadine in persistent allergic rhinitis and health-related quality of life in children 6-11 years: A randomized, double blind, placebo-controlled clinical trial.
Investigators:	There were not any global principal coordinator.
Study centre(s):	The study was conducted in a total of 34 centres: Argentina (12), South-Africa (10), Hungary (8) and Spain (4).
Publication (reference):	None.

Studied period (years): **(date of first enrolment):** 31 March 2009 **(date of last completed):** 10 February 2010	**Phase of development:** III

Objectives:	**Primary:**	To evaluate the efficacy and safety of rupatadine solution over a period of 28 to 42 days in children between 6 and 11 years old with persistent allergic rhinitis (AR).
	Secondary:	To assess the quality of life of children with persistent allergic rhinitis treated with rupatadine solution versus placebo by means of Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ).
Methodology:		Phase III, randomized, multicentre, double-blind, placebo-controlled study.

No. of patients planned: 366 patients

Analysed:

Population	Placebo	Rupatadine solution (1 mg/ml)	Total*
Screened	---	---	445
Randomized	180 (100.0%)	180 (100.0%)	360 (100.0%)
Safety	180 (100.0%)	180 (100.0%)	360 (100.0%)

Diagnosis and main criteria for inclusion:	Persistent allergic rhinitis (according to ARIA guideline; 'persistent' symptoms occur more than 4 days per week, and more than 4 weeks) in children between 6 and 11 years old. The main criteria for inclusion were: children had to weigh ≥ 16 Kg, with a documented history of persistent allergic rhinitis of at least 12 months before the selection visit, skin prick test positive of 3 mm greater than the negative control to at least one of the following: housedust mites, fungal spores, and grass pollens, they were required to have results of standard laboratory tests and a 12-lead ECG within acceptable limits. Girls of childbearing potential were required to have a negative pregnancy test and use contraceptive methods.

Test product:	Rupatadine (fumarate)
dose:	1 mg/mL solution
mode of admin.:	Oral
batch no.:	801 (Spain and Hungary) 802, 804 and 805 (South Africa) 803 (Argentina) Expiration date: 06/2010
Duration of treatment:	42 days
Reference therapy:	Placebo
dose:	N/A
mode of admin.:	Oral
batch no.:	801 (Spain and Hungary) 802, 804 and 805 (South Africa) 803 (Argentina) Expiration date: 06/2010
Criteria for evaluation:	
Efficacy:	Primary: ➢ Change from baseline in the Total 4 Symptoms Score of the patient (T4SS) over 28 days of treatment (reflective 24 hours symptoms assessment). Secondary: ➢ Change from baseline in the Total 4 Symptoms Score (T4SS) after 42 days of treatment. ➢ Change from baseline in the Total Symptoms Score of patient reflective symptoms (T5SS) during the 28 and 42 days of treatment. ➢ Change in the Daily Score for each Symptom (DSS) from baseline during 28 and 42 days. ➢ Mean value of the daily Total Score of Symptoms (mT5SS), which was the average of the sum of all the T5SS in each day of the study. ➢ Time to beginning of action, considered as the first day in which any significant difference was observed. ➢ Maximum value of the Daily Score of each Symptom (DSSmax), considered as the maximum score for a symptom given by the patient during the study. ➢ Maximum value of the Total daily Symptom Score (T5SSmax), considered as the maximum daily score of symptoms of each patient during the study. ➢ Percentage of days during the study period when the maximum daily score was from 0 to 1 (PDmax1) (i.e. only mild symptoms). ➢ Percentage of days during the study period when the maximum daily score was 0 (PDmax0) (i.e. asymptomatic patient). ➢ Percentage of patients who required rescue medication. ➢ Assessment of instantaneous symptoms severity (both patient and investigator). ➢ Assessment of instantaneous effectiveness (both patient and investigator). ➢ Paediatric Rhinoconjunctivitis Quality of Life (PRQLQ).

Safety:	Safety measurements included: ➢ Adverse Events incidence. ➢ Related Adverse Events incidence. ➢ Serious Adverse Events incidence. ➢ Clinical relevant changes in the following: o Physical examination o Vital signs o ECG o Laboratory results
Statistical methods:	The main population for the efficacy analysis was the Intent to Treat population. Additionally, demographic and baseline characteristics and the primary efficacy analysis were done on the Per Protocol population. Demographics and other baseline characteristics were summarized descriptively. Categorical data were summarized with absolute and relative frequencies (percentage), and numerical data were summarized with the number of subjects, mean and standard deviation. The main population for analysis was the Intention to Treat population. An additional approach to the efficacy variables was done on the Per Protocol population. A Safety population was included with all randomized patients that received any medication of the study. An ANCOVA test was used to perform the analysis on the main variable (T4SS) with treatment as the main factor, and including the terms for investigate site as factor and the baseline score as the covariate, the interaction term between factors was assessed. If the heterocedasticity was present, a rank transformation of the original values applied. Similar tests to the primary efficacy variable or ANOVA models were applied to assess continuous secondary variables. In categorical variables the χ^2 test was used, or the Fisher Exact test if applicability conditions were not present.

SUMMARY - CONCLUSIONS:

Efficacy results:

Main efficacy variable:

- Rupatadine solution (1mg/ml) was statistically better than placebo in the change of T4SS from baseline (-3.1 vs -2.5) over the 28-day treatment period, according to patient's assessment of reflective symptoms in the diary for the ITT population (ANCOVA; p=0.018). As percentage of reduction rupatadine improved 43% the T4SS in comparison with the 35% with placebo.

Secondary efficacy variables:

- Rupatadine solution (1mg/ml) was also statistically better than placebo in the change from baseline in the T4SS at 42 days of treatment in the ITT population (ANCOVA; p=0.048).
- Statistically significant differences were found in favour of Rupatadine solution (1mg/ml) versus placebo in the changes from baseline in the Total Symptoms Score (T5SS) of patient reflective symptoms at day 28 for the ITT population (ANCOVA; p=0.030). On the other hand, there were not found statistically significant differences in T5SS at 42 days between treatment groups.
- The results from the daily score for each symptom (DSS) showed statistically significant differences in favour of Rupatadine solution (1mg/ml) for Rhinorrhea (ANCOVA; p=0.008 and ANCOVA; p=0.023) and Itchy nose, mouth throat and/or ears (ANCOVA; p=0.047 and ANCOVA; p=0.040) and for both at 28 and 42 days in the ITT population. When the PP population was analyzed, these differences were found at day 28 for Rhinorrhea (ANCOVA; p=0.030) and Itchy, watery and red eyes (ANCOVA; p=0.027).
- Placebo showed higher values for the mean value of daily symptom scores (T4SS and T5SS) than Rupatadine solution (1mg/ml) for both ITT and PP population during the course of the study.
- Time to beginning of action showed that treatment groups started to make effect at 12 hours after starting treatment. There were statistically significant differences in favour of Rupatadine solution (1mg/ml) for both ITT (ANOVA; p=0.005).
- DSSmax showed that the item Rhinorrhea presented statistically significant differences in favour of Rupatadine solution (1mg/ml) for the ITT (ANCOVA; p=0.009) and the PP (ANCOVA; p=0.037) populations.
- T5SSmax (ANCOVA; p<0.001) showed that placebo presented higher values than Rupatadine solution (1mg/ml).
- Rupatadine solution (1mg/ml) was statistically better than placebo for T5SS after 42 days of treatment according to the patient and the investigator assessment of symptoms severity (ANCOVA; p=0.005 and ANCOVA; p=0.034 respectively).
- Regarding instantaneous effectiveness, in patients' opinion, Rupatadine solution (1mg/ml) was better than placebo at 28 and 42 days of treatment according to patients opinion (ANCOVA; p=0.013 and ANCOVA; p=0.017 respectively).
- Rupatadine solution (1mg/ml) improved the overall PRQLQ domains at 28 (ANOVA; p=0.009) days and 42 (ANOVA; p=0.023) days in comparison with placebo. When domains were analyzed separately, Rupatadine solution was statistically different in comparison with placebo at 28 days in nose symptoms (ANOVA; p=0.042), eye symptoms (ANOVA; p=0.033), practical problems (ANOVA; p=0.013) and activity limitations (ANOVA; p=0.013). After at day 42 nose symptoms (ANOVA; p=0.003) was statistically different compared with placebo.

Safety results:

- The overall incidences of adverse events reported during the study were 30.0% for patients taking placebo and 37.2% for patients taking Rupatadine solution (1mg/ml).
- The most frequently reported adverse events were *Headache* (10 patients (5.6%) in the placebo group and 23 patients (12.8%) in the Rupatadine solution (1mg/ml) group) (Chi-square test; p<0.001) and *Cough* reported in 7 patients (3.9%) in the placebo group.

- *Headache* was considered as of mild intensity in the 92.9% of patients in the placebo group and in the 84.1% of patients in the Rupatadine solution (1mg/ml). Regarding duration, a total of 71.4% of the headaches in the placebo group were resolved within the first day of the start of the event whereas 84.1% in the Rupatadine solution (1mg/ml) had an outcome of resolved that very same day.
- There was only one adverse event (0.9%) related to the study medication (Eczema) in the placebo group.
- No serious adverse events were found for any patients during the study.
- Three patients discontinued due to a clinically relevant abnormality eosinophils one in the placebo group and two in the Rupatadine solution group. In the biochemistry analysis, one patient in the placebo group presented a clinically abnormal value in urea nitrogen.
- For ECG parameters, there were not found any abnormal value clinically relevant in any of the two treatment groups.

Conclusions:

Rupatadine solution (1mg/ml) has shown a better profile in the reduction of nasal and non-nasal symptoms than placebo in children with persistent allergic rhinitis over a 28 days and 42 days, and with a good safety profile.

Date of report: Final version 1.00 28/July/2010