SUMMARY

Sponsor: Fundación para la investigación Biomédica Hospital Clínico San Carlos.	Dossier: NA Volumen:	
Product name: Omeprazole Sandoz capsules 40 mg®	Pag:	
Name of the Active Principle: Omeprazole.		
Essay title: Impact of proton-pump inhibitors on the threshold dose distribution in walnut allergy.		
Researchers: Dr. Montserrat Fernández Rivas, the Allergy Dept. HCSC, Madrid.		
Study Site: Hospital Clínico San Carlos (Madrid)		
Publication:		
Study Duration: 27 months. Recruitment Start Date: April 2016 Estimated date of study completion: 30/06/2018	Clinical Phase: NA	
Primary objectives: ▪ Investigation of effect of Omeprazole on the threshold dose-distribution curve and the severity of the clinical manifestation of walnut allergic patients. Secondary objectives: ▪ Determination of minimal eliciting dose of walnut protein in walnut allergic patients. ▪ Calculation of the dose of walnut protein leading to an allergic reaction in 5% (ED05) and 10% (ED10) of walnut allergic population. ▪ Analysis of differences in walnut threshold distributions curves and severity related to allergen sensitisation pattern and geographical location.		
Study design: Unicentric, randomised, placebo-controlled; cross-over design.		
Number of patients: A sample size of 36 subjects.		

Diagnosis and main inclusion criteria:

- Positive case history of immediate allergic reaction(s) to walnut.

- Age ≥ 18 years.

- Presence of specific IgE to walnut defined as a positive (≥ 3 mm wheal diameter) skin prick test and/or a serum IgE to walnut ≥ 0.35 kU/L (ImmunoCAP).

Experimental medication, dose and route of administration:

Patients were treated with Omeprazole Sandoz capsules 40 mg per day for 5 days before each intervention, i.e. food challenge.

Oral administration. ATC Code: A02BC01.

Treatment duration: The patients were exposed once to Omeprazole Sandoz capsules 40 mg per day during 5 days and twice to placebo (mannitol) during 5 days. The capsules were taken orally 30 min prior breakfast.

Evaluation criteria:

Main Variables:

- The minimal dose of walnut protein leading to a) a subjective and b) an objective allergic reaction was assessed according to food challenge outcomes at V2, V3, and V4.
- All the clinical manifestations observed during the challenges in V2, V3 and V4 was collected carefully in the CRF and used to evaluate severity by means of a 5 grade qualitative score and a quantitative numeric score developed in the iFAAM project.

Secondary variables:

- Determination of threshold dose-distribution curve in walnut allergy, and calculation of ED05 and ED10 values.
- Determination of differences in threshold and severity related to allergen sensitization pattern and geographical location.

Statistical method

Efficiency Analysis:

- The effect of omeprazole on walnut threshold was analysed using hazard ration models such as Cox model, with walnut (presence or absence) and omeprazole (presence or absence) as predictive covariates, and the amount of walnut before first objective symptoms as the predicted value. 95%CI was provided in all cases.
- Descriptive statistics was performed for all subjects in this study in relation to demographic, clinical data, SPT results, and serological/immunological parameters. Data was summarized by absolute (number of subjects) and relative (%) frequencies for categorical variables and by mean and standard deviation, or median and 25th and 75th percentile, for continuous variables that follow or not the normal distribution, respectively

Security analysis:

- Clinical manifestations observed during the DBPCFC in V2, V3 and V4 were used to evaluate severity of walnut allergy applying a 5 grade qualitative score, and a numeric score developed in iFAAM. Percentage of severe reactions (grade 4-5 in the qualitative score) were presented, together with logistic regression over both the qualitative and quantitative scores. Odds-ratios with 95% CI, served for evaluation of significant score variations in severity.
- Threshold dose distributions for walnut were modeled by interval censoring survival analysis using the survival package R , and the ED05 and ED10 values (doses at which an allergic reaction is in 5% or 10% of the walnut allergic population) was calculated using parametric models based on either log-normal, log-logistic or Weibull distributions. Curves with 95% confidence interval (95%CI) were calculated, with comparative analysis of omeprazole vs placebo provocations using t-test.
- Washout effect was also analysed on the walnut thresholds and severity with and without omeprazole. Logistic regression mixed models was used in order to infer how much do prior steps of the assay affect the next ones.
- An intermediate analysis of data was performed once an appropriate number of patients was reached, requiring that at least two to three patients with each sequence combination (in the randomization list) were present. Performance of intermediate results served as a tool for deciding whether or not data collected were enough for the primary study outcomes analysis, with the aim to expose as few patients as possible to the risk of the DBPCFCs.
- As a threshold for risk acceptance, the assay is assumed to have a probability lesser than 20% of resulting into a severe reaction (grades 4-5 into the qualitative scoring system). A binomial distribution with $\alpha=0.2$ was used as test to decide whether or not such assumption is true, once enough patients have been tested (8-10 patients).
- A complete statistical analysis plan was developed before the data base lock.
- All the analysis was performed using statistical analysis packages such as R (version 3.4), STATA (version 12.0) and SPSS (version 15.0). The agreed level of significance for statistical tests will be $p<0.05$.

Efficacy Results:

- The results of the study showed that Omeprazole does not appear to have a significant effect on the threshold dose-distribution curve and the severity of the clinical reactions to walnut in allergic patients.
- The eliciting doses in g walnut protein in the distribution models ranged from 0.02 – 0.04 g for the ED05, and from 0.07 – 0.09 g for the ED10.
- Any possible relationship between the sensitization pattern for individual walnut allergens and the severity and eliciting dose of the allergic reactions were also analysed. The most prevalent allergens were rJug-3 (nsLTP) (62%), low molecular weight (LMW) vicilin nJug r 2 (24 and 46%) and profilin rJug r 7 (24%) using 0.35 kUA/L as cut-off point. The models showed that sensitization to profilin rJug r 7 could be correlated with milder reactions, and that sensitization to profilin rJug r 7 and LMW fraction of nJug r 2 (vicilin) could be correlated with a lower threshold for allergic reactions.

Safety results:

No safety concerns arised during the trial. The frequency of AE during the treatment with omeprazol and placebo were similar (<10%/days of treatment), and none was severe. Out

of 120 double-blind placebo controlled challenges carried out with walnut only 12 challenges (10%) elicited severe reactions (respiratory involvement) that were managed by the investigators at the trial site. No emergency room assistance or hospital/ICU admission was required. There were no occurrences of severe adverse events or deaths in this trial.
Conclusions: The results of the study showed that Omeprazole does not appear to have a significant effect on the threshold dose-distribution curve and the severity of the clinical reactions to walnut in allergic patients. No severe adverse events occurred in relation to the drugs administered or the food challenges performed.