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Sponsor / Company: Sanofi **Drug substance(s):** Ramipril	**Study Identifiers:** NCT00437463 **Study code:** HOE498_6015

Title of the study:	Treatment of Early Immunoglobulin A Nephropathy by Angiotensin Converting Enzyme Inhibitor – A Randomized Controlled Trial (**HOE498_6015)**		
Study center(s):	Single center in Prince of Wales Hospital, Hong Kong		
Study period: Date first subject enrolled: 04-Jul-2004 Date last subject completed: 27-Sep-2010		**Phase of development:** III	
Objectives:	The objective of the study is to evaluate the efficacy of the ACE inhibitor ramipril in the treatment of early IgA nephropathy. The primary end point of the study is any one of the followings: (1) development of hypertension (defined as blood pressure above 140/90 mm Hg or the need of anti-hypertensive therapy); (2) development of proteinuria ≥ 1 g per day; and (3) 20% decline in the estimated glomerular filtration rate (GFR), which was computed by an equation validate in Chinese. The slope of decline of the estimated GFR were also compared.		
Methodology:	The center randomly assigned 60 patients with IgA nephropathy, proteinuria <0.5 g/day, normal blood pressure and renal function, to ramipril 2.5 mg daily or no treatment. Patients were followed for 5 years for the development of hypertension, proteinuria, or impaired renal function		
Number of subjects:	Planned: 60	Randomized: 60	Treated: 60
Evaluated:	60	Safety: 60	
Diagnosis and criteria for inclusion:	Inclusion criteria • age between 18 and 65 • biopsy-confirmed IgA nephropathy • proteinuria less than 0.5 g per day, normal blood pressure, and serum creatinine below 120 mol/l • willingness to give written informed consent and willingness to participate in and comply with the study protocol		

	Exclusion criteria • expected survival less than 2 years • pregnant or nursing mother, or women of childbearing potential without an effective method of birth control • history of myocardial infarction, congestive heart failure, or any other medical indication that necessitate the use of ACE inhibitor • evidence of clinically significant hepatic, gastrointestinal, autoimmune disease • history of malignancy, drug or alcohol abuse • participation in any previous trial on ACE inhibitor • taking other investigational drugs within the past 30 days • history of non-compliance to medical regimens and patients who are considered potentially unreliableknown history of sensitivity / allergy to ACE inhibitor
Investigational product:	Ramipril 2.5mg/d oral
Duration of treatment: 5 years	**Duration of observation:** 5 years
Reference therapy:	Observation only
Criteria for evaluation:	Follow up visits will take place according to the following schedule: week –4 (screening) and 0 (enrollment and randomization) week 4 and 12 after started on ramipril, then every 12 to 24 weeks, as decided by individual nephrologist, for 5 years During every visit, the following parameters will be measured: body weight, blood pressure, pulse and adverse effects of treatment. Renal function test and proteinuria are quantified at –4 and 0 week, and then every 6 months. Proteinuria can be quantified by either 24-hour urinary collection for proteinuria and creatinine clearance, or by spot urine for protein-to-creatinine ratio. The half life of ramipril, and its major active metabolite ramiprilate, is around 12 hours. The effect on blood pressure should be minimal if the patients continue to take the morning dose on the day before clinic visit, omit the dose on the morning of visit, and has their blood pressure measured in afternoon renal clinic. In order to examine the anti-inflammatory action of ACE inhibitor, serum level of interleukin-1 beta (IL-1β), interleukin-6 (IL-6), platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGF-β) will be checked at 0 week, then every 6 months for 2 years, then yearly. This panel of cytokine was chosen because of their documented relevance in IgA nephropathy and progressive renal failure.
Statistical methods:	Statistical analysis was performed by SPSS for Windows software version 15.0 (SPSS Inc, Chicago, IL).Data were expressed in mean ± SD and analyzed on intention-to-treat basis. Data are compared by Chi-square test or Student's t-test as appropriate between treatment groups. Event free survival was computed by the Kaplan Meier analysis; the time to develop primary end point was compared by the log rank test. A p value of below 0.05 was considered significant. All probabilities were two-tailed.

Summary:	The blood pressure of the treatment group was marginally lower than the control group throughout the study period. At 60 months, the event-free survival was marginally higher for the treatment group as compared to the control group (81.1% vs 70.5%, p = 0.27) The proteinuria-free survival was similar at 82.9% and 79.3% for the treatment and control groups, respectively (p = 0.6); hypertension-free survival was 86.4% and 79.3% (p = 0.2). After 60 months of follow up, the estimated GFR was 108.1 ± 29.0 ml/min/1.73m^2 for the treatment group and 105.7 ± 17.7 ml/min/1.73m^2 for the control group (p = 0.7) but the difference was not statistically significant. None of the patient developed impaired renal function. The rate of GFR decline was similar between the treatment and control groups (-0.39 ± 2.57 vs -0.59 ± 1.63 ml/min/1.73m^2 per year respectively, p = 0.7). In general, the study medication was well tolerated. 2 patients needed to stop prematurely because of cough and dizziness.
Date of report:	17 May 2012