Examinations and Lab-diagnostics

(see study protocol Appendix IV for blood volumes)

- **Physical Exam Panel 1:** Vital signs (heart rate, sitting blood pressure, body temperature), body weight, height, assessments to test for additional severe renal or extra-renal disease that might affect Alport syndrome progression.
- **Physical Exam Panel 2:** Vital signs (heart rate, sitting blood pressure, body temperature), body weight, height.
- **Urine Panel 1:** Measured creatinine clearance, gProtein/gCrea and gAlbumin/gCrea (24-hour creatinine, protein, and albumin excretion), estimated gProtein/gCrea, estimated gAlbumin/gCrea, spontaneous sediment.
- **Urine and Blood Panel 3:** Asservation of 2 mL serum and 10 mL urine for the development of serum and urinary markers of renal function. Store at -20°C until despatch (on dry ice) to the Trial Office, Göttingen.
- **Blood Panel 1:** blood count, differential blood count, potassium, blood glucose, serum creatinine, serum urea, serum uric acid, albumin, GOT, GPT, AP, g-GT, bilirubin, cholesterol, CRP, additional parameters at investigator's discretion.
- **Blood Panel 2:** blood count, potassium, blood glucose, serum creatinine, GPT, additional parameters at investigator's discretion
- **Blood Panel 4** (only if indicated): Asservation of 2 mL EDTA-blood for DNA extraction to confirm or re-assess Alport mutations. Store at -20°C until despatch (on dry ice) to the Trial Office, Göttingen.

Reporting of Serious Adverse Events (SAEs)

Please **immediately report** any SAEs, i.e. **within 24 h after occurrence respectively after discovery**, to the Coordinating Principal Investigator (Trial Office, Göttingen) **and** to the Contract Research Organisation (CRO: IFS GmbH, Göttingen)

Fax: +49 (0)551 39 8906 (trial office)
+49 (0)551 39 171293 (CRO)

→ The immediate report needs to be followed by an **extended written report** to the same address.

The protocol can be found in the download area of the study database

alport selbsthilfe

GPN Gesellschaft für Pädiatrische Nephrologie

Bundesministerium für Bildung und Forschung

EARLY PRO-TECT Alport

Early prospective Therapy Trial to Delay Renal Failure in Children with Alport Syndrome

Ramipril *versus* Placebo

Coordinating Principal Investigator: Prof. Dr. Oliver Gross

EudraCT Number: **2010-024300-10**
Protocol: **Version 2.0, 28 February 2012**

Trial Office **O. Gross , J. Krügel , F. Weber**
UNIVERSITY MEDICAL CENTER GÖTTINGEN
Dept. of Nephrology and Rheumatology
Robert-Koch-Str. 40
37075 Göttingen, Germany
Tel: +49 (0)551 - 39-6910
Fax: +49 (0)551 - 39-6911
Email: studie@alport.de
Homepage: www.alport.de/EARLY_PRO-TECT_Alport

and Nick Kidney

GPN Gesellschaft für Pädiatrische Nephrologie

UNIVERSITÄTSMEDIZIN GÖTTINGEN : UMG

GPN-supported trial

Background

ACE-inhibitors (ACEis) are the first-line off-label therapy for proteinuric Alport children for most nephrologists. However, the use of ACEis in Alport children has not been assessed in a prospective, controlled clinical trial. No approved treatment of Alport Syndrome exists to date, and no official treatment recommendation has been made.

Aim of the Study

This is a phase III, multi-center, randomized, placebo-controlled, patient and investigator-blind study to determine the safety and efficacy of the ACEi ramipril in delaying disease progression in paediatric patients with early stages of Alport Syndrome.

Clinical Alport Levels

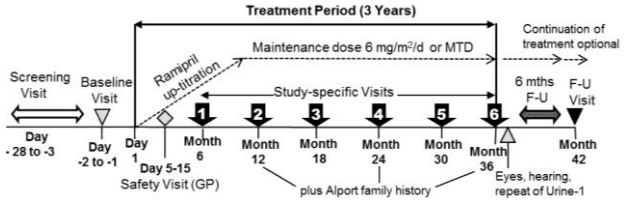
0	**Microhaematuria without microalbuminuria**
I	**Microalbuminuria (30-300 mg albumin/gCrea)**
II	Proteinuria >300 mg albumin/gCrea
III	>25% decline of normal renal function (creatinine clearance)
IV	End stage renal failure (ESRF)

Inclusion Criteria

- **Age**: ≥24 months to <18 years
- Definitive **diagnosis** of Alport syndrome: Kidney biopsy and/or mutation analysis
- **Anamnesis** criteria (family history, ocular changes, labyrinthine hearing loss)
- Alport **level 0 or I** (with or without ACEi therapy) at screening
- **Assent** from patient and/or informed **consent** from parents/legal guardian

Exclusion Criteria

- **Uncertain diagnosis**
- Alport **levels II, III or IV**
- **Allergies or intolerances** to medication
- **Contraindications** to ACEi-therapy
- **Additional diseases** (renal, pulmonary, liver or cardiac or other)
- **Pregnancy and lactation**
- **Alcohol/Drug** abuse



Study Schedule of Events (see also study protocol Appendix II)

- **Screening:** Informed consent, inclusion/exclusion, demographics, medical history, patient/family history of Alport Syndrome, symptoms, AEs, concomitant medication, Physical Examination Panel 1, pregnancy test (if applicable), Urine Panel 1, Blood Panel 1
- **Baseline:** Inclusion/exclusion, enrolment and randomization, AEs, pregnancy test (if applicable), Urine Panel 1, Urine and Blood Panel 3, Blood Panel 4
- **Day 5-15 (general practitioner): Drug safety and tolerability examination:** Dosing of study drug, AEs, Blood Panel 2
- **Treatment period (study visits every 6 months):** Symptoms, dosing of study drug, AEs, concomitant medication, Physical Exam Panel 2, pregnancy test (if applicable), Urine Panel 1 (**month 36**: twice within one week, 1x GP!), Blood Panel 2 (**month 36:** Blood Panel 1!), Urine -and Blood Panel 3
  Additionally in Month 36: eye and hearing examination
  Additionally in Months 12, 24 and 36: family history of Alport Syndrome
- **Follow-up (month 42 or 6 months after premature termination):** AEs, concomitant medication, Physical Exam Panel 1, Blood Panel 2

Dosing Schedule (see also study protocol Appendix V)

Pediatric patients <18 years: starting dose 1 mg/m²/day, up-titration every two months to max. 6 mg/m²/day (or individual max. tolerated dose, MTD)

Mosteller Formula for Body Surface Area (BSA):

$$BSA(m^2) = \sqrt{\frac{weight\ (\mathrm{kg}) \times height\ (\mathrm{cm})}{3600}}$$