Study Title:
European Alport Therapy Registry-
EARLY PRO-TECT Alport XXL

Protocol Code:
EARLY PRO-TECT Alport XXL

Protocol

Version: 1.2 Date: 21.07.2021

Sponsor of the Observational Study

Universitätsmedizin Göttingen
Georg-August-Universität Göttingen Stiftung Öffentlichen Rechts

Coordinating Principal Investigator (LKP)

Prof. Dr. med. Oliver Gross

- Confidential -

The information contained in this protocol has to be kept strictly confidential. Therefore the protocol is only provided to Investigators in confidence for review, to study staff, Independent Ethics Committee/Institutional Review Board, regulatory authorities, CROs, and to obtain written informed consent from patients/parents/legal guardian.

2 Approval Signature Page

The following persons accept the content of this protocol and confirm to conduct this study in compliance with Good Clinical Practice and applicable regulatory requirements.

Approved by:

Prof. Dr. Oliver Gross **Coordinating Principal Investigator**	**Date**

The present study protocol was prepared in accordance with the relevant ICH-GCP criteria.

3 Organisational Structure

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For the Gesellschaft für Pädiatrische Nephrologie (GPN-supported trial):

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Münster: Prof. Dr. Martin Konrad
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Trial Sites:
A list of Trial Sites participating in this trial is on file at the Trial Office, Universitätsmedizin Göttingen (UMG)

Emergency Contact

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5 Synopsis

Study Title	**European Alport Therapy Registry- EARLY PRO-TECT Alport XXL**
Type of Project	Non-interventional, observational prospective (and in parts retrospective) study in oligosymptomatic children with Alport syndrome
Sponsor	Georg-August-Universität Göttingen Stiftung Öffentlichen Rechts Universitätsmedizin Göttingen Vorstand Robert-Koch-Str. 42 37075 Göttingen Tel.: +49 (0) 551 39-61001 Fax: +49 (0) 551 39-61002
Coordinating Principal Investigator	Prof. Dr. Oliver Gross Klinik für Nephrologie und Rheumatologie Universitätsmedizin Göttingen Robert-Koch-Str. 40 37075 Göttingen Tel.: +49 (0) 551 39-65309 Fax: +49 (0) 551 39-65977 Email: gross.oliver@med.uni-goettingen.de
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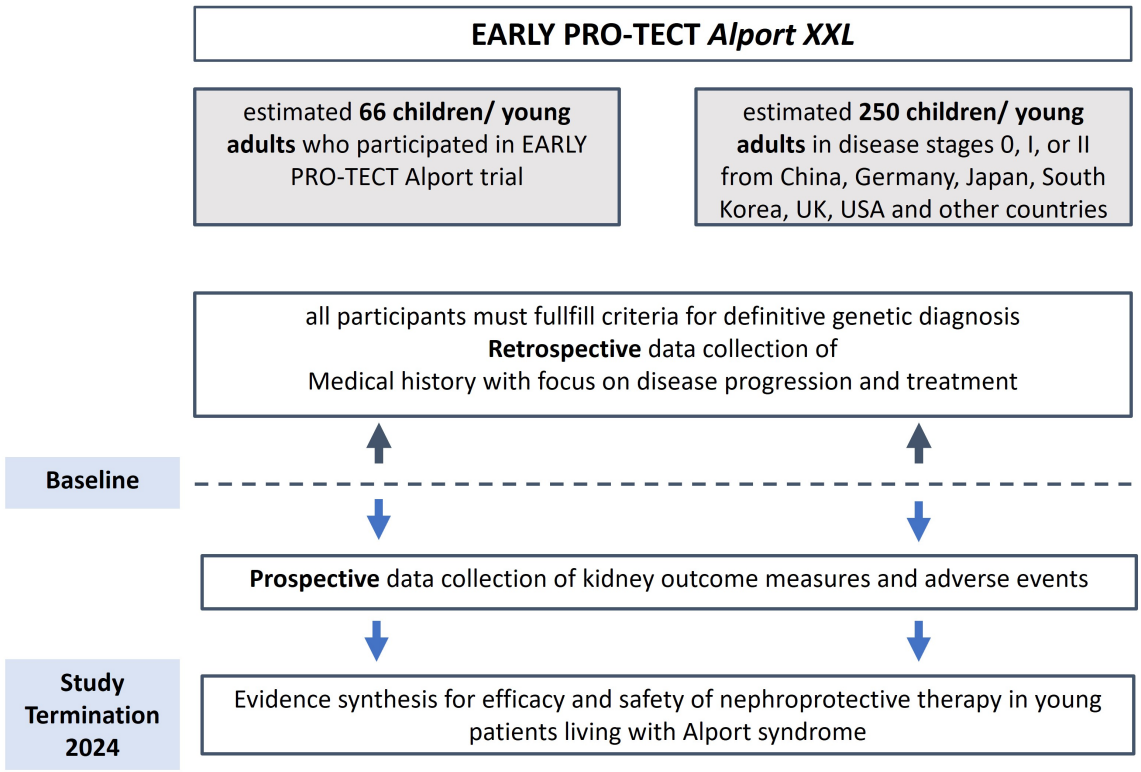
(Sub-) Investigators	A list of sub-investigators participating in this study is kept at the Trial Office (UMG, Göttingen)
Participating Trial Sites	A list of investigators and trial sites participating in this study are kept on file at the Trial Office (UMG, Göttingen).
Hypothesis	Treatment of Alport syndrome with Renin–angiotensin–aldosterone system inhibition from early stages of disease is safe and slows disease progression.
Rationale	The type IV collagen disease Alport syndrome is the second most common monogenic cause of end-stage renal failure. Children with Alport syndrome develop renal failure early in life. Renin–angiotensin–aldosterone system (RAAS) inhibition is the first-line off-label therapy

	for proteinuric children with Alport syndrome and can delay renal failure in a time dependent manner. The EARLY PRO-TECT Alport trial was the first randomized and placebo-controlled trial to evaluate safety and efficacy of RAAS-inhibition in children with Alport syndrome. The trial indicated safety and efficacy of nephroprotective therapy without statistical significance. Aim of this planned study is to analyse renal outcome and adverse effects in the longterm observation of all children of the trial to further increase quality of the original trial results. Adult patients with Alport syndrome suffer from progressive sensorineural hearing loss and eye abnormalities are often found. The development and characteristics of hearing loss and the prevalence of ocular findings in children with Alport syndrome need to be further analyzed. This study also aims to further characterize hearing loss and ocular findings in AS.
Study Medication	Non-interventional observational trial
Placebo	Non-interventional observational trial
Study Design	Strictly observational, non-interventional data acquisition with prospective (and in parts retrospective) data analysis



	Pseudonymized follow-up of the 66 children from the EARLY PRO-TECT Alport trial (with the exception of drop-out patients) as well as inclusion and follow-up of children with Alport syndrome in disease stages 0,I,II (i.e. comparable to the patient group of the EARLY PRO-TECT Alport trial) from South Korea, USA, Canada, China, France, England, Spain and Germany Alport Syndrome disease stages are defined as: 0 Microhaematuria without microalbuminuria I Microalbuminuria (30-300 mg albumin/gCrea) II Proteinuria >300 mg albumin/gCrea III >25% decline of normal creatinine clearance IV End stage renal failure (ESRF) Information on kidney function of the children will be collected as available from existing routine records. Adverse events (hyperkalemia, cough, hypotension, ANV, malignancy, death) will be monitored. Pseudonymized additional data regarding hearing function, ocular findings and genetic results will be obtained by medical reports as available.
Timetable	Date of study / recruitment Start May 2021 Date of termination of recruitment May 2022 Date of study termination May 2024
Total Number of Patients	Total: 90-250
Study population	Oligosymptomatic children and young adults with Alport syndrome in early disease stages
Inclusion Criteria	1. Definitive diagnosis of Alport syndrome by kidney biopsy (patient or affected relative/s), and/or genetic analysis 2. Alport syndrome stages 0, I or II at baseline, if the patient did not participate in EARLY PRO-TECT ALPORT trial 3. Patient expresses willingness to participate in observational study
Exclusion Criteria	1. uncertain Alport diagnosis 2. Alport syndrome stages III or IV at baseline, if the patient did not participated in EARLY PRO-TECT ALPORT trial 3. Patient expresses unwillingness to participate in observational study

Documentation Schedule	Baseline document (at baseline) and follow up document (at every consultation)
Study Objectives	**Study Objectives:** Aim of this planned study is to analyse renal outcome and adverse events in the longterm observation of oligosymptomatic children with Alport syndrome, who participated in the EARLY PRO-TECT ALPORT trial. Treated and untreated children in similar disease stages will be included from South Korea, Germany, UK, France, Spain, USA, Canada and China to further increase evidence and to enable a comparison between treated and untreated children. **Study Endpoints:** **Primary Endpoint:** time to progress of Alport Syndrome to the next disease stage under treatment Stage 0 to I : Albuminuria >30 mg albumin/gCrea in combination with a 3-fold increase from baseline in albuminuria Stage I to II: Albuminuria >300 mg albumin/gCrea or two-fold increase from baseline albuminuria Stage II to III: Two-fold increase from baseline albuminuria **Secondary Endpoint:** Time to progress of Alport Syndrome to the next disease stage under treatment compared to children without treatment **Further exploratory endpoints** will be assessed during this study if data warrant and include, e.g., percentage of patients with disease progression. For future evaluation for upcoming new therapies or for earlier diagnosis or for therapeutic response to therapy bio-material (urine and serum) of individual patients will be stored at the University Medical Center in Goettingen.
Safety	Safety is assessed by recording of adverse events and laboratory parameters.
Data-Safety	All data will be collected in pseudomized form at the trial site in Goettingen. All electronic data will be stored on the internal server of the University Medical Center Goettingen (intranet). Only the local team of the principal investigator will have access to the data with their

	individual personal account (access to be granted by the principal investigator).
Statistical Analysis	Statistical analysis of this study will be the responsibility of the Dept. Medical Statistics, Universitätsmedizin Göttingen, Georg-August-Universität. The primary endpoint 'time to progress of Alport syndrome will be assessed. If indicated, additional potentially confounding variables such as age will be added to the model.
Pharmacological-toxicological Evaluation	Not applicable
Risks, Adverse Drug Reactions, Drug Interactions, Restrictions, Contraindications, Procedures in Case of Emergency	Not applicable
Risk-benefit Analysis	Not applicable