Universität zu Köln

STUDY PROTOCOL

AN INTERNATIONAL MULTICENTER REGISTRY STUDY ON AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASES (ARPKD) - AREGPKD

Principal Coordinating Investigator:

Dr. Max Christoph Liebau
Department of Pediatrics
Cologne University Hospital
Kerpener Strasse 62
50937 Cologne
Germany

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I. Signatures

All persons who made a significant contribution to the preparation of the study protocol (protocol development committee) should sign this page.

Max Christoph Liebau		01.03.2013
(Principal Coordinating Investigator, PCI)	Signature	Date
On behalf of University of Cologne		
Markus Feldkötter		01.03.2013
(Deputy of the PCI)	Signature	Date
On behalf of University of Cologne		
Barbara Hero		01.03.2013
(Head of Pediatric Study Center)	Signature	Date
On behalf of University of Cologne		
Jörg Dötsch		01.03.2013
(Chair of Pediatrics)	Signature	Date
On behalf of University of Cologne		
Anja Sander		01.03.2013
(Statistician)	Signature	Date
Department of Medical Biometry, Heidelberg University Hospital		

II. Synopsis

Principal Coordinating Investigator:	University of Cologne Albertus-Magnus-Platz 50923 Cologne Germany Represented by: Dr. Max Christoph Liebau Department of Pediatrics Cologne University Hospital Kerpener Strasse 62 50937 Cologne Germany
Title of the clinical study:	An International Multicenter Registry Study on Autosomal Recessive Polycystic Kidney Diseases (ARPKD) - ARegPKD
Type of study, study design, methodology:	Non-interventional, multicenter, multinational, open, non-randomized registry study
Primary study objective:	Deep Phenotyping and detailed analysis of longterm clinical courses of ARPKD patients. Associated biobanking, reference histology and Next Generation Sequencing approach to understand underlying pathophysiological mechanisms.

Medical Condition and Key inclusion criteria:	Medical condition or disease to be investigated: • Autosomal Recessive Polycystic Kidney Disease (ARPKD) Key inclusion criteria: • Autosomal Recessive Polycystic Kidney Disease (ARPKD) of any age, diagnosed either o by histology o by molecular assessment o or clinically according to the criteria established by Zerres et al. (1996, Acta Paediatr. 85:437-455) • informed consent of patient and/or parents resp. legal representatives Key exclusion criteria: • Genetic proof of other cystic kidney disorders (e.g. NPHP, ADPKD) • Histological proof of other cystic kidney disorder • Clinical Proof of other cystic kidney disorder
Time plan:	Start registry study: 1. August 2012

Statistician:	Anja Sander, M. Sc. Insitute of Medical Biometry and Informatics University of Heidelberg Im Neuenheimer Feld 305 69120 Heidelberg Germany
Statistical methods:	Standard appropriate statistical approaches to compare follow-ups of patient's survival, renal function etc. In case of missing data appropriate methods (e.g. multiple imputation) will be used to handle them. Furthermore the aspect of multiple testing will be considered.
GCP conformance:	As far as applicable the present study will be conducted in accordance with the valid versions of the study protocol and the internationally recognised Good Clinical Practice Guidelines (ICH-GCP), including archiving of essential documents.

III. Table of contents

III.a) List of tables

III.b) List of figures

IV. Abbreviations

abbreviation	meaning
ARPKD	Autosomal recessive polycystic kidney disease
ADPKD	Autosomal dominant polycystic kidney disease
ARegPKD	Acronym of the ARPKD registry study consortium
ESCAPE	European Study Consortium for Chronic Kidney Disorders Affecting Pediatric Patients
GPN	Gesellschaft für Pädiatrische Nephrologie
NGS	Next Generations Sequencing
SC	Steering Committee
PCI	Principal Coordinating Investigator
PKHD1	Polycystic Kidney and Hepatic Disease 1
RCAD	Renal cysts and diabetes syndrome

1. *Introduction*

Polycystic kidney disease represents a major socio-economic medical problem within the EU. The adult-onset Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a very frequent monogenetic diseases and a major cause of dialysis-requiring end stage renal failure. Autosomal Recessive Polycystic Kidney Disease (ARPKD) is the rare pediatric form of cystic kidneys. It has a tremendous and early impact on child health e.g. frequently requiring breathing assistance within the first year of life. Kidneys are often grossly enlarged at birth and there is mandatory hepatic involvement. ARPKD occurs with an estimated incidence of 1:20.000. Still, ARPKD is responsible for up to 50% of patients with cystic kidneys in pediatric centers. There is major unexplained phenotypic variability. ARPKD is caused by mutations in a single gene *PKHD1*, wich encodes a huge transmembrane protein called Fibrocystin. The protein localizes to primary cilia of cells, classifying ARPKD as a ciliopathy. Fibrocystin is also involved in the regulation of pathways affected in ADPKD.

2. Objectives of the registry study

2.1. Rationale for the registry study

Cystic kidney diseases are a major cause of dialysis-requiring end stage renal failure in Europe. While some insights into the underlying pathomechanisms have been obtained there is still no effective treatment for this common and severe group of disorders. ARegPKD addresses this issue by studying the most severe form of cystic kidney diseases, ARPKD. The pathophysiology, clinical heterogeneity and long-term evolution of ARPKD remain poorly understood, explaining why there is currently no causative treatment. Even in most-advanced medical centers mortality remains high at up to 30% mainly related pulmonary problems. Kidney dysfunction is progressive leading to early end stage renal failure, and a need for dialysis and kidney transplantation in ~50% of the patients within the first two decades of life. In addition liver affection is obligatory, so severe liver fibrosis and a portal hypertension develop in a major fraction of patients. Combined liver and kidney transplantation is required in case of renal and hepatic failure. Severe and very early arterial hypertension is common and treatment often remains challenging. No clinical classifications, clinical risk factors or treatment guidelines for these challenges have been established so far and experience remains sparse even in large pediatric centers.

Therefore a multicenter, multinational approach is needed to perform deep phenotyping along with genetic analysis of a well-described cohort to increase our knowledge about this severe kidney disorder. Furthermore, the international comparison of current treatment strategies is required to establish international evidence-based treatment standards.

2.2. Primary objective

ARegPKD aims to contribute to the fight against life-threatening disorders of early childhood as well as the fight against end stage renal failure.

ARegPKD will increase insight into the pathomechanisms underlying ARPKD and set up conditions for the establishment of clinical studies on ARPKD. Using a web-based database

we will collect initial and follow up clinical data of ARPKD patients. Deep phenotyping will be combined with a Next Generation Sequencing Approach to study genetic modifiers that would explain the phenotypic variations seen in ARPKD. We will also look for clinical or biochemical risk markers. An ARPKD bio-repository as well as reference histology will be set up to generate a deeply characterized cohort that may be important for the set-up of future clinical trials.

2.3. Secondary and other objectives

As a multinational European registry with involvement of EU-neighbouring countries ARegPKD can differentiate incidence, available treatment options and outcomes in the different regions of Europe and unmask inequalities in access to health care and quality of disease management in this rare disorder. At the same time the scientific exchange within the project will make state-of-the-art medical decisions in the field of pediatric cystic kidney diseases available for affected children in all included areas. ARegPKD will also be able to establish equal standards in participating countries for this life-threatening and little understood disorder.

As a consequence of our project current emerging molecular therapies for autosomal dominant polycystic kidney disease (ADPKD) can be evaluated for the rare but by far more dramatic ARPKD in an existing and deeply-characterized cohort. These clinical studies will be the first step to evidence-based treatment in a severe disorder of early childhood with the potential to fundamentally reduce mortality.

3. Organisational and administrative aspects of the study

3.1. Principal Coordinating Investigator

Principal Coordinating Investigator (PCI): Dr. Max Christoph Liebau
Department of Pediatrics
Cologne University Hospital
Kerpener Strasse 62
50937 Köln
Germany

3.2. Statistics

Statistician: Anja Sander, M. Sc.
Medical Biometry and Informatics
Heidelberg University Hospital
Im Neunheimer Feld 305
69120 Heidelberg
Germany

3.3. Further committees

3.3.1. Steering Committee

A Steering Committee (SC) has been formed who, together with the PCI, continuously monitor the progress of the study, and who take majority decisions on all major questions concerning ARegPKD, e.g. changes in items of questionnaires.

The Steering Committee will also be in charge of the distribution of samples collected in the ARPKD biobank. Biosamples will be obtained in the participating centers (see 4.5). They will then be stored at the biobank facility of the Pediatric Research Center of the Medical University of Hannover. Researchers can apply for access to biosamples for scientific reasons only. The project for which the samples shall be used has to be related to cystic kidney diseases. A written application with a statement of a responsible Ethics Committee is sent to the PCI as representative of the Steering Committee at least four weeks in advance of a Steering Committee meeting. The Steering Committee will then decide on the application. The decision will be based on the Ethics vote and scientific value of the suggested project. Given a positive vote of the Steering Committee biosamples can be sent to the applying researcher. However, potentially remaining parts of the sample have to be sent back to the biobank after the end of the project.

A list of the members of the current Steering Committee (April 2012) is given in Appendix 11.2.

3.4. Study laboratories and other technical services

ARegPKD will have various institutions and technical services involved.

The establishment of reference histology in addition to local histological examination will be an important factor for maintaining highest security and standards concerning the correct diagnosis of ARPKD. Standardized histological work-up will be carried out at the Department of Pathology of the University Hospital of Cologne.

Prof. Dr. Reinhard Büttner
Institut für Pathologie
Kerpener Str. 62
50937 Köln
Germany

Biobanking of ARPKD samples can take place in the modern, established biobanking facility of the Children's Hospital of the University in Hannover, Germany. Storage and electronic sample administration will be taken over by the staff of the facility.

Prof. Dr. Thomas Illig
Pädiatrisches Forschungszentrum
Medzinische Hochschule Hannover
Carl-Neuberg-Str. 1
30625 Hannover
Germany

ARPKD is currently considered a monogenetic disorder. However, the clinical heterogeneity cannot yet be explained by unidimensional genotype-phenotype correlations. In cooperation with our collaborators ARegPKD will therefore look for genetic modifiers of disease manifestation and progression by a Next Generation Sequencing (NGS) approach patient samples. The collaborators currently are:

Prof. Dr. Carsten Bergmann
Bioscientia Institut für Medizinische Diagnostik GmbH
Labor Ingelheim mit Zentrum für Humangenetik
Konrad-Adenauer-Straße 17
55218 Ingelheim
Germany

Prof. Dr. Klaus Zerres
Institut für Humangenetik
Uniklinik Aachen
Pauwelstraße 30
52074 Aachen
Germany

The data obtained will only be used for scientific reasons. There will be no overlap with commercial data obtained by Bioscentia. It is intended that rests of biosamples for genetic studies shall be returned to the biobank in Hannover.

3.5. Central organisation units

This section should be used to describe which departments or service providers will be performing the various tasks required. These activities are generally governed by separate contracts (e.g. sponsor contracts) and accompanying descriptions of the terms of reference of the tasks delegated.

Project management:	Principal Coordinating Investigator (PCI) at University Hospital of Cologne
Data management:	PCI at University Hospital of Cologne
Scientific advice:	Steering Committee

3.6. Investigators and study sites

This clinical study will be carried out as a multicenter open non-randomized registry study at ~90 international study sites. If necessary, further qualified study sites may be recruited to the study.

Regional coordinators will be named for groups of centers. In addition to the central study coordinators these regional coordinators can help the study sites with regulatory requirements (e.g. ethics committee) and are contact persons for potential problems of data acquisition or data entry.

A list of study sites involved, including information on the principal investigators and the corresponding regional coordinators will be kept and continuously updated. A list of the study with names of the principal investigators is given in Appendix 11.1.

Requirements for investigators and study sites

Investigators should have ample experience in the field of pediatric nephrology. As most Centers have been involved in previous either GPN- or ESCAPE-based studies these partners know the course of a web-based registry. Sites need to have access to the internet.

4. Study conduct

4.1. General aspects of study design

ARegPKD is an open, non randomized, observational registry study with an associated biobank and reference histology.

4.1.1. Time plan

Patients will be seen in their corresponding center during routine visits. After informed consent doctors will introduce the data into the web-based data base and will fill-in an initial questionnaire on clinical presentation etc. Initially this will be retrospectively done, but prospective recruitment will develop over the year. Patients will then be followed by a yearly follow-up questionnaire.

Data of some patients may have also been included in other comparable pediatric nephrology studies or trials, e.g. the 4C study (The Cardiovascular Comorbidity in Children with Chronic Kidney Disease Study). After explicit informed consent specific data points (e.g. date of birth, prenatal history, laboratory values on kidney function etc.) may be transferred from the corresponding database to the ARegPKD database. This will only affect data points that have already been obtained.

Table 1: Time plan of the registry study

Start registry study	1 August 2012

End of the clinical study

ARegPKD is a retro- and prospective registry study without a defined time limit.

4.2. Discussion of study design

ARegPKD will collect pseudonymized information from patients suffering from ARPKD. Web-based registry studies are an innovative, highly efficient and data protection-sensitive approach to collect information in rare disease conditions. Encompassing the majority of European countries and citizens, making use of dedicated, highly specialized pediatric nephrology units and embarking into innovative analytical approaches such as genome-wide sequencing combined with tissue expression studies, the ARegPKD consortium will take full advantage of the population size, the excellent organization of high-end health care and the biotechnological lead of the European Community as a whole.

4.3. Selection of study population

As a registry for a rare disease, ARegPKD will initially mainly affect patients suffering from autosomal recessive polycystic kidney disease (ARPKD). The estimated incidence of this disease is 1:20.000. Within the ARegPKD we estimate that there are at least 300-500 pediatric patients included into the registry who will initially benefit e.g. by access to chronic health care. All male and female, pediatric and adult ARPKD patients that are currently seen in the participating centres can be included. However, as ARPKD is mainly a pediatric disorder, most of the patients will be children.

4.3.1. Inclusion criteria

- Autosomal Recessive Polycystic Kidney Disease (ARPKD) of any age, diagnosed either
    - by histology
    - by molecular assessment
    - by clinical parameters according to the criteria established by Zerres et al. (1996, Acta Paediatr. 85:437-455).
- informed consent of patient and/or parents resp. legal representatives

4.3.2. Exclusion criteria

- Genetic proof of other cystic kidney disorders (e.g. Nephronophthisis, ADPKD)
- Histological proof of other cystic kidney disorder
- Clinical proof of other cystic kidney disorder

As ARegPKD aims to detect the full spectrum of clinical ARPKD variability in as many patients as possible, the following conditions are not considered to be exclusion criteria:

- Other underlying disorders
- Medical treatment
- Inclusion in other studies, clinical studies or registries.

4.4. Withdrawal of participants after registry start

The participation in the study is completely voluntary. Patients can withdraw their/their child's participation in the study at any time without specification of reasons. There will be no negative consequences concerning the medical attendance of the patient in the case of withdrawing. By request, all data collected for the study will be deleted or anonymized (meaning this data cannot be linked to the patient in any way) and all remaining samples will be destroyed unless there are storage obligations by the law, by statutes or by contracts. If patients/parents decide to quit the study they can decide whether to give their consent to the analysis of the data or samples already collected. The results attained up to this point will not be affected by the withdrawal of the consent.

4.5. Measures within ARegPKD

ARegPKD is an open, non-randomized, non-interventional, observational registry study. This means that the following measures will be taken within the frame of ARegPKD:

1.) Patients will be included in ARegPKD by entering disease-related data into a password-restricted secure web-based data-base, installed on a server of the University of Cologne. Patient data will be entered in a pseudonymous way. Name,

address or exact date of birth will not be entered. The name is replaced by an ID. The medical staff entering the patient data will enter the ID and the corresponding name into a separate list that will be stored in a safe place at the corresponding center. These lists will thus not be open e.g. to the study coordinators. In exceptional cases the regional coordinator or the coordinators of the study may help medical staff at site.

Some patients that are suitable for ARegPKD may have already been included in other pediatric nephrology studies like the 4C study (Cardiovascular Comorbidity in Children with Chronic Kidney Disease Study). For these patients selected data point that have already been obtained within the frame e.g. of the 4C study may, after informed consent, pseudonymously be imported from the corresponding study database into the ARegPKD database (e.g. age, height, selected laboratory values at defined timepoints etc.).

2.) Yearly follow-up questionnaires on disease-related data will be filled in by medical staff of the corresponding center.

3.) After informed consent blood and biopsy/tissue samples will be stored pseudonymously in a biobank at the Pediatric Research Center Hannover. Initial blood samples include e.g. serum, plasma and EDTA. Yearly follow-up blood samples (e.g. serum, plasma) shall be collected if possible. The blood samples will be available for basic and translational scientific projects (e.g. identification and establishment of biomarkers) as well as samples for genetic analysis with modern high-resolution and high-throughput methods. Biosamples will only be available for research linked to cystic kidney diseases in case of approval of a written application by the Steering Committee. They must not be used for other purposes. Pseudonymization must not be broken for such projects. A vote of a responsible Ethics Committee has to be included in the written application. Potentially remaining biosamples have to be sent back to the biobank in Hannover by the corresponding scientist after finalization of the scientific analysis. Alternatively, biosamples have to be destroyed by the scientist. Scientists will also have to ensure that domestic and foreign supervisory bodies (e.g. for data protection), and the competent federal authorities have the right to review study documentation at any time.

If obtained genetic data requires genetic counselling of patients and families, this counselling shall be performed by persons, that are formally qualified according to the corresponding national or federal regulations.

Figure 1 shows a flow sheet of ARegPKD for the first years including the collection of biosamples.

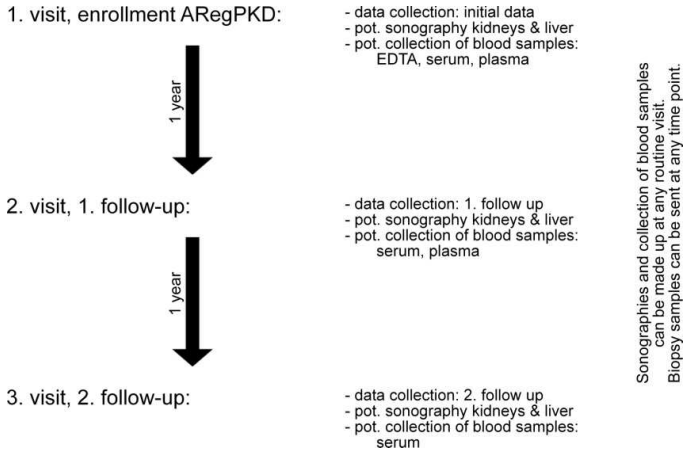

Figure 1: ARegPKD flow sheet for the first years

4.) Reference histology of biopsy samples is offered to patients. For reference histology participating centers can send biopsy samples to the Institute of Pathology of the University Hospital of Cologne. Work-up and evaluation will take place in Cologne. Histological samples will be scanned by a Mirax (Zeiss) slide scanner and uploaded to a central server connected to a web-based virtual histology discussion platform. This will save and store all histological samples in a pseudonymous fashion and make them available for discussion and inspection for all members of the ARegPKD. Samples will be stored for at least 10 years.

No study treatment will be given. Previous medication may be continued as considered appropriate by the responsible centre.

4.6. Data quality assurance

4.6.1. Data management

Well-established methods will be used to achieve the specific goals of ARegPKD. Via the participating centers of the German Pediatric Nephrology association (GPN) and the European Study Consortium for Chronic Kidney Disorders Affecting Pediatric Patients (ESCAPE Network) we recruit patients suffering from autosomal recessive polycystic kidney disase (ARPKD). After informed consent patient data will pseudonymously be entered into a web-based database. Data protection will be secured by use of SSL-connections and password restriction of the webpage.

To minimize the risks that data quality might suffer from incomplete or erroneous data entries in the web-based data base, the online forms will require mandatory inclusion of key variables, and include automated entry checks using predefined plausibility ranges. By these precautions the risk of data entry errors will be minimized. Data entries will also be reviewed by a pediatric nephrologist in random checks and during regular interims analysis. Queries will be sent to the local investigators in cases of implausibility or doubt. In case of major problems with accomplishing regular local data entries, the associated partner in charge will provide support by sending staff to educate local investigators or take over data entry tasks.

4.6.2. Archiving

All important study documents will be archived for at least 10 years in accordance with §13 Sec. 10 of the GCP Regulations. The pseudonymized biomsamples will be stored in the Biobank of the Pediatric Research Center of the Hannover Medical School. As ARPKD is a rare disease and this biorepository will represent a unique tool to study this disorder these samples will be stored without time limit.

5. Ethical and regulatory aspects

5.1. Independent ethics committee

The registry study project has been revised and the PCI has been advised by the Ethics Committee of the University Hospital of Cologne.

In each study site, it is the responsibility of the local investigator to ascertain whether a local Ethics committee needs to be informed or involved and whether a vote by this Ethics committee is required.

5.2. Ethical basis for the clinical study

The present study protocol and any amendments were and will be prepared in accordance with the Declaration of Helsinki in the version of October 2008 (Seoul, South Corea).

5.2.1. Legislation and guidelines used for preparation

As far as applicable the present registry study will be conducted in accordance with the published principles of the guidelines for Good Clinical Practice (ICH-GCP). These principles cover, amongst other aspects, ethics committee procedures, the obtaining of informed consent from registry study subjects, adherence to the study protocol, administrative documentation, data collection and registry study subjects' medical records (source documents). All investigators and other staff directly concerned with the study will be informed that domestic and foreign supervisory bodies and the competent federal authorities have the right to review registry study documentation and the study subjects' medical records at any time.

5.3. Obtaining informed consent from study subjects

Registry study subjects may not be enrolled into the present registry study unless they and/or their parents/guardians have consented to take part in it after having been informed verbally

and in writing in comprehensible language of the nature, scope and possible consequences by a study investigator. Together with the consent to take part in the registry study, the subject must also agree to the competent supervisory or federal authorities having access to the data recorded within the framework of the study. The subject will be informed of the potential benefit and possible side effects of the registry study, and of the need and reasons to conduct it. It must be clear to study subjects that he or she can withdraw his or her consent at any time without giving reasons and without jeopardizing his/her further course of treatment.

The originally signed consent form is archived at the participating center. Registry study subjects receive copies of the written information sheet, and the signed informed consent form.

The informed consent has to be renewed when patients come of age.

The patient information sheet, and the informed consent form handed out to the study subject must be submitted for revision to the ethics committee before use.

5.4. Data protection

The provisions of data protection legislation will be observed. It is assured by the sponsor that all investigational materials and data will be pseudonymised in accordance with data protection legislation before scientific processing. Data protection will also be secured by use of SSL-connections and password restriction of the webpage. Patient data will be saved on a server of the University of Cologne and will thus be subject to regular periodic maintenance. Patient data will be entered in a pseudonymous way. Name, address or exact date of birth will not be entered. The name is replaced by an ID. The medical staff entering the patient data will enter the ID and the corresponding name into a separate list that will be stored in a safe place at the corresponding center. These lists will thus not be open e.g. to the study coordinators. In exceptional cases the regional coordinator or the coordinators of the study may help medical staff at site.

The participating centers will be able to review the data of patients from their individual center. Modifications of entered data will only be possible in exceptional cases and only after

contact of the study coordinators. The patients will only be able to review data via the medical staff of his corresponding center. There will be no direct access for patients. The participating centers will not be able to review data from other centers.

Subjects will be informed that their pseudonymised data will be passed on in accordance with provisions for documentation and notification pursuant to § 12 and § 13 of the GCP Regulations to the recipients described there. Subjects who do not agree that the information may be passed on in this way will not be enrolled into the study.

6. Statistical methods and sample size calculation

6.1. Statistical and analytical plan

ARegPKD will collaborate with a statistician with great experience in the field of registries and clinical studies in pediatric nephrology.

Statistical analysis will mainly focus on description including calculation of relative and absolute frequencies for binary/ categorical variables and for continuous variables calculation of mean, standard deviation, median, interquartile range, minimum and maximum.

Inferential analyses regarding previously mentioned research questions will be planned based on first results of intermediate analyses and predefined in detail in a statistical analysis plan (SAP).

Further longitudinal data regarding outcomes of markers of renal and hepatic function, overall survival and e.g. kidney size will be analyzed using appropriate statistical methods such as mixed modeling.

In case of missing data appropriate methods (e.g. multiple imputation) will be used to handle them. Furthermore the aspect of multiple testing will be considered.

Potential sources of bias will be examined and considered in the analyses.

7. Use of findings and publication

7.1. Publication

It is planned to publish the study results, in mutual agreement with the PCI, in a scientific journal and at German or international congresses. Publication of the results of the study as a whole is intended. Any publication will take account of the ‘Uniform requirements for manuscripts submitted to biomedical journals (International Committee of Medical Journal Editors’ (ICMJE) [JAMA 1997;277:927-34]).

Any published data will observe data protection legislation covering the study subject and investigators. Success rates or individual findings at individual study sites are known only to the sponsor.

8. Amendments to the study protocol

In the interests of a consistent and valid data analysis, changes to the provisions of this study protocol are not planned. In exceptional cases, however, changes may be made to the study protocol. Such changes can only be made if agreed by the steering committee. Any changes to the study procedures must be made in writing and must be documented with reasons and signed by all Authors of the original study protocol.

Amendments made in accordance with § 10 Secs. 1 and 4 GCP Regulations that require approval are submitted to the ethics committee and will not be implemented until reviewed. Exceptions to this are amendments made to avoid immediate dangers.

9. Appendices

9.1. Study sites and principle investigators

Hospital	Department 1	Department 2	Street	Postal Code	City	Country	Principal Investigator	Regional coordinator
Medical University Innsbruck	Department of Pediatrics I		Anichstrasse 35	A-6020	Innsbruck	Austria	Dr. Gérard Cortina	Köln
University Children's Hospital	Pediatric Nephrology		Währinger Gürtel 18-20	1090	Vienna	Austria	Dr. Klaus Arbeiter	Köln
UZ Gent	Pediatric Nephrology		De Pintelaan 185	9000	Gent	Belgium	Prof. Johan Vande Walle	Lyon
University Medical Center	Division of Pediatric Nephrology		Patriotske lige 81	71000	Sarajevo	Bosnia and Herzegovina	Dr. Admir Hadzimuratovic	Vilnius
Curitiba					Curitiba	Brazil	Dr. Lucymary Sylvestre	Köln
Hospital Luis Calvo Mackenna-Facultad de Chile	Unidad de Nefrología Infantil		Av. Antonio Varas 360	7500539	Santiago de Chile	Chile	Dr. Marta Azocar	Köln
Roberto del Rio Children Hospital					Santiago de Chile	Chile	Dr. Lily Quiroz	Köln
Hospital Pablo Tobon Uribe			Calle 78 B No. 69-240		Medellin, Antioquia	Colombia	Dr. Lina Maria Serna Higuita	Köln
University Hospital Motol	Pediatrics		V uvalu 84	15006	Prague	Cseh Republic	Dr. Jiri Dusek	Vilnius
Kasr Al Ainy School of Medicine	Center of Pediatric Nephrology and Transplantation	Cariro University Children´s Hospital	99 El-Manial Street	11451	Cairo	Egypt	Neeven A. Soliman	Köln
SORARE Service de Pédiatrie	Centre de référence maladies rénales rares du Sud-Ouest (SORARE)	Service de Pédiatrie	CHU de Bordeaux	33076	Bordeaux	France	Dr. Jérôme Harambat	Lyon
Hôpital Femme	Service de	Centre de		69677	Lyon	France	Dr. Bruno Ranchin	Lyon

Mère Enfant & Université de Lyon	Pédiatrie & Inserm U820	Référence des Maladies Rénales Rares						
Hôpital de Hautepierre	Pole Médico-Chirurgical de Pédiatrie	Pédiatrie 1	Avenue Molière	67098	Strasbourg	France	Prof. Michel Fischbach	Lyon
M. Iashvili Children Central Hospital			2/6 Lubliana Str.		Tbilisi	Georgia	Dr. Tinatin Davitaia	Vilnius
Charité Children's Hospital	Pediatric Nephrology		Augustenburger Platz 1	13353	Berlin	Germany	Prof. Uwe Querfeld Dr. Jutta Gellermann	Köln
University Children's Hospital	Pediatric Nephrology Immunology und Hypertensiology		Kerpener Straße 62	50937	Cologne	Germany	Prof. Dr. Bernd Hoppe	Köln
University Children's Hospital	Pediatric Nephrology		Loschgestr. 15	91054	Erlangen	Germany	Prof. Dr. W. Rascher	Köln
University Children's Hospital	Pediatric Nephrology		Hufelandstr. 55	45122	Essen	Germany	PD Dr. Rainer Büscher	Köln
Center for Pediatrics and Adolescent Medicine	Division of Pediatric Nephrology		Mathildenstraße 1	79106	Freiburg	Germany	Dr. Charlotte Gimpel	Köln
UKE	University Children's Hospital		Martinistr. 52	20246	Hamburg	Germany	Prof. Dr. Markus Kemper	Köln
Hannover Medical School	Pediatric Nephrology		Carl-Neuberg-Straße 1	30625	Hannover	Germany	Prof. Dr. Anette Melk PhD	Köln
Center for Pediatrics and Adolescent Medicine	Division of Pediatric Nephrology		Im Neuenheimer Feld 430	69120	Heidelberg	Germany	Prof. Franz Schaefer	Köln
Klinik für Kinder- und Jugendmedizin	Sektion Pädiatrische Nephrologie	KfH-Nierenzentrum für Kinder und Jugendliche	Kochstr. 2	7740	Jena	Germany	Dr. Michael Pohl	Köln
City Hospital St. Georg	Children's Dialysis Center		Delitzscher Str. 141	4129	Leipzig	Germany	Dr. Simone Wygoda	Köln

KfH Kidney Center for Children			Baldinger Straße	35043	Marburg	Germany	Prof. Dr. Günter Klaus	Köln
Klinikum Memmingen	Kindernephrologie	KfH Nierenzentrum für Kinder und Jugendliche	Bismarckstr. 23	87700	Memmingen	Germany	Dr. Tobias Hampel	Köln
University Hospital Munich	Dr. von Haunersches Kinderspital	Department of Pediatric Nephrology	Lindwurmstr. 4	80337	München	Germany	Prof. Lutz Weber	Köln
University Children's Hospital	Pediatric Nephrology		Waldeyer Str. 22	48149	Münster	Germany	Dr. B. Kranz	Köln
Children's Hospital	Pediatric Nephrology		Rembrandtstr. 16/17	18057	Rostock	Germany	Prof. Marianne Wigger	Köln
Children's Hospital Olgahospital			Bismarckstr. 8	70176	Stuttgart	Germany	PD. Dr. H. E. Leichter	Köln
Aristotle University	Hippokration General Hospital	1st Department of Pediatrics	Konstantinoupoleos 49	54642	Thessaloniki	Greece	Dr. Nikoleta Printza	Milano
Semmelweis University	1st Dept. of Pediatrics	Pediatric Nephrology	Bokay Janos Str. 53-54	1083	Budapest	Hungary	Dr. Peter Sallay	Vilnius
Isfahan University of Medical Science	Pediatric Nephrology Department	St. Al Zahra Hospital	Soffeh Street		Isfahan	Iran	Dr. Alaleh Gheissari	Köln
S. Orsola-Malpighi Hospital	Unit of Pediatric Nephrology and Dialysis		Via massarenti 11	40123	Bologna	Italy	Dr. Giovanni Montini	Milano
Istituto Giannina Gaslini	Nephrology		Largo G. Gaslini 5	16147	Genova	Italy	Dr. Antonella Trivelli	Milano
Fondazione OSP Maggiore Policlinico	Pediatric Nephrology and Dialysis		Via Commenda 9	20122	Milano	Italy	Dr. Sara Testa Dr. Gianluigi Ardissino	Milano
University of Padova	Dialysis and Transplantation	Department of Pediatrics	Via Gustiniani 3	35128	Padova	Italy	Dr. Luisa Murer Dr. Elisa Benetti	Milano
Fondazione IRCCS Policlinico San Matteo	Department of Pediatrics		P. le Golgi 19	27100	Pavia	Italy	Dr. Silvia Magni Manzoni	Milano
Bambino Gesu	Nephrourology		Piazza S. Onofrio 4	163	Rome	Italy	Dr. Stefano Picca Prof. Francesco Emma	Milano

University Clinical Centre of Cosova	Pediatric Clinic	Nephrology Department		10000	Prishtina	Kosovo	Dr. Valbona Nushi Stavileci	Milano
Notre Dame de Secours University Hospital Byblos	Pediatric Nephrology Unit				Byblos	Lebanon	Dr. Pauline Abou-Jaoudé	Köln
Rafic Hariri University Hospital	Pediatric Nephrology				Beirut	Lebanon	Dr. Bilal Aoun	Köln
Vilnius University	Children's Hospital		Santariskiu 4	8406	Vilnius	Lithuania	Prof. Augustina Jankauskiene	Vilnius
University of Bialystok	Department of Pediatric Nephrology		ul. Waszyngtona 17	15-546	Bialystok	Poland	Dr. Anna Wasilewska	Warsaw
Pediatrics and Oncology Center in Chorzow	Department of Pediatric Nephrology		Truchana 7	41-500	Chorzow	Poland	Dr. Ewa Gacka	Warsaw
Medical University	Dept. of Pediatric & Adolescent Nephrology		Debinki 7	80211	Gdansk	Poland	Prof. Aleksandra Zurowska	Warsaw
University Children's Hospital	Dialysis Unit		265 Wielicka	30-663	Krakow	Poland	Dr. Dorota Drozdz	Warsaw
Polish Mothers Memorial HospitalResearch Institute	Department of Paediatrics and Immunology	Nephrology Division		93-338	Lodz	Poland	Dr. Marcin Tkaczyk	Warsaw
Medical University Lublin	Pediatric Nephrology				Lublin	Poland	Dr. Halina Borzecka	Warsaw
Poznan University of Medical Sciences	Department of Nephrology and Dialysis		ul. Szpitalna 27/33	60-572	Poznan	Poland	Dr. Magdalena Silska	Warsaw
Clinic of Pediatrics	Pomeranian Acad.of Medicine		ul. Unii Lubelskiej	71-344	Szczecin	Poland	Dr. Tomasz Urasinski	Warsaw
Wojewodzki Szpital Dzieciecy	Oddzial Pediatrii	Nefrologii ze Stacja Dializ	Konstytucji 3 Maja 42	87-100	Torun	Poland	Dr. Agnieszka Firszt-Adamczyk	Warsaw
Children's Memorial Health Institute	Nephrology	Kidney Transplantation and Hypertension	Al. Dzieci Polskich 20	04-730	Warsaw	Poland	Prof. Mieczyslaw Litwin	Warsaw
Centrum Zdrowia Dziecka	Department of Pediatric				Warsaw	Poland	Dr. Joanna Ksiazek	Warsaw

	Nephrology							
University of Warsaw	Department of Pediatric Nephrology		Marszalkowska 24	00-576	Warsaw	Poland	Dr. Elzbieta Kuzma-Mroczkowska	Warsaw
Medical University Wroclaw	Department of Pediatric Nephrology		ul. M. Sklodowskiej-Curie 50/52	50-369	Wroclaw	Poland	Dr. Anna Medynska	Warsaw
Medical University of Silesia in Katowice	Department and Clinics of Pediatrics	Dialysis Division for Children	ul. 3 Maja 13/15	41-800	Zabrze	Poland	Dr. Maria Szczepanska	Warsaw
Hospital Sao Joao	Pediatrics	Alameda Professor Hernani Warsaw Monteiro		4200	Porto	Portugal	Prof. Caldas Afonso	Lyon
University Children's Hospital			Tirsova 10	11000	Belgrade	Serbia	Prof. Amira Peco-Antic	Vilnius
Institute of Mother and Child Healthcare of Serbia	Department of Nephrology		8 R Dakica St	11070	Belgrade	Serbia	Dr. Radovan Bogdanovic	Vilnius
Karolinska University Hospital	Division of Pediatrics			14186	Stockholm	Sweden	Dr. Rafael T. Krmar	Vilnius
Inselspital	Children's Hospital			3010	Bern	Switzerland	Dr. Giacomo Simonetti	Köln
University Children's Hospital	Nephrology Unit		Steinwiesstr. 75	8032	Zürich	Switzerland	Dr. Guido Laube	Köln
Kidney Hospital of Damascus	Department of Pediatric Nephrology		P.O. Box: 8298		Damascus	Syria	Dr. Bassam Saeed	Köln
Cukurova UniversitesiTip Fakultesi	Cocuk Nefrolojisi Bilim Dali	Balcali		1330	Adana	Turkey	Prof. Ali Anarat	Ankara
Ankara University Faculty of Medicine	Pediatric Nephrology			6100	Ankara	Turkey	Dr. Fatos Yalcinkaya	Ankara
Akdeniz University					Antalya	Turkey	Prof. Sema Akman	Ankara
Ankara Research and Training Hospital	Department of Pediatric Nephrology		38. Cadde	5/20	Cukurambur, Ankara	Turkey	Dr. Banu Acar	Ankara
Baskent University					Ankara	Turkey	Prof. Dr. Esra	Ankara

Faculty of Medicine							Baskin	
Diskapi Childrens Hospital					Ankara	Turkey	Assoc. Prof. Dr. Nilgun Cakar	Ankara
Gazi University Hospital	Pediatric Nephrology	Besevler		6500	Ankara	Turkey	Prof. Oguz Soylemezoglu	Ankara
Hacettepe Medical Faculty	Pediatric Nephrology	Sihhiye		6100	Ankara	Turkey	Prof. Ali Duzova Prof. Fatih Ozaltin	Ankara
Sami Ulus Childrens Hospital					Ankara	Turkey	Assoc. Prof. Dr. Gulay Demircin Dr. Ozlem Erdogan	Ankara
Dortcelik Children's Hospital					Bursa	Turkey	Dr. Hakan Erdogan	Ankara
Uludag University					Bursa	Turkey	Prof. Dr. Osman Donmez	Ankara
University of Gaziantep	Department of Pediatric Nephrology				Gaziantep	Turkey	Prof. Dr. Ayse Balat	Ankara
Bakirkoy Children Hospital	Pediatric Nephrology				Istanbul	Turkey	Dr. Nur Canpolat	Ankara
Cerrahpasa Tip Fakultesi	Çocuk Nefrolojisi	Kocamustafa pasa		34303	Istanbul	Turkey	Prof. Salim Caliskan	Ankara
Goztepe Educational and Research Hospital	Pediatric Nephrology				Istanbul	Turkey	Dr. Cengiz Candan	Ankara
Haseki Educational and Research Hospital					Istanbul	Turkey	Dr. Mahmut Civilibal	Ankara
Istanbul Medical Faculty	Dept. of Pediatric Nephrology			34360	Istanbul	Turkey	Prof. Sevinc Emre	Ankara
Marmara University Medical Faculty					Istanbul	Turkey	Dr. Harika Alpay	Ankara
Sisli Educational and Research Hospital	Pediatric Nephrology				Istanbul	Turkey	Dr. Gul Ozcelik	Ankara
Ege University	Faculty of Medicine	Pediatric Nephrology		35100	Bornova Izmir	Turkey	Prof. Dr. Sevgi Mir	Ankara

Tepecik Training and Research Hospital					Izmir	Turkey	Dr. Onder Yavascan	Ankara
Gulhane Military Medical Academy						Turkey	Dr. Faysal Gok	Ankara
Gulhane Military Academy of Medicine	Pediatric Nephrology Unite		Ilkahim Mh Dayanisma Sk. 27/18		Dikmen/Ankara	Turkey	Dr. Onur Sakallioglu	Ankara
Inonu University Medial School	Department of Pediatric Nephrology				Malatya	Turkey	Dr. Yilmaz Tabel	Ankara
Celal Bayar University	Pediatric Nephrology Department				Manisa	Turkey	Assoc. Prof. Pelin Ertan Dr. Ipek Akil	Ankara
Sanliurfa Children's Hospital	Pediatric Nephrology				Sanliurfa	Turkey	Dr. Ebru Yilmaz	Ankara
Ondokuz Mayis University	Faculty of Medicine	Department of Pediatric Nephrology			Samsun	Turkey	Prof. Ozan Özkaya	Ankara
Karadeniz Technical University	Faculty of Medicine	Pediatric Nephrology Department		61187	Trabzon	Turkey	Prof. Mukaddes Kalyoncu	Ankara
Al Qassimi Hospital	Department of Pediatric Nephrology				Sharjah	United Arab Emirates	Dr. Entesar Alhammadi	Köln
Great Ormond Street Hospital	Nephrology		Great Ormond Street	WC1N 3JH	London	United Kingdom	Dr. Rukshana Shroff Prof. Robert Kleta	Köln
Children´s Hospital New Orleans	LSU Health Sciences Center			70118	New Orleans, Louisiana	USA	Dr. Diego H. Aviles	Köln
Mayo Clinic	Division of Nephrology and Hypertension			MN55905	Rochester, Minnesota	USA	Dr. Marie Hogan	Köln

9.2. Protocol Agreement Form

9.3. Current Steering Committee

Dr. Max Christoph Liebau	University Children's Hospital	Pediatric Nephrology Immunology und Hypertensiology	Kerpener Straße 62	50937	Cologne	Germany
Dr. Markus Feldkötter	University Children's Hospital	Pediatric Nephrology Immunology und Hypertensiology	Kerpener Straße 62	50937	Cologne	Germany
Prof. Dr. Jörg Dötsch	University Children's Hospital	Pediatric Nephrology Immunology und Hypertensiology	Kerpener Straße 62	50937	Cologne	Germany
Prof. Dr. Bernd Hoppe	University Children's Hospital	Pediatric Nephrology Immunology und Hypertensiology	Kerpener Straße 62	50937	Cologne	Germany
Prof. Dr. Franz Schaefer	Center for Pediatrics and Adolescent Medicine	Division of Pediatric Nephrology	Im Neuenheimer Feld 430	69120	Heidelberg	Germany
Prof. Dr. Reinhard Büttner	University Hospital of Cologne	Institute of Pathology	Kerpener Straße 62	50937	Cologne	Germany
Prof. Dr. Carsten Bergmann	Universitaetsklinikum Freiburg/ Bioscientia Institut für Medizinische Diagnostik GmbH		Hugstetter Straße 55/Konrad-Adenauer-Straße 17	79106/ 55281	Freiburg/ Ingelheim	Germany
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Prof. Dr. Martin Konrad	University Children's Hospital	Pediatric Nephrology	Waldeyer Str. 22	48149	Münster	Germany
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Dr. Mieczyslaw Litwin	Children's Memorial Health Institute	Nephrology/ Kidney Transplantation and Hypertension	Al. Dzieci Polskich 20	04-730	Warsaw	Poland
Dr. Sara Testa	Fondazione OSP Maggiore Policlinico	Pediatric Nephrology and Dialysis	Via Commenda 9	20122	Milano	Italy
Prof. Dr. Augustina Jankauskiene	Vilnius University	Children's Hospital	Santariskiu 4	8406	Vilnius	Lithuania
Dr. Bruno Ranchin	Hôpital Femme Mère Enfant & Université de Lyon	Service de Pédiatrie & Inserm U820	Centre de Référence des Maladies Rénales Rares	69677	Lyon	France
Prof. Dr. Ali Duzova	Hacettepe Medical Faculty	Pediatric Nephrology/ Sihhiye		6100	Ankara	Turkey

9.4. Study laboratories and other technical resources

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