CLINICAL STUDY PROTOCOL

INTENT Study

EudraCT No.: 2014-001991-76

Version 6.0/20181205

Initial treatment of idiopathic nephrotic syndrome in children with mycophenolate mofetil *vs.* prednisone: A randomized, controlled, multicenter study (INTENT Study)

Investigational drugs:	Mycophenolate mofetil
Reference drug:	Prednisone
Indication:	Idiopathic nephrotic syndrome in children
Phase of study:	Phase III
Registration number:	DRKS 00006547

Sponsor:

Ruprecht-Karls-University Heidelberg,
Medical Faculty represented by
Universitätsklinikum Heidelberg and its
Commercial Director

Irmtraut Gürkan

Im Neuenheimer Feld 672

69120 Heidelberg

Phone: 06221 56 7002

Fax: 06221 56 4888

E-Mail:
Irmtraut.Guerkan@med.uni-heidelberg.de

Principal Investigator/Coordinating Investigator (Leiter der klinischen Prüfung*):

University Hospital Heidelberg

Department of Pediatrics I,
University Children's Hospital Heidelberg

Prof. Dr. med. Burkhard Tönshoff

Im Neuenheimer Feld 430

69120 Heidelberg

Phone 06221 56 8401

Fax 06221 56 4203

E-Mail:
burkhard.toenshoff@med.uni-heidelberg.de

* According to § 40 German Drug Law (AMG)

GCP Statement: The study will be conducted in compliance with Good Clinical Practices (ICH-GCP) and the Declaration of Helsinki, and in accordance with applicable legal and regulatory requirements, including archiving of essential documents.

Sponsored by BMBF (Bundesministerium für Bildung und Forschung), Förderkennzeichen: 01KG1301

Administrative Structure

Clinical Project Management

University Hospital Köln
Department of Pediatrics
University Children's Hospital Köln

Dr. med. Marcus R. Benz
Dr. med. Rasmus Ehren
Prof. Dr. med. Lutz T. Weber

Kerpenerstrasse 62
50937 Köln
Phone: 0221 478 4319
Mobil: 01520 9032703 or 01520 9032699
Fax: 0221 478 5835
E-Mail: Lutz.Weber@uk-koeln.de
Marcus.Benz@uk-koeln.de
Rasmus.Ehren@uk-koeln.de

Biometrics

University of Heidelberg
Institute of Medical Biometry and Informatics
Marsilius-Arkaden – Turm West

Anja Sander, M.Sc.

Im Neuenheimer Feld 130.3
69120 Heidelberg
Phone: 06221 56 5859
Fax: 06221 56 4195
E-Mail: sander@imbi.uni-heidelberg.de

Data Management

University of Heidelberg
Institute of Medical Biometry and Informatics
Marsilius-Arkaden – Turm West

Jacek Stermann
Im Neuenheimer Feld 130.3
69120 Heidelberg
Phone: 06221 56 37235
Fax: 06221 56 4195
E-Mail: stermann@imbi.uni-heidelberg.de

Pharmacovigilance

KKS (Coordination Center for Clinical Trials) **Heidelberg**
am Universitätsklinikum Heidelberg
Marsilius-Arkaden – Turm West

Organisation: Dr. med. Jacek Hajda
Im Neuenheimer Feld 130.3
69120 Heidelberg
Phone: 06621 56 34507
Fax: 06221 56 33508
E-Mail: Jacek.Hajda@med.uni-heidelberg.de

Monitoring

KKS (Coordination Center for Clinical Trials) **Heidelberg**
am Universitätsklinikum Heidelberg
Marsilius-Arkaden – Turm West

Gabriele Kuhn
Im Neuenheimer Feld 130.3

69120 Heidelberg, Germany

Organisational Project Management

KKS (Coordination Center for Clinical Trials) **Heidelberg**
am Universitätsklinikum Heidelberg
Marsilius-Arkaden – Turm West

Dr. rer. nat. Marion Nonn-Anastasiadis
Im Neuenheimer Feld 130.3

69120 Heidelberg, Germany

Phone: 06221 56 36647
Fax: 06221 56 33508
E-Mail: Gabriele.Kuhn@med.uni-heidelberg.de

Phone: 06221 56 38218
Fax: 06221 56 39039
E-Mail: Marion.Nonn-Anastasiadis@med.uni-heidelberg.de

The following committees are set up to monitor certain aspects of the study: data and safety monitoring board (DSMB) and Steering Committee (SC). The working methods of these committees are based on the guideline EMEA/CHMP/EWP/5872/03 Corr.

Data and safety monitoring board (DSMB)

Ensuring the ethical conduct of the study and protecting the rights and welfare of the patients are the tasks of the DSMB.

A Data and Safety Monitoring Board made up of independent experts will be set up. It consists of two physicians and one statistician, who are not involved in the conduct of the study. The DSMB will held telephone conferences on a regular basis every 6 months. The task of the DSMB is to oversee the safety of the study subjects in the clinical study by periodically assessing the safety of the study therapy, the recruitment and data quality, and to monitor the integrity and validity of the data collected and the conduct of the clinical study.

Throughout this process of surveillance, the DSMB provides the sponsor with recommendations with regard to continuing the study (e.g. termination or modification) based on the data collected. The data necessary for the DSMB to fulfill this function are provided by the sponsor as determined by the DSMB. Amongst other information, these must include listings providing information on serious adverse events and further variables that the DSMB considers necessary.

Data Safety Monitoring Board (DSMB)		
1	Prof. Dr. Michael Fischereder	Head of Nephrology, Department of Internal Medicine, University of Munich (LMU), Germany
2	Prof. Dr. Nicholas Webb	Consultant pediatric nephrologists, Royal Manchester Children's Hospital, Manchester, UK
3	Dr. E. Graf, Statistician	Clinical Trials Unit and Center for Medical Biometry and Medical Informatics, Medical Center - University of Freiburg, Freiburg, Germany

Steering Committee (SC)

The steering committee comprises the coordinating investigator, the clinical project management, and his supporting co-investigators (if possible, clinical experts not directly involved in the clinical study) and the responsible biometrician. The steering committee is responsible for the scientific integrity of the study protocol, the quality of the study conduct as well as for the quality of the final study report. The Steering committee will decide on the recommendations made by the DSMB.

Members of the Steering Committee:

University Hospital Köln
Department of Pediatrics
University Children's Hospital Köln

Prof. Dr. Med. Jörg Dötsch

University Hospital Heidelberg
Department of Pediatrics I,
University Children's Hospital Heidelberg

Prof. Dr. med. Burkhard Tönshoff

PD Dr. med. Lutz T. Weber
Dr. med. Marcus R. Benz
Dr. med. Rasmus Ehren
Kerpenerstrasse 62
50937 Köln
Phone: 0221 478 86081
Fax: 0221 478 87475
E-Mail: Lutz.Weber@uk-koeln.de
Marcus.Benz@uk-koeln.de
Rasmus.Ehren@uk-koeln.de

PD Dr. med. Britta Höcker
Dr. med. Alexander Fichtner
Im Neuenheimer Feld 430
69120 Heidelberg
Phone: 06221 56 8401
Fax: 06221 56 4203
E-Mail: burkhard.toenshoff@med.uni-heidelberg.de
britta.hoecker@med.uni-heidelberg.de
alexander.fichtner@med.uni-heidelberg.de

University Hospital Berlin Charité
Department of Pediatrics
University Children's Hospital Berlin
Prof. Dr. med. Uwe Querfeld
Dr. med. Jutta Gellermann
Augustenburger Platz 1
13353 Berlin
Phone: 030 450 516026
Fax: 030 450 516912
E-Mail: uwe.querfeld@charite.de
jutta.gellermann@charite.de

University Hospital Essen
Department of Pediatrics
University Children's Hospital Essen
Prof. Dr. med. Peter Hoyer
Hufelandstr. 55
45122 Essen
Phone: 0201 723 2810
Fax: 0201 723 5947
E-Mail: peter.hoyer@uk-essen.de

Asklepios Clinic North - Heidberg
Department of Pediatrics
Prof. Dr. med. Markus Kemper
Tangstedter Landstr. 400
22417 Hamburg
Phone: 040 1818-873351
Fax: 040 1818-873468
E-Mail: m.kemper@asklepios.com

University Hospital Hannover
Department of Pediatrics
University Children's Hospital Hannover
Prof. Dr. med. Dieter Haffner
Carl-Neuberg-Str. 1
30625 Hannover
Phone: 0511 532 3213
Fax: 0511 532 3911
E-Mail: Haffner.Dieter@mh-hannover.de

University Hospital Münster
Department of Pediatrics
University Children's Hospital Münster

University of Heidelberg
Institute of Medical Biometry and Informatics

Prof. Dr. med. Martin Konrad
Waldeyerstr. 22
48149 Münster
Phone: 0251 981 3331
Fax: 0251 981 3336
E-Mail: konradma@uni-muenster.de

Anja Sander, M.Sc.
Im Neuenheimer Feld 305
69120 Heidelberg
Phone: 06221 56 5859
Fax: 06221 56 4195
E-Mail: sander@imbi.uni-heidelberg.de

PARTICIPATING SITES
The INTENT study is a multicenter study with app. 45 participating sites planned.

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PROTOCOL SYNOPSIS

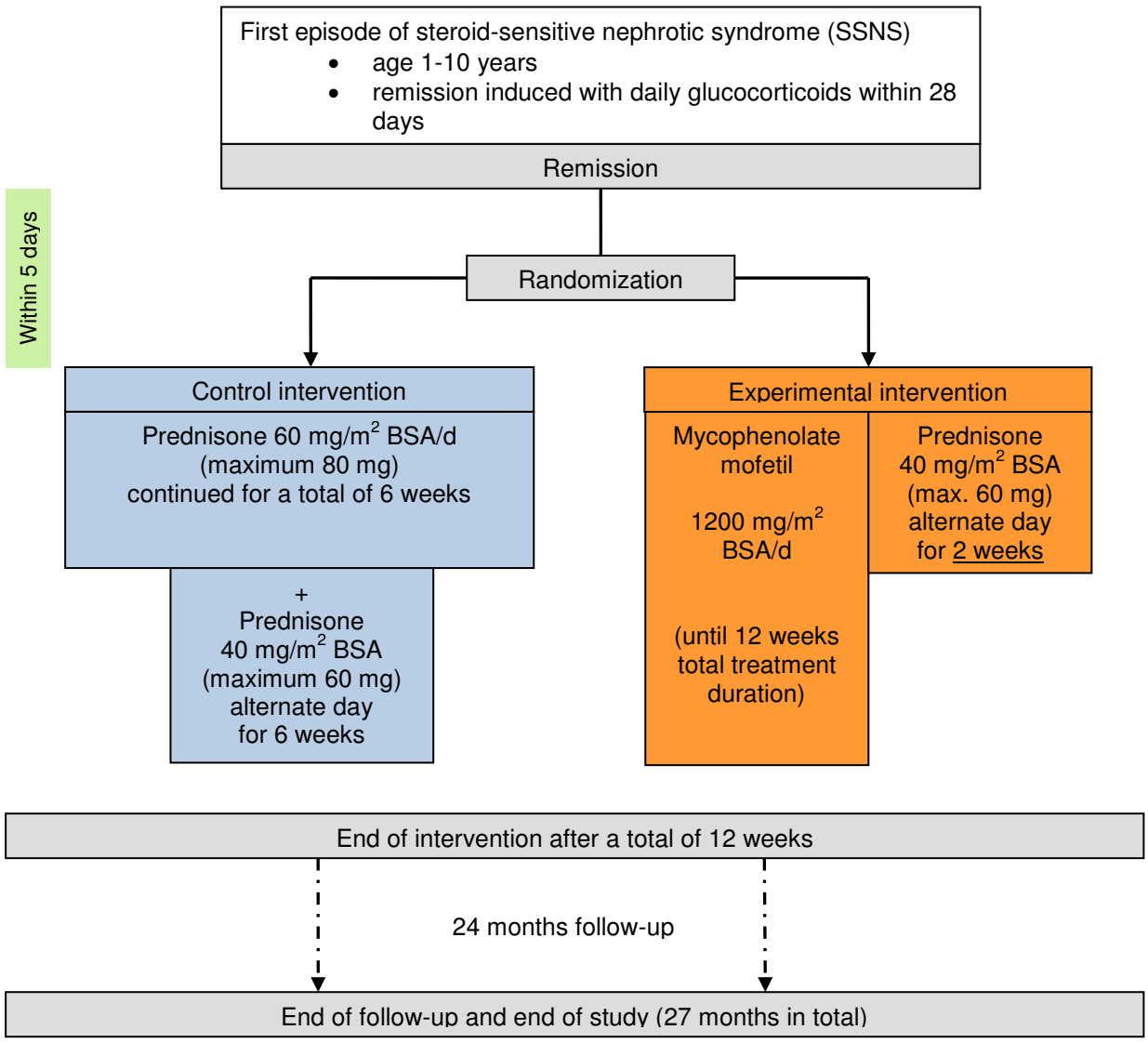
TITLE	Initial treatment of idiopathic nephrotic syndrome in children with mycophenolate mofetil *vs.* prednisone: A randomized, controlled, multicenter study
CLINICAL STUDY CODE	INTENT study
EUDRACT NO.	2014-001991-76
PROTOCOL VERSION	Version 5.0; 201600405
INDICATION	First episode of steroid-sensitive nephrotic syndrome (SSNS) in children in remission (N04.9) Nephrotic syndrome: MedDRA term 10029164 (version: 16.2, LLT)
OBJECTIVES	To demonstrate that mycophenolate mofetil as initial treatment is not inferior to standard treatment with prednisone related to relapse rate within 24 months **Primary efficacy endpoint:** Occurrence of treated relapse within 24 months after end of initial treatment (non-inferiority) **Key secondary endpoint(s):** • Course of the disease: Time from remission to first relapse; number of relapses; mean relapse rate per patient and year; incidence of frequent relapsers • Prednisone-associated toxicity: Cumulative prednisone dose (mg/m² BSA); body mass index (standard deviation score); striae; hypertrichosis; acne; arterial hypertension; disturbances of carbohydrate and lipid metabolism; growth failure; cataract; glaucoma; psychological disturbances • MMF-associated toxicity: diarrhea; blood cell count disturbances, infections
PHASE	III
INVESTIGATIONAL MEDICINAL PRODUCT(S)	INN: Mycophenolate mofetil (MMF) ATC-code: L04AA06 MMF is administered in liquid form (CellCept suspension®, Roche AG) Mycophenolate mofetil (MMF) 1200 mg/m^2 body surface area (BSA) per day, until a total initial treatment duration of 12 weeks is reached (induction of remission with prednisone + maintenance of remission with MMF (intervention).

	MMF is administered in conjunction with alternate day prednisone 40 mg/m^2 BSA for the first 2 weeks.
REFERENCE DRUG	INN: Prednisone ATC-code: H02AB07 Prednisone is administered as tablet Continuing the standard protocol for children with first episode of SSNS according to GPN guidelines: 60 mg prednisone/m^2 BSA per day for 6 weeks followed by alternate day prednisone 40 mg/m^2 BSA for another 6 weeks
STUDY DESIGN	Prospective, randomized, multicenter, controlled, open, parallel group study
STUDY POPULATION	Inclusion Criteria • First episode of steroid-sensitive nephrotic syndrome (SSNS) • In remission induced by daily glucocorticoids within 28 days • Male and female children aged ≥ 1 year and ≤ 10 years at beginning of study (typical age range of patients with SSNS) • Ability of the persons having care and custody of the child to understand character and individual consequences of clinical study • Written informed consent of the persons having care and custody of the child. Exclusion Criteria • Secondary nephrotic syndrome • estimated glomerular filtration rate (eGFR) <90 ml/min x 1.73 m^2 BSA • Ongoing treatment with systematically administered glucocorticoids or other immunosuppressive drugs at time of first episode of nephrotic syndrome • Hemoglobin concentration of ≤9 g/dL • Leucocyte count of ≤2.500/µl • Severe chronic gastrointestinal disease • History of hypersensitivity to mycophenolate mofetil or to any drug with similar chemical structure or to any excipient present in the pharmaceutical form of suspension of mycophenolate mofetil (CellCept suspension®) • Refusal of subject (please see also chapter 10.5) • Participation in other clinical studies or observation period of competing studies, respectively

SAMPLE SIZE	To be assessed for eligibility (n = 400) To be allocated to study (n = 340) To be analyzed (n = 272, according to per protocol)
STUDY DURATION	Total study duration: [78 months] Duration of clinical phase: [63 months] Beginning of the preparation phase: [03/2014] FSI (first subject in): [01/2015] LSI (last subject in): [01/2018] LSO (last subject out): [04/2020] DBL (database lock): [07/2020] Statistical analyses completed: [08/2020] Study report completed: [04/2021]
STATISTICAL ANALYSIS	Efficacy/test accuracy: Non-inferiority analysis to compare the relapse rates using the Farrington-Manning test. Description of the primary efficacy/test accuracy analysis and population: Confirmatory analysis will be based on the per-protocol population as well as the intention to treat population. Secondary endpoints: Descriptive p-values of the corresponding statistical tests comparing the treatment groups and associated 95% confidence intervals will be given. Safety: Rates of adverse and serious adverse events will be calculated with 95% confidence intervals for treatment group comparisons.
NUMBER OF CENTRES	app. 45 centers planned
FINANCING	BMBF (Bundesministerium für Bildung und Forschung), Förderkennzeichen: 01KG1301

FLOW CHART/ STUDY SCHEDULE

1. Study flow



alternate day = every second day

ABBREVIATIONS

AE	Adverse Event
AMG	German Drug Law (Deutsches Arzneimittelgesetz)
ATC	Anatomical-Therapeutic-Chemical Code, part of WHO-DRL (Drug Reference List)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices, Germany)
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CRF	Case Report Form
DBL	Data Base Lock
DFG	Deutsche Forschungsgemeinschaft
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
Echo	Echocardiogram
eGFR	estimated glomerular filtration rate
FD	Financial Disclosure
FPI	First Patient In
GCP	Good Clinical Practice
GCP-V	Good Clinical Practice Ordinance (GCP-Verordnung)
GPN	German Society for Pediatric Nephrology
IB	Investigator´s Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH GCP	ICH harmonized tripartite guideline on GCP
IMBI	Institute of Medical Biometry and Informatics
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
INN	International Nonproprietary Name
ISF	Investigator Site File
ITT	Intention-to-Treat
KKS	Coordination Center for Clinical Studies (Koordinierungszentrum für Klinische Studien)
LKP	Coordinating Investigator according to AMG (Leiter der klinischen Prüfung)
LPO	Last Patient Out
LSI	Last Subject In
LSO	Last Subject Out
MedDRA	Medical Dictionary for Regulatory Activities
MMF	Mycophenolate mofetil
PI	Principal Investigator

PP	Per-Protocol
Q	Quarter (time span)
SAE	Serious Adverse Event
SC	Steering Committee
SmPC	Summary of Product Characteristics
SSNS	Steroid-sensitive nephrotic syndrome
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDM MPA	therapeutic drug monitoring of mycophenolic acid
TMF	Trial Master File
WHO	World Health Organization

1 INTRODUCTION

1.1 Scientific Background

Idiopathic nephrotic syndrome in childhood

Clinical course and epidemiology

Idiopathic nephrotic syndrome in childhood, defined as the combination of heavy proteinuria (>40 mg/m^2 body surface area (BSA) per h) and hypalbuminemia (<25 g/L), accompanied by edema and hyperlipidemia, is a rare, relapsing disease with an incidence of 1.8 per 100.000 children below 16 years of age in Germany (ESPED registry 2005-2006), resulting in an annual rate of 200-250 patients [1]. The classification according to the four following categories is important for the clinical diagnostics, treatment and prognosis of the nephrotic syndrome in childhood: etiology, age at onset, histology, response to glucocorticoids. The primary idiopathic nephrotic syndrome with a typical onset of age (1-10 years of age) should be differentiated from patients with secondary causes or patients with age of onset younger than one year (congenital and infantile forms) or elder than 10 years of age. Approximately 80% of the children with idiopathic nephrotic syndrome have minimal change disease in renal biopsy, approximately 7% focal segmental glomerulosclerosis. The most important prognostic factor is steroid-sensitivity occurring in over 90% of the patients.

Treatment

The treatment of the first episode implies two aspects: (i) induction of remission, (ii) sustainment of remission. The German Society for Pediatric Nephrology (GPN), formerly known as Arbeitsgemeinschaft für pädiatrische Nephrologie (APN), formed the foundation for the standard of care of children with the nephrotic syndrome [2-7]. Thus, the recent guideline for the initial treatment of the first episode of a nephrotic syndrome recommends in detail: 60 mg prednisone/m^2 BSA per day for 6 weeks followed by alternate day prednisone 40 mg/m^2 BSA for another 6 weeks [8]. In case of steroid-sensitivity remission usually occurs within 7-14 days of treatment; the over-all duration of initial prednisone treatment is 12 weeks in order to sustain remission. This regimen has a relapse rate of 51% within 24 months after initial prednisone therapy, and a rate of frequent relapsers of 29% is expected.

Side effects of treatment

Even though being effective, this treatment is associated with pronounced glucocorticoid-associated toxicity due to high-dose prednisone administration over a prolonged period of time. The major side effects, which have been shown consistently in previous studies [3,4,9], comprise obesity, striae, hypertrichosis, cataract, glaucoma, arterial hypertension, psychological disturbances, growth failure, disturbances in carbohydrate and lipid metabolism, osteopenia, and avascular bone necrosis. Not all of these side effects are fully reversible after cessation of steroid therapy. In one study for example, excess weight gain during initial steroid therapy persisted in a significant subset (47%) of patients following cessation of glucocorticoid therapy [10]. Excess weight following cessation of glucocorticoid therapy was associated with hyperlipidemia, which might enhance the cardiovascular risk of these patients in the long-run [11]. Furthermore, a recent GPN study on the initial treatment of the nephrotic syndrome revealed no advantage of an intensified immunosuppressive protocol in terms of occurrence of relapses during a follow-up of 24 months [5]. Other studies have shown that higher exposure to glucocorticoids in the initial therapy leads to more toxicity without a substantial gain of efficacy, which is prevention of future relapses [8,12].

Treatment of relapses

Relapses of idiopathic nephrotic syndrome in childhood are generally treated with glucocorticoids according to a standard regimen 60 mg prednisone/m^2 BSA per day until the urine is free of protein for three consecutive days followed by alternate day prednisone 40 mg/m^2 BSA for 4 weeks. Depending on the number of relapses this aggravates the side effects. In case of frequent relapses a glucocorticoid-free therapy (cyclosporine, mycophenolate mofetil) for sustaining remission has to be considered.

Role of mycophenolate mofetil in the treatment of nephrotic syndrome in childhood

Mycophenolate mofetil (MMF), the pro-drug of its active moiety mycophenolic acid (MPA), is a potent, selective and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), the key enzyme of *de novo* purine synthesis in activated lymphocytes. Mycophenolate mofetil is effective in sustaining remission in patients with frequently relapsing or glucocorticoid-dependent nephrotic syndrome. Analysis via the PubMed search engine using the key words “nephrotic syndrome” “children” “mycophenolate mofetil” AND “clinical trials” revealed 12 studies, 6 of them prospective, including one phase II Bayesian trial [13-18]. Four prospective studies in patients with frequently relapsing or glucocorticoid-dependent nephrotic syndrome explored the possibility of withdrawing prednisone, which was successful in >50% of patients without further relapses [13,15-17]. In children with glucocorticoid-dependent nephrotic syndrome on MMF, Dorresteijn *et al.* reported of relapse rates of 25% after 6 months and 45% after 12 months, respectively [18]. In a phase II Bayesian trial, Baudouin et al. confirmed the effect of MMF in reducing relapse rates and glucocorticoid dose in children with glucocorticoid-dependent nephrotic syndrome [14]. A recent GPN study on the maintenance of remission in children with frequently relapsing or steroid-dependent SDNS has shown that MMF in adequate exposure is as effective as cyclosporine (CsA) in sustaining remission without the burden of CsA-induced nephrotoxicity and neurotoxicity (ISRCTN61976169) [19]. Benz *et al.* have shown that the efficacy of MMF regarding the prevention of relapses in these patients can be optimized by achieving a MPA exposure (MPA-AUC_{0-12}) of >64 mg x h/L with a sensitivity of 100% and a specificity of 89% without any relevant toxicity [20].

So far, no studies with mycophenolate mofetil for the initial treatment of the steroid-sensitive nephrotic syndrome in children have been performed. However, it seems coherent to use the efficacy of MMF also for sustaining remission in the initial treatment of SSNS after achieved remission and to benefit from its lower toxicity compared to glucocorticoids.

1.2 Study Rationale/Justification

The initial treatment of the idiopathic nephrotic syndrome in children requires sufficient immunosuppressive therapy to induce and sustain remission, but should avoid toxicity, since the intensity of the initial treatment does not influence the long-term course of the disease. Our hypothesized novel treatment protocol has the potential to reduce the burden of glucocorticoid-associated side effects and associated cardiovascular risk factors, if the novel protocol is equally efficacious as the standard therapy. If our hypothesis turns out to be true, this novel therapy will become the standard of care for the initial treatment of steroid-sensitive nephrotic syndrome in children.

1.3 Risk-benefit Assessment

MMF is effective in sustaining remission in patients with the frequently relapsing steroid-sensitive nephrotic syndrome [13,14,19]. Therefore, after achieved remission the risk for immediate relapse is low, even during the initial manifestation of SSNS. If the number of patients with relapses after intervention is higher than expected (experimental intervention is inferior to control group), prednisone will be given anyway for induction of remission; the over-all

prognosis will therefore not be influenced. On the other hand, the patients in the experimental group have the potential to benefit significantly because of less glucocorticoid-associated toxicity.
The most frequently observed side effects of mycophenolate mofetil are gastrointestinal symptoms such as nausea, vomiting, stomach pain and diarrhea, hematological symptoms such as leukopenia, anemia and rarely thrombocytopenia and an enhanced susceptibility for infections. In general, these side effects occur more frequently and have a higher clinical significance, when MMF is administered in conjunction with other immunosuppressive medications such as cyclosporine or tacrolimus, as indicated after solid organ transplantation. When MMF is administered as monotherapy, for example in patients with frequently relapsing steroid-sensitive nephrotic syndrome, the frequency and severity of these side effects are markedly lower [13-18] and these side effects will be systematically evaluated during the study visits.
In order to acknowledge recent reported adverse events (hypogammaglobulinemia and bronchiectasia) in patients after solid organ transplantation and treated with MMF together with other immunosuppressive co-medication in the long-time run, these adverse events are monitored closely in the INTENT study (see 5.4.7.), despite these events are very unlikely to happen due to the short administration period.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Primary Endpoint

The main purpose of the study is to show that MMF in the initial treatment of SSNS in children is not inferior regarding maintenance of initial remission and subsequent relapse rate compared to the standard high-dose prednisone regimen.

The primary efficacy endpoint is occurrence of treated relapse within 24 months after completion of initial treatment (rationale: this endpoint was chosen in all previous studies on the initial treatment of SSNS in children and is also the primary endpoint in various meta-analyses on this topic [3,4,5,7,8]).

Relapses of the SSNS will primarily be detected by daily urine dip stick analysis (Albustix®, PZN 1266154), which is performed and documented by the patients and parents themselves. Definition of relapse: Relapse is denoted by a reappearance of proteinuria for 3 consecutive days:

Albustix® ≥2+ (first or second morning urine) (for interpretation see Albustix®)

or

urine protein/creatinine (Up/c) ratio ≥2 g/g (first or second morning urine)

or

urine protein level of ≥40mg/m^2 BSA/h (urine collection for minimum 12 hours)

Relapses with and without treatment are documented. The primary endpoint is fulfilled by the first treated relapse.

2.2 Secondary Objectives and Secondary Endpoints

Secondary endpoints are divided into five items:

1. Course of the disease as described by the following criteria
    a. Time from remission to first relapse
    b. Number of relapses during follow-up
    c. Mean relapse rate per patient and year
    d. Number of frequent relapsers
    e. Time from remission to intensification of immunosuppressive treatment with other drugs due to glucocorticoid-induced toxicity
    f. Rate of patients who require more intense immunosuppressive treatment
2. Glucocorticoid-associated toxicity:
    a. Cumulative prednisone dose as mg/m^2
    b. As there is no validated score for glucocorticoid-induced toxicity, each item is registered separately. At visits 1-8, body mass index, arterial hypertension, and growth failure will be checked for quantitative influence, striae, hypertrichosis, acne, and psychological disturbances by yes or no for qualitative influence. Additionally, at visits 1, 5, and 8, patients will be checked for cataract and glaucoma (by yes or no).

3. Mycophenolate mofetil-associated toxicity: At all visits, patients will be checked for known side effects of MMF, especially diarrhea, blood cell count disturbance, and infections.
4. Health-related quality of life, which is impaired in children with nephrotic syndrome [21], will be measured with a validated questionnaire (DISABKIDS) at visits 1/5/8.
5. Days missing school attendance and days of hospitalization will be documented as a measure for the impact of the disease on everyday life.

It is expected that MMF-based regimen will avoid acute and long-term glucocorticoid-associated toxicity and is therefore superior regarding the benefit/risk ratio. However, this will not be tested confirmatorily since there exists no endpoint/score summarizing the different aspects of side effects.

3 STUDY DESIGN AND DESCRIPTION

3.1 Study design

This is a prospective, randomized, multicenter, controlled, open, parallel group phase III study.

After initiation of the study, patients will be screened consecutively and eligible patients will be enrolled into the study at each center. To achieve comparable intervention groups and to minimize a potential selection bias, patients will be allocated in a concealed fashion by means of randomization using a centralized web-based tool (www.randomizer.at).
Each sites' principal investigator has to declare to the coordinating investigator/sponsor that he/she will conduct the study according to the protocol, ethical rules, and to provide the support as needed. To minimize a potential performance bias, this will be fixed in a contract prior to commencing the study. The clinical monitor will introduce the sites in detail to study procedures and documentation in advance.
Bias by potential influential factors will be addressed by inclusion as covariates into the statistical analysis. Independent clinical on-site monitoring to ensure patients safety and integrity of the clinical data in adherence to study protocol will focus on source data documentation, correctness of data, and adherence to study procedures, e.g. randomization and treatment.
Based on the performed interventions and planned analysis blinding is not feasible to minimize a detection bias, because the interventions can easily be differentiated due to visible side effects such as obesity, which is only expected in the control group. Furthermore, MMF is used in liquid form and prednisone as a tablet. The primary endpoint is based on standardized diagnostic work-up results, i.e. is an objective criteria.

3.2 Study Duration and Schedule

The duration of the study for each subject is expected to be 27 months (including 24 months follow-up after intervention)

Study duration:

Total study duration:	[78 months]
Duration of clinical phase:	[63 months]
Beginning of the preparation phase:	[03/2014]
FSI (first subject in):	[01/2015]
LSI (last subject in):	[01/2018]
LSO (last subject out):	[04/2020]
DBL (database lock):	[07/2020]
Statistical analyses completed:	[08/2020]
Study report completed:	[04/2021]

4 SELECTION OF SUBJECTS

4.1 Number of Subjects

As calculated in section 8.1 Sample Size Calculation, 400 patients should be assessed for eligibility, 340 subjects should be enrolled in the clinical study, i.e. 170 subjects per treatment group. Recruitment and treatment of subjects should be performed in multiple study centers.

The study will be conducted on a multicenter basis. The rarity of the disease implicates a nationwide recruitment. The planned app. 45 study centers will be evenly distributed over Germany.

4.2 Inclusion Criteria

Subjects meeting all of the following criteria will be considered for admission to the study:

- First episode of steroid-sensitive nephrotic syndrome (SSNS)
- In remission induced by daily glucocorticoids within 28 days
- Male and female children aged ≥ 1 year and ≤ 10 years at beginning of study (typical age range of patients with SSNS)
- Ability of the persons having care and custody of the child to understand character and individual consequences of clinical study
- Written informed consent of the persons having care and custody of the child (must be available before enrolment in the study)

4.3 Exclusion Criteria

Subjects presenting with any of the following criteria will not be included in the study:

- Secondary nephrotic syndrome
- estimated glomerular filtration rate (eGFR) <90 ml/min x 1.73 m^2 BSA[1]
- Ongoing treatment with systematically administered glucocorticoids or other immunosuppressive drugs at time of first episode of nephrotic syndrome.
- Hemoglobin concentration of ≤9 g/dL
- Leucocyte count of ≤2.500/µl
- Severe chronic gastrointestinal disease
- History of hypersensitivity to mycophenolate mofetil or to any drug with similar chemical structure or to any excipient present in the pharmaceutical form of suspension of mycophenolate mofetil (CellCept suspension®)
- Refusal of subject (please see also chapter 10.5)

[1] Estimated glomerular filtration rate

Formula = (K * height [cm])/serum creatinine [mg/dl]

K = constant (determined by regression analysis) depends on the method of creatinine measurement:

- Jaffé method (photometric, kinetic measurement with picric acid)
  constant for age 1-13 years: K = 0.55 (Schwartz et al., 1976)
- Enzymatic measurement
  constant K = 0.413 (Schwartz et al., 2009)

- Participation in other clinical studies or observation period of competing studies, respectively.

No subject will be allowed to enroll in this study more than once.

4.4 Withdrawal/premature closure

4.4.1 Withdrawal of Patients

a. Any patient can withdraw from treatment and/or from 24 months lasting follow-up at any time without personal disadvantages and without having to give any reason.

- Patients who discontinue treatment temporarily or completely (control intervention or experimental intervention) should be followed up until the end of study. The time and reason of treatment discontinuation must be documented in the patient file and in the eCRF.
- In patients, who discontinue participation in the INTENT-study, visit 8 (final visit) should be tried to be performed. The time and reason of study discontinuation must be documented in the patient file and in the eCRF. Patients who discontinue participation in the INTENT-study should be routinely treated by a physician or a pediatric nephrologist inside the study center or outside in an institution not taking part in the INTENT study. If the persons having care and custody of the child agree, routinely recorded data (e.g. relapse and treatment of relapse, serious adverse events (see 7.2), treatment with immunosuppressive drugs) may be used for the INTENT study. A separate informed consent form is available for this case (see separate informed consent form).

b. The investigator may withdraw a patient from the treatment because of adverse events. These patients should be followed up until the end of study. In case of discontinuing mycophenolate mofetil (experimental intervention), the patient should be given the standard treatment (see control intervention). The time and reason of treatment discontinuation must be documented in the patient file and in the eCRF.

4.4.2 Premature Closure of the Clinical Study or a Site

If new information on the risk-to-benefit ratio of the drug or on the treatment methods used in the study is obtained in the meantime and safety concerns arise, the sponsor reserves the right to interrupt or terminate the project. Premature termination is also possible if the sponsor notices and agrees upon that patient recruitment is insufficient and that this cannot be expedited by appropriate measures.

Premature termination of a single center is also possible if the sponsor notices that the conduction of the study is not compliant with ICH-GCP and/or is not according to the protocol, the patient recruitment and/or the quality of the data is insufficient.

The DMSB can recommend interruption or termination of the study or of treatment arms based on the results of the intermittent SAE evaluation or of accumulating information on the above mentioned reasons.

The ethics committee (EC) and the competent authorities must be informed about the premature closure of the study or one of the treatment arms within 15 days by the sponsor. Furthermore, the ethics committee(s) and competent authorities themselves may decide to stop or suspend the study.

All involved investigators have to be informed immediately about a cessation/suspension of the study. The decision is binding to all study centers and investigators.

When the study is closed, all study materials (study medication etc.) must be sent to the sponsor.

5 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

5.1 Study medication

5.1.1 General Information

The sponsor will provide the quantity of study medication required for the clinical study. The medication provided must be used only in the context of this clinical study. Careful records will be kept of the study medication supplied to the centers and distributed to the patients. At the end of the study, all unused medication will be returned to sponsor. If deficiencies of the study medication are noticed, the monitor and project manager must be informed immediately.

5.1.2 Characterization of study medication

1. Mycophenolate mofetil

Proprietary name:	CellCept suspension®
International Nonproprietary Name (INN):	Mycophenolate mofetil (MMF)
ATC code, if officially registered:	L04AA06
Manufacturer:	Roche Registration Ltd.
Pharmaceutical formulation:	MMF is administered in liquid form (CellCept suspension® (Roche Registration Ltd.))
Mode of administration:	orally
Storage instructions:	The suspension expires 2 months after its assembly Storage of suspension below 30°C

2. Prednisone

Prednisone is used as standard therapy because it was used in the former studies of the GPN (standard treatment).

Proprietary name:	Decortin® (Merck Serono), Prednison GALEN®, (Galenpharma), Prednison acis® (Acis), Prednison Hexal® (Hexal), Prednison ratiopharm® (Ratiopharm), Cutason ® (Mibe), Predni Tablinen® (Zentiva)
International Nonproprietary Name (INN):	Prednisone
ATC code, if officially registered:	H02AB07
Manufacturer:	Merck Serono, Galenpharma, Acis, Hexal, Ratiopharm, Mibe, Zentiva
Pharmaceutical formulation:	tablet
Mode of administration:	orally
Storage instructions:	Storage of below 25°C

Note: Due to its pharmacokinetic characteristics prednisolone is not equal prednisone. The systemic availability of prednisolone after oral administration is 99%. The systemic availability of prednisone after oral administration differs between 62-99% in different publications (median: 79%) [22]. Some hospitals do not stock prednisone anymore, but only prednisolone. In case of admission of a study patient to these hospitals, prednisolone can be administered in a dose of 80% of the corresponding prednisone dose.

5.2 Packaging and Labelling

The study medication will be packed by the “Herstellbetrieb der Apotheke” of University Hospital Heidelberg. The study medication will be labeled and sent to the study sites by this pharmacy according to § 5 of GCP-V. The amount of medication per patient will be calculated according to body surface area and treatment strategy (both see 5.4) in the time period from day of randomization to end of intervention. The applicated amount of medication will be documented in the CRF.

5.3 Supplies and Drug Accountability

The investigator will confirm correct receipt of the study medication in writing and ensure that the medication is stored safely and correctly. The study medication must be carefully stored in accordance with manufacturer’s instructions at room temperature and dry at the study sites and at the patient’s home, in a locked area with restricted access, separately from other drugs, and kept out of the reach and sight of children. The investigator will document the distribution to and return of the study medication from the patient with the date, recording the quantity distributed and used on the forms provided for this purpose. The site monitor will periodically check the supplies of study medication held by the investigator to ensure the correct accountability of all study medication used. At the end of the study, all unused study medication and all medication containers will be completely disposed by the study centers. It will be assured that a final report of the drug accountability is prepared and maintained by the investigator.

5.4 Administration of study medication

5.4.1 Assignment of Identification Codes
For allocation to a treatment arm (randomization) see 5.5
Medication will be only provided to patients included into the study after randomization. The distribution of the medication will take place according to randomization.

5.4.2 Dosage Schedule
Maximum duration of treatment: 12 weeks after first day of initial treatment of SSNS. Patients will receive the whole medication for the complete intervention period.

Control intervention:

- The Prednisone, which is continued for a total of 6 weeks with the dosage of 60 mg/m^2 BSA/d (maximum 80 mg), is given once a day (quaque die (QD)), twice a day (bis in die (BID)) or three times daily (ter in die (TID)).
  plus
- The Prednisone, which is given for another total of 6 weeks with the dosage of 40 mg/m^2 BSA (maximum 60 mg) is given on alternate days (every other day) in one dose in the morning

Resorption of prednisone is independent of food intake.

Experimental intervention:

- Mycophenolate mofetil (MMF) is given in a dosage of 1200 mg/m^2 BSA/d as a suspension (200 mg/mL) until 12 weeks total treatment duration. MMF is given twice a day (bis in die (BID) = every 12 hours (± one hour).
- The suspension of MMF should be mixed in the study center (according to the *Fachinformation*).
- The persons having care and custody of the child are informed, that MMF should be given 30 minutes before or 60 minutes after food intake.
- For the first two weeks from randomization/visit1 on, prednisone is given with the dosage of 40 mg/m^2 BSA (maximum 60 mg) on alternate days (every other day) in one dose in the morning

5.4.3 Adherence
Adherence will be recorded by the patients' diary.

5.4.4 Prior and Concomitant Diseases
Relevant additional diseases present at the time of informed consent are regarded as concomitant diseases and will be documented on the appropriate pages of the case report form (CRF).

Abnormalities which appear for the first time or worsen (intensity, frequency) during the study are adverse events (AEs) and must be documented on the appropriate pages of the CRF.

5.4.5 Prior and Concomitant Medication
The treatment of accompanying illnesses not subject to the exclusion criteria is permissible if this is not expected to have any effect on the outcome measures used in this study and to interfere with the study medication.

In particular, the following drug groups are **not permitted** as concomitant medication:

Systematically administered glucocorticoids or other immunosuppressive drugs

If concomitant drugs are administered, these must be recorded in the patient file and in the CRF.

5.4.6 Adjustments to dosage of the IMP in the individual study subject
Dosage is adjusted according to individual body surface area.

5.4.7 Dose modification
Dosage modifications, if treatment related toxicities occur during the study.

a. Mycophenolate mofetil

Adverse events concerning gastrointestinal tract

- vomiting (defined as a frequency of more than 2 times per day, lasting for ≥48 hours)
  - Split daily mycophenolate mofetil dose into up to 4 doses
  - If there is no improvement within 48 hours reduce mycophenolate mofetil dose by 50% in addition
  - In case of repeated episodes (≥3) or prolonged vomiting (>6 days) discontinuation of mycophenolate mofetil by investigator
- diarrhea (defined as a frequency of more than 3 watery stools per day, lasting for ≥48 hours)
  - Split daily mycophenolate mofetil dose into up to 4 doses
  - If there is no improvement within 48 hours reduce mycophenolate mofetil dose by 50% in addition
  - In case of repeated episodes (≥3) or prolonged diarrhea (>6 days) discontinuation of mycophenolate mofetil by investigator
- nausea (defined by duration >5 days and medical declaration of association to mycophenolate mofetil)
  - Split daily mycophenolate mofetil dose into up to 4 doses
  - If there is no improvement within 72 hours reduce mycophenolate mofetil dose by 50% in addition

Adverse events concerning blood count

- hemoglobin concentration of ≤10 g/dL at visit 2 or visit 3
  - Reduction of daily dose of mycophenolate mofetil by 50%, control of hemoglobin concentration after 7-10 days
  - Upon resolution (hemoglobin concentration ≥10g/dL), resumption of maintenance study drug dosing should be attempted
  - In case of hemoglobin concentration ≤8 g/L discontinuation of mycophenolate mofetil by investigator
- leucocyte count of ≤4.000/µl at visit 2 or visit 3
  - Reduction of daily dose of mycophenolate mofetil by 50%, control of leucocyte count after 7-10 days
  - Upon resolution (leucocyte count ≥4.000/µL), resumption of maintenance study drug should be attempted
  - In case of leucocyte count ≤2.500/µL discontinuation of mycophenolate mofetil by investigator
- thrombocyte count of ≤100.000/µL at visit 2 or visit 3
  - Reduction of daily dose of mycophenolate mofetil by 50%, control of thrombocyte count after 7-10 days
  - Upon resolution (thrombocyte count ≥100.000/µL), resumption of maintenance study drug should be attempted
  - In case of leucocyte count ≤50.000/µL discontinuation of mycophenolate mofetil by investigator

Adverse events concerning infections

- Severe bacterial infection or severe verified viral infection (e.g. Herpes zoster, Varicella, EBV, CMV,…)
    - Stop of mycophenolate mofetil medication until clinical resolution. Then restart mycophenolate mofetil with 50% of the last maintenance dose

Other adverse events

- recurrent infections/ suspected hypogammaglobulinemia at visit 2 or visit 3
    - Determine serum immunoglobulins. If newly diagnosed hypogammaglobulinemia is confirmed: discontinuation of mycophenolate mofetil by investigator
- Pulmoniary symptoms, e.g. cough or dyspnoe at visit 2 or visit 3
    - Physical examination, if bronchiectasia is suspected, performance of chest X-ray. If bronchiectasia confirmed: discontinuation of mycophenolate mofetil by investigator

In any adverse event due to mycophenlate mofetil and in individual situations which are not defined clearly in the study protocol (5.4.7.) the investigator may decide, if discontinuation of mycophenolate mofetil should be temporary or permanent. The Clinical Project Management supports the investigator in decision-making.

b. Glucocorticoids

Glucocorticoids are given according to center practice, since this is the control intervention

- In case of diabetes mellitus (glucocorticoid-induced, primary manifestation or pre-existing) prednisone is allowed to be given daily instead of alternate-day (with the same cumulative dose, e.g. 10 mg per day instead of 20 mg alternate-day) in order to falicitate management of the diabetes.

5.5 Randomization

5.5.1 Randomization method

All patients who seem suitable for study participation and take part in the screening, will be registered in a screening log and receive a screening number. Together with the center id this will be the unique identification number throughout the study. At the end of the screening phase the suitability of the patient is assessed finally.

When the patient is included in the study (all inclusion criteria fit and none of the exclusion criteria apply), he will be given a consecutive randomization number according to the randomization tool. Patients withdrawn from the study retain their number.

To achieve comparable intervention groups, patients will be allocated in a concealed fashion by means of randomization using a centralized web-based tool (www.randomizer.at).
Randomization will be performed stratified by age groups (grouped: <7 years of age, ≥7 years of age), because age is known to influence the occurrence of relapses. If the randomizer is not available in urgent cases the Institute of Medical Biometry and Informatics can be contacted (06221-56-4141) and a biometrician or data manager will perform the randomization.

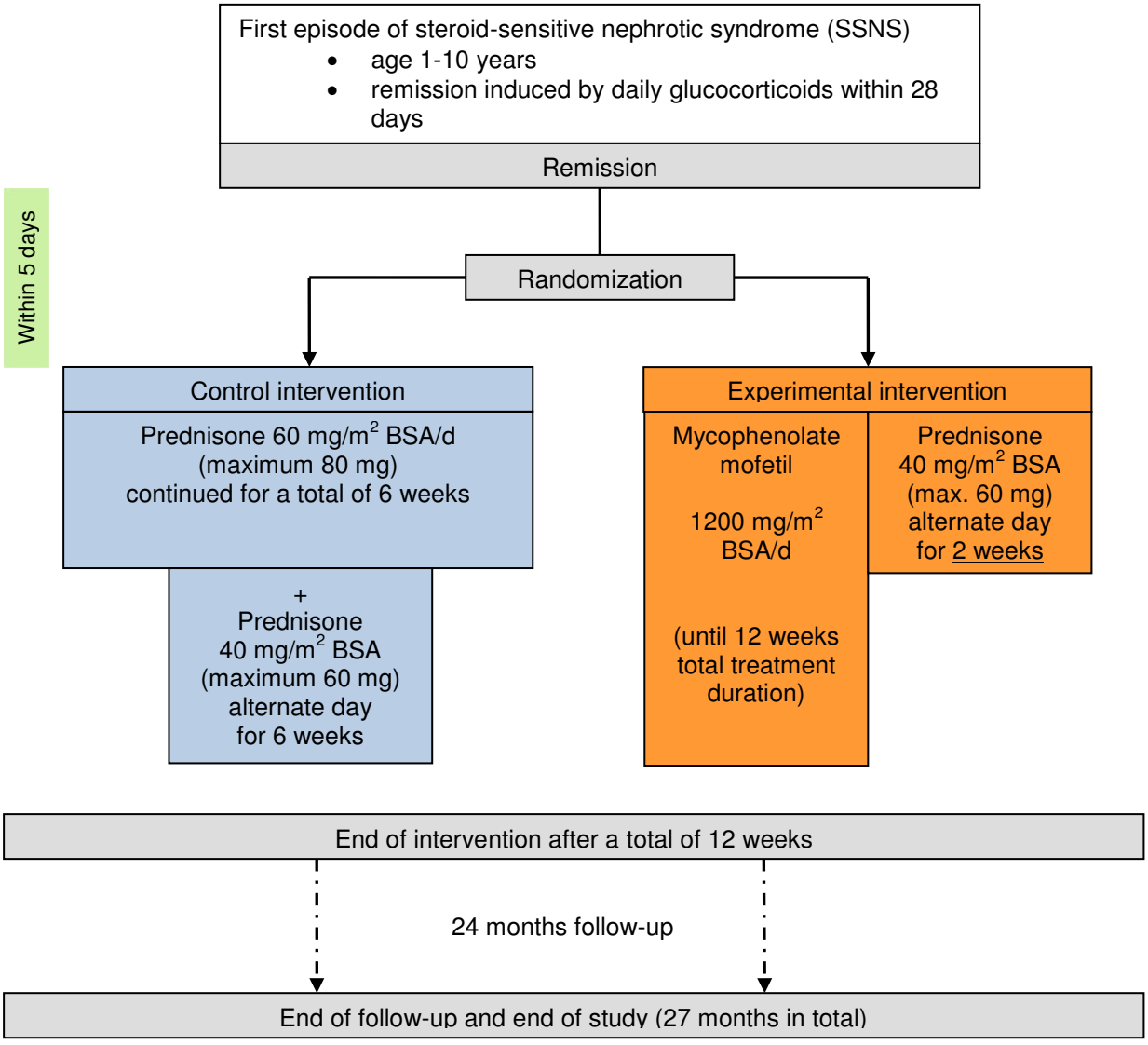
5.5.4 Emergency Treatment
During and following a subject's participation in the study, the investigator should ensure that adequate medical care is provided to a subject for any AE including clinically significant

laboratory values. The investigator should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

6 STUDY METHODS

6.1 Time Sequence and Frames

FLOW CHART/STUDY SCHEDULE



alternate day = every second day

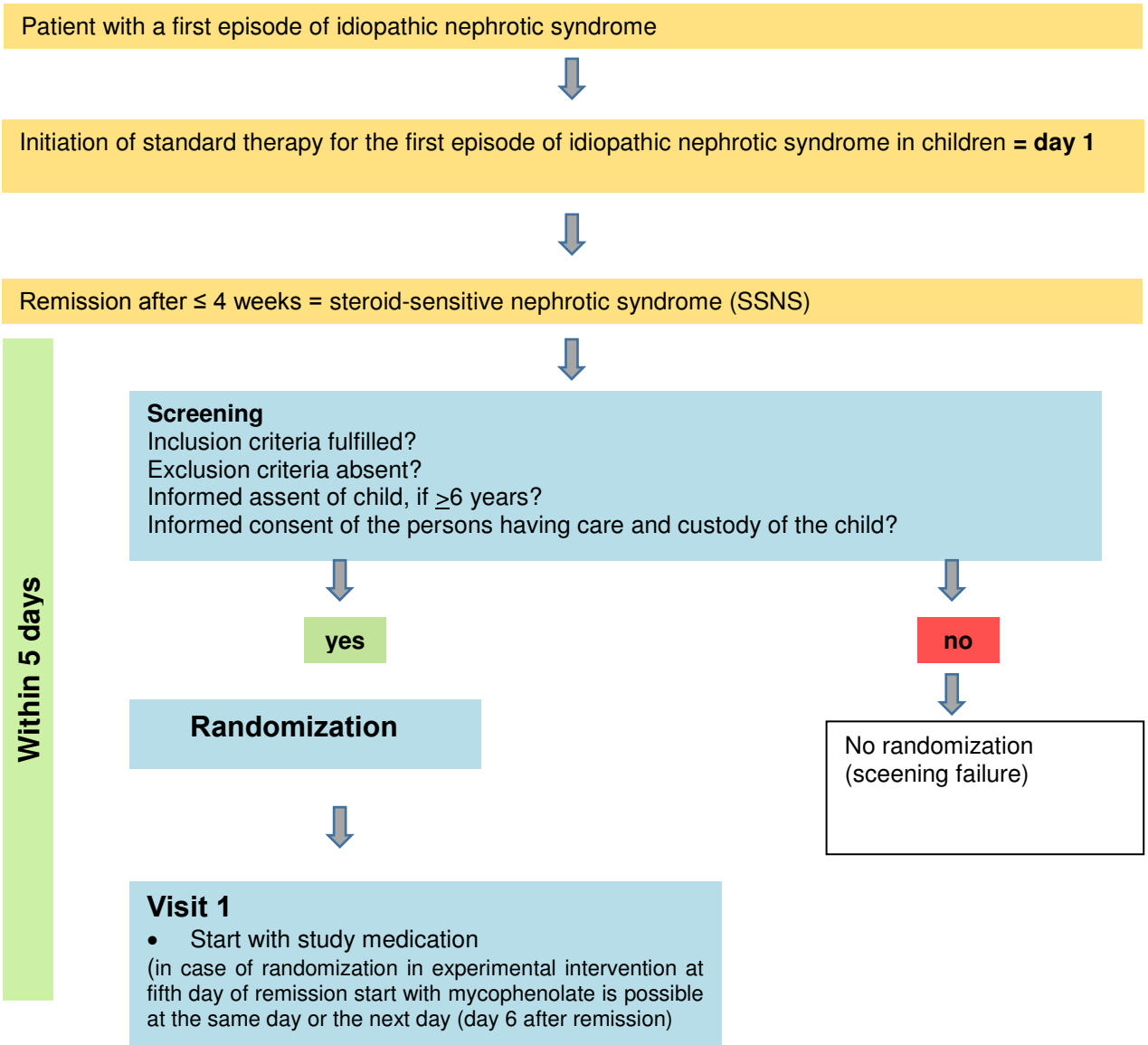
All patients who seem suitable for study participation and take part in the screening, will receive a screening number. At the end of the screening phase the suitability of the patient is assessed finally.

Parents of children with initial episode of idiopathic nephrotic syndrome aged between 1 and 10 years and treated with standard regime will be informed about the ongoing INTENT study either by the study center or by their pediatrician who will inform the study center as well.

If the child with initial episode of idiopathic nephrotic syndrome is steroid-sensitive (remission within 28 days), the patient fulfills the inclusion criteria. The persons having care and custody of the child and the patient, if ≥6 years of age, will be informed about the INTENT study by the study center and give written assent/consent.

The maximum time period between remission (=screening) and visit 1 are 5 days.

Allocation to INTENT study in detail

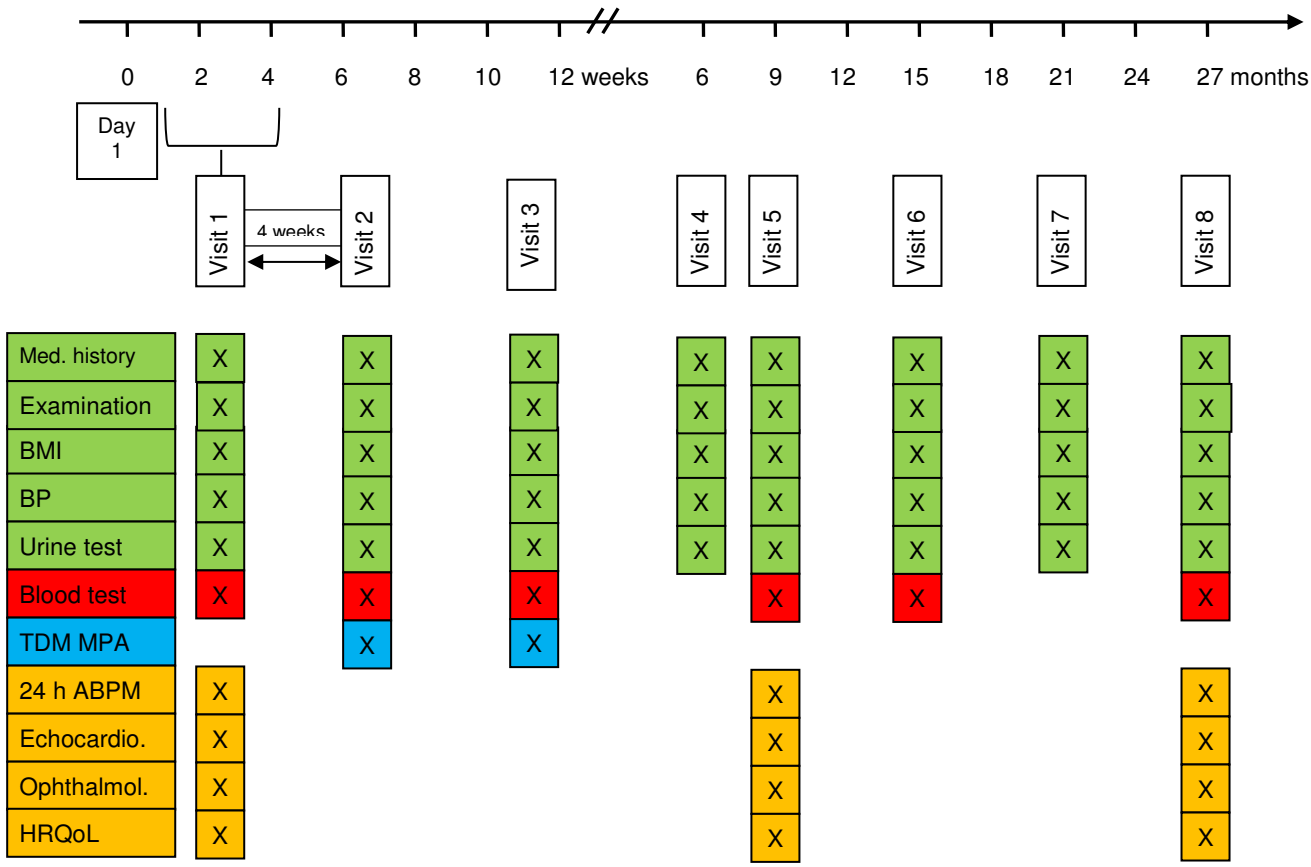


(Day1: Start with standard therapy for first episode of idiopathic nephrotic syndrome in children)

Screening

In the screening, date of diagnosis of nephrotic syndrome, date of start with standard therapy for nephrotic syndrome, and date of remission is documented in the eCRF besides the proven inclusion and exclusion criteria. For checking the exclusion criteria concerning eGFR, leucocyte count and hemoglobin concentration the most recent lab values should be used; they should have been obtained no more than 28 days prior to visit 1. In addition, infections and vaccinations are documented that have taken place within two weeks prior to the diagnosis of nephrotic syndrome.

Scope and frequency of study visits



Time Sequence and frames

Visit	Visit no.	Time	Time window [days]
Screening/Start of study treatment	Visit 1		0-5 days after date of remission*
Interim visit	Visit 2	4 weeks after visit 1	± 5 days

Last week of treatment visit	Visit 3	11 weeks after day 1 (=first day of treatment with standard therapy)	± 7 days
First follow-up	Visit 4	6 months after day 1 (= first day of treatment with standard therapy)	± 14 days
Second follow-up	Visit 5	9 months after day 1 (= first day of treatment with standard therapy)	± 14 days
Third follow-up	Visit 6	15 months after day 1 (= first day of treatment with standard therapy)	± 14 days
Fourth follow-up	Visit 7	21 months after day 1 (= first day of treatment with standard therapy)	± 14 days
End of study	Visit 8	27 months after day 1 (= first day of treatment with standard therapy)	± 14 days

* In case the patient is randomized into the experimental intervention group at the fifth day after remission has been achieved start of mycophenolate mofetil is possible at the same day or the next day (i.e. day 6 after remission).

Visit 1

Visit 1 is scheduled at the point in time of allocation to the INTENT study and randomization (0-5 days after date of remission). The exact date depends on the time between first day of treatment with standard therapy for first episode of idiopathic nephrotic syndrome in children (= day 1) and the point in time of remission (this may vary between day 5 until day 28).

At visit 1 the history of the patient is documented: Age, gender, postal code (first 4 of 5 digits), known allergies, other chronic diseases, family history concerning kidney disease. Furthermore side effects of the previous standard treatment are retrieved in yes/no manner (Behavioral disturbances since diagnosis: child feels sad, anxious, irritable, as well as euphoric state, aggressive state, nausea, vomiting (defined as a frequency of more than 1 times per day), diarrhea (defined as a frequency of more than 4 loose stools daily), headache, muscle weakness, any new infection (e.g. respiratory tract infection, gastroenteritis, urinary tract infection)). Application of any current medication (other than immunosuppressive agents) is documented.

The physical examination contains investigation of the skin in yes/no manner (acne, cushingoid facies, striae, and hypertrichosis), further pathological organ-specific findings in yes/no/not done manner (lymphadenopathy, pharyngitis, otitis media, heart murmur, arrhythmia, respiratory tract infection, abdominal pain, and muscle weakness) and pubertal status.

Measurement of weight, height (BMI is computed) and blood pressure after 3 minutes rest are done and documented.

A sample of spot urine is analyzed with dip stick (Albustix®) and quantitatively for creatinine, protein, albumin in the laboratory of the study center (urine protein/creatinine ratio is computed).

The blood test contains: blood cell count (leukocytes, erythrocytes, hemoglobin, and thrombocytes), HbA_{1c}, creatinine, blood urea/blood urea nitrogen (BUN), uric acid, calcium, phosphate, alkaline phosphatase, 25-OH Vitamin D, total protein, albumin, GPT/ALT, IgG, IgE, Cholesterol.

Study specific investigations are:

- **24 h ambulatory blood pressure measurement (24h-ABPM)** performed by the study center with documentation of the median of systolic blood pressure (day), of the median of diastolic blood pressure (day), the median of systolic blood pressure (night), the median of diastolic blood pressure (night).
- **Ophthalmologic investigation** performed by any ophthalmologist will document cataract (yes/no) and glaucoma (yes/no)
- **Health related quality of life (HRQoL)** DISABKIDS as standardized questionnaires to assess health related quality of life is used. There exists a parental questionnaire, a questionnaire for children aged ≥8 years and one for children aged 4-7 years of age. Children below 4 years of age will not receive a questionnaire.
- **Echocardiography (Echocardio.)** is optional for the INTENT study and will be performed by a pediatric cardiologist. The documented parameters are: LVID (left ventricular internal diastolic diameter), LVIS (left ventricular internal systolic diameter), PWT (posterior wall thickness), and IVST (interventricular septic thickness). The LVID index, the LV FS (Left ventricular fractional shortening), LVM (left ventricular mass), LVM index, and LVH (Left ventricular hypertrophy) are computed.

These study specific investigations can be performed in a time frame of -21 days/ +7 days around the visit date.

The persons having care and custody of the child and the patient will be informed about the randomized medication, especially its handling, dosing, intake in relation to food intake and storage (see 5.4.2).

Further, the use of the patients´ diary is explained. Daily dip stick (Albustix®), given medication (if control intervention: dosage of prednisone in mg; if experimental intervention: dosage of MMF in ml and dosage of prednisone in mg), as well as days of missing school, infections, hospitalization, or other events the persons having care and custody of the child feel important to document.

The persons having care and custody of the child are instructed to interpret the results of the Albustix® and are instructed to react as described. In doubt the persons having care and custody of the child are encouraged to contact the study center early.

Albustix™	Interpretation	Consequence
Negative	No relapse	Nothing to do
Trace		
30 mg/dL = +	doubtful value	• Daily weight • investigation for edema (yes/no) • The urine protein/creatinine ratio (Up/c) or a specimen of a urine collection has to be analyzed, if 1+ appears for 3 days or 1+ is combined with ≥2+ within 3 days.
100 mg/dL = ++	Relapse, if detected on 3 consecutive days	Contact study center
300 mg/dL = +++		
≥2000 mg/dL = ++++		

Visit 2

Visit 2 is scheduled at 4 weeks after visit 1 (± 5 days).

At visit 2, the history since visit 1 is documented, especially if one or more relapses occurred since visit 1.. In case of a relapse, date of first day of relapse (definition fulfilled) is documented. For each relapse, it is documented, according to which criteria the relapse was diagnosed: Albustix ≥ 2+ (>30mg/dL) for 3 consecutive days, Spot urine: Up/c ratio ≥ 2 g/g, or collecting urine: Up excretion of ≥ 40 mg/m² BSA/h. If the relapse was treated, the medication is recorded. Further, date of remission is documented (see definitions). In order to document possible trigger factor infections during relapse (e.g. respiratory tract infection, gastroenteritis) and vaccinations within two weeks prior to the relapse are recorded, too. All information from the diary (days missing school attendance, days of hospitalization since last visit are recorded. According to diary and patients´ inquiry adherence to study medication is assessed (Reduction of study medication > 50%?, Pause of study medication > 3 days?).

Side effects of the treatment are retrieved in yes/no manner (Behavioral disturbances since visit 1: child feels sad, anxious, irritable, as well as euphoric state, aggressive state, nausea, vomiting (defined as a frequency of more than 1 times per day), diarrhea (defined as a frequency of more than 4 loose stools daily), headache, muscle weakness, any new infection).

Application of any current medication (other than immunosuppressive agents) is documented.

The event of renal biopsy since last visit is recorded with histology.

The physical examination contains investigation of the skin in yes/no manner (acne, cushingoid facies, striae, and hypertrichosis), further pathological organ-specific findings in yes/no/not done manner (lymphadenopathy, pharyngitis, otitis media, heart murmur, arrhythmia, respiratory tract infection, abdominal pain, and muscle weakness) and pubertal status.

Measurement of weight, height (BMI is computed) and blood pressure after 3 minutes rest are done and documented.

A sample of spot urine is analyzed with dip stick (Albustix®) and quantitatively for creatinine, protein, albumin in the laboratory of the study center (urine protein/creatinine ratio is computed).

The blood test contains: blood cell count (leukocytes, erythrocytes, hemoglobin, and thrombocytes), HbA_{1c}, creatinine, blood urea/blood urea nitrogen (BUN), uric acid, calcium, phosphate, alkaline phosphatase, 25-OH Vitamin D, total protein, albumin, GPT/ALT, IgG, IgE, Cholesterol.

Study specific investigations are, if treated with MMF:

- **Therapeutic drug monitoring of mycophenolic acid (TDM MPA)**
  - Therapeutic drug monitoring of mycophenolic acid (TDM MPA) is optional and should be performed, if possible due to local facilities. These data will be helpful for retrospective analysis.
    - The blood test of visit 2 is schedulded before taking MMF.
    - For taking blood, an indwelling venous cannula is inserted in order to reuse it after 60 and 120 minutes without pain.
    - Intake of MMF is immediately after taking blood sample
    - Blood is drawn from the indwelling venous cannula after 60 and 120 minutes
    - For every sample 1,2 ml EDTA blood is necessary
    - Centrifugate EDTA blood
    - Plasma should be stored at -20°C
    - Tube is labeled with ID, number of TDM and time (0 min, 60 min or 120 min)
    - All samples could be sent (adress see below) together
    - Samples have to be sent on dry ice
  - Plasma is sent to

    University Cologne

    Pharmakologisches Institut

    Gleuelerstrasse 24

    50931 Köln

    Phone: 0221 478-88729

    Fax: 0221 478-89049

    E-Mail: sekretariat-pharmakologie@uk-koeln.de
  - The level of mycophenolic acid (MPA) in plasma before and 60 minutes as well as 120 minutes after intake of mycophenolate mofetil will be analyzed centrally and interpreted retrospectively. Therefore, the study centers will not be informed about the results and dosage of mycophenolate mofetil will not be adjusted.

Visit 3

Visit 3 is scheduled at 11 weeks (± 7 days) after day 1 (= first day of treatment with standard therapy for first episode of idiopathic nephrotic syndrome in children).

At visit 3, the history since visit 2 is documented, especially if one or more relapses occurred since visit 2. In case of a relapse, date of first day of relapse (definition fulfilled) is documented. For each relapse, it is documented, according to which criteria the relapse was diagnosed: Albustix ≥ 2+ (>30mg/dL) for 3 consecutive days, Spot urine: Up/c ratio ≥ 2 g/g, or collecting urine: Up excretion of ≥ 40 mg/m² BSA/h. If the relapse was treated, the medication is recorded. Further, date of remission is documented (see definitions). In order to document possible trigger factor infections during relapse (e.g. respiratory tract infection, gastroenteritis) and vaccinations within two weeks prior to the relapse are recorded, too. All information from the diary (days missing school attendance, days of hospitalization) since last visit are recorded. According to diary and patients´ inquiry adherence to study medication is assessed (Reduction of study medication > 50%?, Pause of study medication > 3 days?).

Side effects of the treatment are retrieved in yes/no manner (Behavioral disturbances since visit 2: child feels sad, anxious, irritable, as well as euphoric state, aggressive state, nausea, vomiting (defined as a frequency of more than 1 times per day), diarrhea (defined as a frequency of more than 4 loose stools daily), headache, muscle weakness, any new infection).

Application of any current medication (other than immunosuppressive agents) is documented.

The event of renal biopsy since last visit is recorded with histology.

The physical examination contains investigation of the skin in yes/no manner (acne, cushingoid facies, striae, and hypertrichosis), further pathological organ-specific findings in yes/no/not done manner (lymphadenopathy, pharyngitis, otitis media, heart murmur, arrhythmia, respiratory tract infection, abdominal pain, and muscle weakness) and pubertal status.

Measurement of weight, height (BMI is computed) and blood pressure after 3 minutes rest are done and documented.

A sample of spot urine is analyzed with dip stick (Albustix®) and quantitatively for creatinine, protein, albumin in the laboratory of the study center (urine protein/creatinine ratio is computed).

The blood test contains: blood cell count (leukocytes, erythrocytes, hemoglobin, and thrombocytes), HbA_{1c}, creatinine, blood urea/blood urea nitrogen (BUN), uric acid, calcium, phosphate, alkaline phosphatase, 25-OH Vitamin D, total protein, albumin, GPT/ALT, IgG, IgE, Cholesterol.

Study specific investigations are, if treated with MMF:

- **Therapeutic drug monitoring of mycophenolic acid (TDM MPA)**
    - Therapeutic drug monitoring of mycophenolic acid (TDM MPA) is optional and should be performed, if possible due to local facilities. These data will be helpful for retrospective analysis.
        - The blood test of visit 3 is schedulded before taking MMF.
        - For taking blood, an indwelling venous cannula is inserted in order to reuse it after 60 and 120 minutes without pain.
        - Intake of MMF is immediately after taking blood sample
        - Blood is drawn from the indwelling venous cannula after 60 and 120 minutes
        - For every sample 1,2 ml EDTA blood is necessary
        - Centrifugate EDTA blood
        - Plasma should be stored at -20°C
        - Tube is labeled with ID, number of TDM and time (0 min, 60 min or 120 min)
        - All samples could be sent (adress see below) together
        - Samples have to be sent on dry ice

- Plasma is sent to

  University Cologne

  Pharmakologisches Institut

  Gleuelerstrasse 24

  50931 Köln

  Phone: 0221 478-88729

  Fax: 0221 478-89049

  E-Mail: sekretariat-pharmokologie@uk-koeln.de

- The Level of mycophenolic acid (MPA) in plasma before and 60 minutes as well as 120 minutes after intake of mycophenolate mofetil will be analyzed centrally and interpreted retrospectively. Therefore, the study centers will not be informed about the results and dosage of mycophenolate mofetil will not be adjusted.

Visit 4

Visit 4 is scheduled at 6 months (± 14 days) after day 1 (= first day of treatment with standard therapy for first episode of idiopathic nephrotic syndrome in children).

At visit 4, the history since visit 3 is documented, especially if one or more relapses occurred since visit 3. In case of a relapse, date of first day of relapse (definition fulfilled) is documented. For each relapse, it is documented, according to which criteria the relapse was diagnosed: Albustix ≥ 2+ (>30mg/dL) for 3 consecutive days, Spot urine: Up/c ratio ≥ 2 g/g, or collecting urine: Up excretion of ≥ 40 mg/m² BSA/h. If the relapse was treated, the medication is recorded. Further, date of remission is documented (see definitions). In order to document possible trigger factor infections during relapse (e.g. respiratory tract infection, gastroenteritis) and vaccinations within two weeks prior to the relapse are recorded, too. All information from the diary (days missing school attendance, days of hospitalization) since last visit are recorded. According to diary and patients´ inquiry adherence to study medication is assessed (Reduction of study medication > 50%?, Pause of study medication > 3 days?).

Side effects of the treatment are retrieved in yes/no manner (Behavioral disturbances since visit 3: child feels sad, anxious, irritable, as well as euphoric state, aggressive state, nausea, vomiting (defined as a frequency of more than 1 times per day), diarrhea (defined as a frequency of more than 4 loose stools daily), headache, muscle weakness, any new infection).

Application of any current medication (other than immunosuppressive agents) is documented.

Application of further immunosuppressive agents after termination of study intervention are recorded.

The event of renal biopsy since last visit is recorded with histology.

The physical examination contains investigation of the skin in yes/no manner (acne, cushingoid facies, striae, and hypertrichosis), further pathological organ-specific findings in yes/no/not done manner (lymphadenopathy, pharyngitis, otitis media, heart murmur, arrhythmia, respiratory tract infection, abdominal pain, and muscle weakness) and pubertal status.

Measurement of weight, height (BMI is computed) and blood pressure after 3 minutes rest are done and documented.

A sample of spot urine is analyzed with dip stick (Albustix®) and quantitatively for creatinine, protein, albumin in the laboratory of the study center (urine protein/creatinine ratio is computed).

Visit 5

Visit 5 is scheduled at 9 months (± 14 days) after day 1 (= first day of treatment with standard therapy for first episode of idiopathic nephrotic syndrome in children).

At visit 5, the history since visit 4 is documented, especially if one or more relapses occurred since visit 4. In case of a relapse, date of first day of relapse (definition fulfilled) is documented. For each relapse, it is documented, according to which criteria the relapse was diagnosed: Albustix ≥ 2+ (>30mg/dL) for 3 consecutive days, Spot urine: Up/c ratio ≥ 2 g/g, or collecting urine: Up excretion of ≥ 40 mg/m² BSA/h. If the relapse was treated, the medication is recorded. Further, date of remission is documented (see definitions). In order to document possible trigger factor infections during relapse (e.g. respiratory tract infection, gastroenteritis) and vaccinations within two weeks prior to the relapse are recorded, too. All information from the diary (days missing school attendance, days of hospitalization) since last visit are recorded.

Side effects of the treatment are retrieved in yes/no manner (Behavioral disturbances since visit 4: child feels sad, anxious, irritable, as well as euphoric state, aggressive state, nausea, vomiting (defined as a frequency of more than 1 times per day), diarrhea (defined as a frequency of more than 4 loose stools daily), headache, muscle weakness, any new infection).

Application of any current medication (other than immunosuppressive agents) is documented.

Application of further immunosuppressive agents since visit 4 are recorded.

The event of renal biopsy since last visit is recorded with histology.

The physical examination contains investigation of the skin in yes/no manner (acne, cushingoid facies, striae, and hypertrichosis), further pathological organ-specific findings in yes/no/not done manner (lymphadenopathy, pharyngitis, otitis media, heart murmur, arrhythmia, respiratory tract infection, abdominal pain, and muscle weakness) and pubertal status.

Measurement of weight, height (BMI is computed) and blood pressure after 3 minutes rest are done and documented.

A sample of spot urine is analyzed with dip stick (Albusitx®) and quantitatively for creatinine, protein, albumin in the laboratory of the study center (urine protein/creatinine ratio is computed).

The blood test contains: blood cell count (leukocytes, erythrocytes, hemoglobin, and thrombocytes), HbA_{1c}, creatinine, blood urea/blood urea nitrogen (BUN), uric acid, calcium, phosphate, alkaline phosphatase, 25-OH Vitamin D, total protein, albumin, GPT/ALT, IgG, IgE, Cholesterol

Study specific investigations are:

- **24 h ambulatory blood pressure** measurement (24h-ABPM) performed by the study center with documentation of the median of systolic blood pressure (day), of the median of diastolic blood pressure (day), the median of systolic blood pressure (night), the median of diastolic blood pressure (night).
- **Ophthalmologic investigation** performed by any ophthalmologist will document (Cataract (yes/no) and Glaucoma (yes/no))
- **Health related quality of life (HRQoL)** DISABKIDS as standardized questionnaires to assess health related quality of life is used. There exists a parental questionnaire, a questionnaire for children aged ≥8 years and one for children aged 4-7 years of age. Children below 4 years of age will not receive a questionnaire.

- **Echocardiography (Echocardio.)** is optional for the INTENT study and will be performed by a pediatric cardiologist. The documented parameters are: LVID (left ventricular internal diastolic diameter), LVIS (left ventricular internal systolic diameter), PWT (posterior wall thickness), and IVST (interventricular septic thickness). The LVID index, the LV FS (Left ventricular fractional shortening), LVM (left ventricular mass), LVM index, and LVH (Left ventricular hypertrophy) are computed.

These study specific investigations can be performed in a time frame of ±28 days around the visit date.

Visit 6

Visit 6 is scheduled at 15 months (± 14 days) after day 1 (= first day of treatment with standard therapy for first episode of idiopathic nephrotic syndrome in children).

At visit 6, the history since visit 5 is documented, especially if one or more relapses occurred since visit 5. In case of a relapse, date of first day of relapse (definition fulfilled) is documented. For each relapse, it is documented, according to which criteria the relapse was diagnosed: Albustix ≥ 2+ (>30mg/dL) for 3 consecutive days, Spot urine: Up/c ratio ≥ 2 g/g, or collecting urine: Up excretion of ≥ 40 mg/m² BSA/h. If the relapse was treated, the medication is recorded. Further, date of remission is documented (see definitions). In order to document possible trigger factor infections during relapse (e.g. respiratory tract infection, gastroenteritis) and vaccinations within two weeks prior to the relapse are recorded, too. All information from the diary (days missing school attendance, days of hospitalization) since last visit are recorded.

Side effects of the treatment are retrieved in yes/no manner (Behavioral disturbances since visit 5: child feels sad, anxious, irritable, as well as euphoric state, aggressive state, nausea, vomiting (defined as a frequency of more than 1 times per day), diarrhea (defined as a frequency of more than 4 loose stools daily), headache, muscle weakness, any new infection).

Application of any current medication (other than immunosuppressive agents) is documented.

Application of further immunosuppressive agents since visit 5 are recorded.

The event of renal biopsy since last visit is recorded with histology.

The physical examination contains investigation of the skin in yes/no manner (acne, cushingoid facies, striae, and hypertrichosis), further pathological organ-specific findings in yes/no/not done manner (lymphadenopathy, pharyngitis, otitis media, heart murmur, arrhythmia, respiratory tract infection, abdominal pain, and muscle weakness) and pubertal status.

Measurement of weight, height (BMI is computed) and blood pressure after 3 minutes rest are done and documented.

A sample of spot urine is analyzed with dip stick (Albustix®) and quantitatively for creatinine, protein, albumin in the laboratory of the study center (urine protein/creatinine ratio is computed).

The blood test contains: blood cell count (leukocytes, erythrocytes, hemoglobin, and thrombocytes), HbA_{1c}, creatinine, blood urea/blood urea nitrogen (BUN), uric acid, calcium, phosphate, alkaline phosphatase, 25-OH Vitamin D, total protein, albumin, GPT/ALT, IgG, IgE, Cholesterol.

Visit 7

Visit 7 is scheduled at 21 months (± 14 days) after day 1 (= first day of treatment with standard therapy for first episode of idiopathic nephrotic syndrome in children).

At visit 7, the history since visit 6 is documented, especially if one or more relapses occurred since visit 6. In case of a relapse, date of first day of relapse (definition fulfilled) is documented. For each relapse, it is documented, according to which criteria the relapse was diagnosed: Albustix ≥ 2+ (>30mg/dL) for 3 consecutive days, Spot urine: Up/c ratio ≥ 2 g/g, or collecting urine: Up excretion of ≥ 40 mg/m² BSA/h. If the relapse was treated, the medication is recorded. Further, date of remission is documented (see definitions). In order to document possible trigger factor infections during relapse (e.g. respiratory tract infection, gastroenteritis) and vaccinations within two weeks prior to the relapse are recorded, too. All information from the diary (days missing school attendance, days of hospitalization) since last visit are recorded.

Side effects of the treatment are retrieved in yes/no manner (Behavioral disturbances since visit 6: child feels sad, anxious, irritable, as well as euphoric state, aggressive state, nausea, vomiting (defined as a frequency of more than 1 times per day), diarrhea (defined as a frequency of more than 4 loose stools daily), headache, muscle weakness, any new infection).

Application of any current medication (other than immunosuppressive agents) is documented.

Application of further immunosuppressive agents since visit 6 are recorded.

The event of renal biopsy since last visit is recorded with histology.

The physical examination contains investigation of the skin in yes/no manner (acne, cushingoid facies, striae, and hypertrichosis), further pathological organ-specific findings in yes/no/not done manner (lymphadenopathy, pharyngitis, otitis media, heart murmur, arrhythmia, respiratory tract infection, abdominal pain, and muscle weakness) and pubertal status.

Measurement of weight, height (BMI is computed) and blood pressure after 3 minutes rest are done and documented.

A sample of spot urine is analyzed with dip stick (Albustix®) and quantitatively for creatinine, protein, albumin in the laboratory of the study center (urine protein/creatinine ratio is computed).

Visit 8 (end of study)

Visit 8 is scheduled at 27 months (± 14 days) after day 1 (= first day of treatment with standard therapy for first episode of idiopathic nephrotic syndrome in children).

At visit 8, the history since last visit is documented, especially if one or more relapses occurred since visit 7. In case of a relapse, date of first day of relapse (definition fulfilled) is documented. For each relapse, it is documented, according to which criteria the relapse was diagnosed: Albustix ≥ 2+ (>30mg/dL) for 3 consecutive days, Spot urine: Up/c ratio ≥ 2 g/g, or collecting urine: Up excretion of ≥ 40 mg/m² BSA/h. If the relapse was treated, the medication is recorded. Further, date of remission is documented (see definitions). In order to document possible trigger factor infections during relapse (e.g. respiratory tract infection, gastroenteritis) and vaccinations within two weeks prior to the relapse are recorded, too. All information from the diary (days missing school attendance, days of hospitalization) since last visit are recorded.

Side effects of the treatment are retrieved in yes/no manner (Behavioral disturbances since last visit: child feels sad, anxious, irritable, as well as euphoric state, aggressive state, nausea, vomiting (defined as a frequency of more than 1 times per day), diarrhea (defined as a frequency of more than 4 loose stools daily), headache, muscle weakness, any new infection).

Application of any current medication (other than immunosuppressive agents) is documented.

Application of further immunosuppressive agents since last visit are recorded.

The event of renal biopsy since last visit is recorded with histology.

The physical examination contains investigation of the skin in yes/no manner (acne, cushingoid facies, striae, and hypertrichosis), further pathological organ-specific findings in yes/no/not done manner (lymphadenopathy, pharyngitis, otitis media, heart murmur, arrhythmia, respiratory tract infection, abdominal pain, and muscle weakness) and pubertal status.

Measurement of weight, height (BMI is computed) and blood pressure after 3 minutes rest are done and documented.

A sample of spot urine is analyzed with dip stick (Albustix®) and quantitatively for creatinine, protein, albumin in the laboratory of the study center (urine protein/creatinine ratio is computed).

The blood test contains: blood cell count (leukocytes, erythrocytes, hemoglobin, and thrombocytes), HbA_{1c}, creatinine, blood urea/blood urea nitrogen (BUN), uric acid, calcium, phosphate, alkaline phosphatase, 25-OH Vitamin D, total protein, albumin, GPT/ALT, IgG, IgE, Cholesterol.

Study specific investigations are:

- **24 h ambulatory blood pressure measurement (24h-ABPM)** performed by the study center with documentation of the median of systolic blood pressure (day), of the median of diastolic blood pressure (day), the median of systolic blood pressure (night), the median of diastolic blood pressure (night).
- **Ophthalmologic investigation** performed by any ophthalmologist will document (Cataract (yes/no) and Glaucoma (yes/no))
- **Health related quality of life (HRQoL)** DISABKIDS as standardized questionnaires to assess health related quality of life is used. There exists a parental questionnaire, a questionnaire for children aged ≥8 years and one for children aged 4-7 years of age. Children below 4 years of age will not receive a questionnaire.
- **Echocardiography (Echocardio.)** is optional for the INTENT study and will be performed by a pediatric cardiologist. The documented parameters are: LVID (left ventricular internal diastolic diameter), LVIS (left ventricular internal systolic diameter), PWT (posterior wall thickness), and IVST (interventricular septic thickness). The LVID index, the LV FS (Left ventricular fractional shortening), LVM (left ventricular mass), LVM index, and LVH (Left ventricular hypertrophy) are computed.

These study specific investigations can be performed in a time frame of ±28 days around the visit date.

Recording of primary endpoint

Daily dipstick testing of urine and documentation in a standardized diary by a person having care and custody of the child is common current practice in the care of patients with nephrotic syndrome in all pediatric nephrology centers in Mid-Europe.

Treatment of relapses:

No guideline exists on whether standard relapse treatment with prednisone should be started immediately when definition of relapse is fulfilled to avoid the associated complications of an edematous relapse or whether treatment should be deferred for several days to determine whether proteinuria resolves spontaneously. Therefore, in the INTENT study a time period of up

to 10 days is allowed for a possible spontaneous remission, before standard therapy for relapse is initiated.

Treatment of a relapse has to be performed according to standard therapy of the GPN (see Appendix 1).

Relapses with and without treatment are documented in the eCRF.

Treatment of frequently relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS) with other medications than prednisone are carried out according to center practice, because there is no internationally accepted guideline on this topic. The performed treatment with immunosuppressive agents such as cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil, rituximab, or levamisole is documented in the eCRF.

After the completion of the study, patients will be continuously treated according to center practice.

Withdrawals allowing use of routinely recorded data (see 4.4.1)

If a patient withdraws from study participation but the persons having care and custody agree in writing that data routinely recorded by a physician not taking part in the INTENT study can be used for INTENT the following procedure is established:

When a study visit is due, the investigator contacts the physician in order to get routinely recorded data (e.g. relapse and treatment of relapse, serious adverse events, immunosuppressive drugs) and enters the data into the eCRF.

7 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event

According to GCP, an adverse event (AE) is defined as follows: Any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An AE may be:

- New symptoms/medical conditions
- New diagnosis
- Changes of laboratory parameters
- Intercurrent diseases and accidents
- Worsening of medical conditions/diseases existing before clinical study start
- Increase of frequency or intensity of episodical diseases.

A pre-existing disease or symptom will not be considered an adverse event unless there will be an untoward change in its intensity, frequency or quality. This change will be documented by an investigator.

AEs are classified as "non-serious" or "serious".

7.1.2 Serious Adverse Event

A serious adverse event (SAE) is one that at any dose:

- Results in death
- Is life-threatening (the term life-threatening refers to an event in which the subject was at risk of death at the time of event and not to an event which hypothetically might have caused death if it was more severe)
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect or
- Is otherwise medically relevant

Hospitalization for performing protocol-required procedures or administration of study treatment is not classified as an SAE. Hospitalizations for disease-related procedures (imaging, laboratory tests) or any procedures planned before entry into the study are not considered SAEs. Hospitalizations for social reasons in the absence of an adverse event are not classified as SAEs either.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations - such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious (examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; or convulsions that do not result in hospitalization).

7.1.3 Serious Adverse Reaction
SAEs that potentially may be attributed to the investigational medicinal product (IMP) are to be classified as Serious Adverse Reactions (SARs).

7.1.4 Expectedness
An 'unexpected' adverse reaction is one the nature or severity of which is not consistent with the applicable product information, e.g., Summary of Product Characteristics (SmPC). Furthermore, reports which add significant information on specificity or severity of a known adverse reaction constitute 'unexpected' events.

7.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)
SAEs that are both 'suspected', i.e., possibly related to the study drug (investigational medicinal product (IMP)) and 'unexpected', i.e., the nature and/or severity of which is not consistent with the applicable product information are to be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs).

In case, either the investigator who primary reported the SAE or the second assessor, classifies the SAE as 'suspected' [either as 'definitely' or 'probable' or 'possible' related to IMP or 'not assessable'] and the SAE is unexpected the event will be categorized as a SUSAR.

All SUSARs are subject to an expedited reporting to the responsible ethics committee(s), the competent authority and to all participating investigators.

7.1.6 Grading of AEs
The grading of AEs in this study will be carried out on the basis of the 5-grade scale defined in the CTCAE v4.3:

Grade 1:	Mild
Grade 2:	Moderate
Grade 3:	Severe
Grade 4:	Life-threatening or causing disablement
Grade 5:	Death

The grading of all AEs listed in the CTCAE v4.3 will be based on the information contained therein. The grading of all other AEs, i.e., those which are not listed in the CTCAE v4.3 will be performed by a responsible investigator, based on definitions given above.

7.1.7 Relationship and Outcome of AEs
The investigator will evaluate each AE that occurred after administration of the IMP regarding the **relationship** with the administration of the IMP:

Definitely related:	There is a reasonable possibility that the event may have been caused by the IMP. A certain event has a **strong temporal relationship** and an alternative cause is unlikely.
Probable:	An AE that has a reasonable possibility that the event is likely to have been caused by the IMP. The AE has a **timely relationship** and **follows a known pattern of response**, but a potential alternative cause may be present.
Possible:	An AE that has a reasonable possibility that the event may have been caused by the IMP. The AE has a **timely relationship** to the IMP; **however, the pattern of response is untypical**, and an alternative cause seems more likely, or there is significant uncertainty about the cause of

the event.

Unlikely:	Only a remote connection exists between the IMP and the reported adverse event. Other conditions including concurrent illness, progression or expression of the disease state or reaction of the concomitant medication appear to explain the reported adverse event.
Not related:	An AE that does not follow a reasonable temporal sequence related to the IMP and is likely to have been produced by the subject's clinical state, other modes of therapy or other known etiology.
Not assessable:	There is insufficient or incomplete evidence to make a clinical judgment of the causal relationship.

All subjects who have reportable AEs, whether considered associated with the use of the study medication or not, must be monitored to determine the **outcome**. The clinical course of the AE will be followed up until resolution or normalization of changed laboratory parameters or until it has changed to a stable condition. This also holds for ongoing AEs/SAEs of withdrawn subjects.

The outcome of an AE at the time of the last observation will be classified as:

Recovered/resolved:	All signs and symptoms of an AE disappeared without any sequels at the time of the last interrogation.
Recovering/resolving:	The intensity of signs and symptoms has been diminishing and/or their clinical pattern has been changing up to the time of the last interrogation in a way typical for its resolution.
Not recovered/not resolved:	Signs and symptoms of an AE are mostly unchanged or worsened at the time of the last interrogation.
Recovered/resolved with sequel:	Actual signs and symptoms of an AE disappeared but there are sequels related to the AE.
Fatal:	Resulting in death. If there are more than one adverse event only the adverse event leading to death will be characterized as 'fatal'.
Unknown	The outcome is unknown or implausible and the information cannot be supplemented or verified.

The action taken with the IMP will be assigned to one of the following categories:

Dose not changed:	No change in the dose of the IMP.
Dose reduced:	Reduction in the dose of the IMP.
Dose increased:	Increase in the dose of the IMP.
Drug withdrawn:	Discontinuation of the IMP.
Unknown:	The information is unknown or implausible and it cannot be supplemented or verified
Not applicable:	The question is implausible (e.g. the subject is dead).

The term "countermeasures" refers to the specific actions taken to treat or alleviate adverse events or to avoid their sequels. Following categories will be used to categorize the countermeasures to adverse events:

None:	No action taken.
Drug treatment:	Newly-prescribed medication or change in dose of a medication.
Others:	Other countermeasures, e.g. an operative procedure.

7.2 Period of Observation and Documentation

Adverse events (AEs) will be ascertained by the investigators using non-leading questions, noted as spontaneously reported by the patients to the medical staff or observed during any measurements on all study days. The observation period begins with the first administration of the IMP and ends with visit 4, (i.e. 6 months after day 1 [= first day of treatment with standard therapy]). The patient or his primary care physician should report any AE during the outpatient period via phone to the investigator.
AEs will be documented in the patient file and in the CRF. All subjects who present AEs, whether considered associated with the use of the study medication or not, will be monitored by the responsible investigator to determine their outcome; this applies to withdrawals too.
All SAEs and their relevance for the benefit/risk assessment of the study will be evaluated continuously during the study and for the final report. All SAEs will be documented in the "Serious Adverse Event" form (see 7.3).

Withdrawals allowing use of routinely recorded data (see 4.4.1)

If a patient withdraws from study participation but the persons having care and custody agree in writing that data routinely recorded by a physician not taking part in the INTENT study can be used for INTENT the following procedure is established:

The observation period for AEs ends 6 months after day 1 (same as for non-withdrawals). Adverse events reported via the physician will be recorded in the eCRF by the study site. AEs that are serious will be marked in the eCRF but not reported via SAE forms.

For a regular assessment of the benefit-risk-ratio SAE listings of these withdrawals will be generated by the data management every 3 months and forwarded to the Second Assessor (see 7.4). The Second Assessor documents review of the data and forwards the assessment to the KKS Heidelberg (fax number 06221 / 56 33725 or e-mail to kks_sae@med.uni-heidelberg.de). If the benefit/risk assessment is changed the Coordinating Investigator will be informed promptly and adequate measures will be initiated.

7.3 Reporting of Serious Adverse Events by Investigator

All SAEs must be reported by the investigator to the Department of Pharmacovigilance at the KKS Heidelberg within 24 hours after the SAE becomes known using the "Serious Adverse Event" form. The initial report must be as complete as possible including details of the current illness and (serious) adverse event and an assessment of the causal relationship between the event and the study medication.

The reporting will be performed by faxing a completed ‘SAE Form’ to the KKS Heidelberg:

Fax number:
06221 – 56 – 33725

7.4 Expedited Reporting

SUSARs are to be reported to the responsible ethics committee, the competent authority (BfArM) and to all participating investigators within defined timelines, i.e. they are subject to an expedited reporting.

All SAEs will be subject to a second assessment by a designated person or his deputy, who will be independent from the reporting investigator.

The second assessor will fill out a 'Second Assessment Form' for each SAE and send it back per fax to the responsible person at the KKS Heidelberg within 48 hours:

Fax-number:
06221 – 56 – 33725

The 'Second Assessment Form' will contain the following information:

I) assessment of relationship between SAE and IMP (causality)

II) assessment of expectedness of SAE (SmPC)

III) statement if the benefit/risk assessment for the study did change as a result of SAE.

The expedited reporting (to competent authority, responsible ethics committee and investigators) will be carried out by a responsible Safety Officer at KKS Heidelberg. Fatal and life-threatening SUSARs must be reported without delay, but not later than 7 calendar days after becoming aware of the minimum reporting criterias. SUSARs that are not fatal or life-threatening must be reported without delay, at least within 15 calandar days after becoming aware of the minimum reporting criterias.Only SUSARs occurring after administration of IMP will undergo expedited reporting.

7.5 Development Safety Update Reports (DSURs)

The sponsor will prepare annual Development Safety Update Reports (DSURs) for competent higher federal authority (BfArM) as required. The reference date for the calculation of the Data Lock Points is the "date of the initial approval of the study by the competent higher authority" (BfArM). The format of the DSUR is in accordance with the ICH guideline E2F "Note for guidance on development safety update reports".

For purposes of safety analyses the sponsor is responsible to record all AE in a clinical database. To ensure the basis for expedited and periodic notification of authorities, SAEs will be additionally recorded in the drug safety database.

8 BIOSTATISTICAL CONSIDERATIONS

This section describes the considerations underlying the choice of the sample size as well as the statistical methodology applied for the analysis of primary and secondary outcome variables. More details can be found in the statistical analysis plan which will be finalized prior to performing any analyses.

8.1 Sample Size Calculation

The sample size calculation is based on the primary efficacy endpoint “occurrence of treated relapse within 24 months after completion of the initial treatment”. In the literature different information are given regarding the relapse rate for the control group receiving standard prednisone therapy. We have decided to assume a relapse rate of 51% according to Gipson et al. [8] which gives the worst case resulting in a conservative sample size estimation. The same rate is expected for the experimental group. If the relapse rate in the experimental group accounts to less than 15% above the relapse rate of the control group, this will be considered as clinically irrelevant based upon clinical judgment. Therefore the margin is set to δ=0.15. As the direction of the difference to be established is known for non-inferiority studies and as - due to the rareness of the disease and the related limited available number of patients - the study could otherwise not be performed with sufficient power, a one-sided significance level of 5% is applied. Testing at a one-sided significance level of α = 5% and aspiring a power of 80%, a total of 272 patients (136 per group) are required (calculations performed with AddPlan 6.0). To account for 10% drop-out rate and major protocol violations in a further 10% 340 patients will be randomized.

8.2 Compliance/Rate of loss of follow up

The nephrotic syndrome in children is mostly an acutely presenting disease, and parents are very concerned about their child. With standard prednisone treatment we observe an adherence to therapy of more than 95%. According to our previous experience in performing studies in pediatric nephrology we assume that a minimum of 85% of patients assessed for eligibility will be allocated to study [4,5,19]. Due to the exclusive care of these patients in specialized pediatric nephrology centers we calculate with a loss of follow-up of maximum 20% which corresponds to our previous studies [4,5,19]. The recent study of the GPN, showing that MMF is efficacious in sustaining remission in children with frequently relapsing nephrotic syndrome, had only a drop-out rate of 4%. Therefore, for the entire study, we estimated 400 children with steroid-sensitive nephrotic syndrome to be assessed for eligibility, 340 to be allocated to study and 272 patients to be analyzed per protocol. However, in cases of premature withdrawal by a patient the persons having care and custody of this patient will be asked for informed consent so that routinely recorded data by the responsible physician can be used for the INTENT study. In this manner as many data as possible are recorded for evaluation of treatments in this rare disease.

8.3 Analysis Populations

The primary analysis will be performed for both the per-protocol population (PP) and the intention-to-treat population (ITT). The PP population comprises all patients, who were treated according to the randomized treatment as outlined in the protocol without major protocol violations (e.g., reduction of study medication of >50% or interruption of study medication of >3 days, violation of in- or exclusion criteria).The ITT population will compromise all patients randomized into the study. In this set, every patient is analyzed according to the group randomized into.

Since there may be patients who withdraw from the study after the treatment period or within the treatment period but consent to the incorporation of routinely recorded data was given the inclusion of these patients into the ITT population will be decided case by case before database lock and defined when writing the SAP. As appropriate, a third population will be defined for analysis of the primary and important secondary endpoints. How to deal with these patients and their data in detail depends on the time point of withdrawal and the amount and reliability of the routinely collected data.

The safety set will comprise all patients who have received study medication at least once, and will allocate the patients to the treatment they actually received, regardless of randomization. Whether routinely collected data of patients who withdraw prematurely can be included herein depends on the reliability of the collected safety data.

8.4 Statistical Methods

The primary efficacy endpoint is the occurrence of a treated relapse within 24 months after completion of initial treatment. The non-inferiority of the experimental group *vs.* control group will be evaluated using the test according to Farrington and Manning [17]. The one-sided significance level is set to 5%.

The hypotheses to be assessed in the primary efficacy analysis are formulated as follows:
H_0: p_MMF – p_Prednisone ≥ δ (δ=0.15, non-inferiority margin, see Section 8.1 Sample Size Calculation for justification)
H_1: p_MMF – p_Prednisone < δ, where p_* denotes the relapse rate in the respective group.

Before database closure the assignment of patients to the PP population (patients with no major protocol violations) and the ITT population (as classified by the intent-to-treat principle) are defined in the statistical analysis plan. The confirmatory analysis is performed for both the PP population and the ITT population. This approach reflects the equal importance of both anaylsis sets in a non-inferiority trial [29]. . For the PP analysis missing values for the primary endpoint are not expected. In the ITT population missing values will be replaced according to Higgins [27]. As appropriate, a third population will be defined to adequately incorporate routinely collected data of patients who withdraw prematurely but gave informed consent for usage of routinely collected data. Details on inclusion of such data into sensitivity analyses of primary and secondary endpoints will be defined in more detail in the SAP. In case of uncertainty regarding data quality and reliablility these patients will only be analysed descriptively.
Additionally, binary logistic regression models will be performed as sensitivity analysis for the intervention comparison of the relapse rates adjusting for age, gender, center (grouped), and for results of therapeutic drug monitoring (grouped) based on different populations (PP, ITT, with values of drop-outs set to worst case).
All secondary outcomes will be evaluated descriptively, using appropriate statistical methods based on the underlying distribution of the data. Descriptive p-values are reported together with 95% confidence intervals for the corresponding effects. Descriptive statistics for continuous parameters and scores include number of non-missing observations, mean, standard deviation, median, minimum and maximum, performed for treatment groups as well as subgroups and overall. The description of categorical variables (ordinal or nominal) includes the number and percentage of patients belonging to the relevant categories in the study population as well as to each treatment group.
Rates of adverse and serious adverse events will be calculated with 95% confidence intervals for treatment group comparisons.
Statistical methods are used to assess the quality of the data, homogeneity of treatment groups, endpoints and safety of the two intervention groups. Details of the statistical analysis will be fixed at the latest in the Statistical Analysis Plan (SAP) to be prepared within the first year after start of patient recruitment. All persons taking part in the preparation of the SAP and possible

later changes to it will only have access to blinded data to avoid introduction of bias. All analyses will employ SAS Version 9.2 or higher.

8.5 Interim Analyses

For the INTENT study, no interim analysis at a fixed time point is performed for the following reason: The recruitment phase is planned to be 36 months. The primary endpoint is occurrence of treated relapse within 24 months after end of initial treatment. Therefore, information on the primary endpoint for a first portion of the study patients will be available not before end of the recruitment phase. For this reason, a group-sequential approach was not pursued.

However, an independent DSMB will closely monitor the recruitment, the reported adverse events and the data quality of the study thus ensuring the ethical conduct of the study and protecting the safety interests of patients.

9 DATA MANAGEMENT

9.1 Data Management and Quality Assurance

The investigator or a designated representative must enter all protocol-required information in the electronic case report form (eCRF). The eCRF should be completed as soon as possible after the information is collected, preferably on the same day when a study subject is seen for an examination, treatment, or any other study procedure. The reason for missing data should be provided. The investigator is responsible for ensuring that all sections of the eCRF are completed correctly and that entries can be verified in accordance with the source data. Any entry and correction in the Remote Data Entry System will be documented automatically in an audit file.
Completeness, validity and plausibility of data will be checked in time of data entry (edit-checks) and using validating programs, which will generate queries. The investigator or the designated representatives are obliged to clarify or explain the queries. If no further corrections are to be made in the database it will be closed and used for statistical analysis. All data management procedures will be carried out on validated systems and according to the current Standard Operating Procedures (SOPs) of the IMBI.

9.2 Archiving of Essential Documents

The investigator(s) will archive all study data (source data and Investigator Site File (ISF) including subject identification list and relevant correspondence) according to the section 4.9 of the ICH Consolidated Guideline on GCP (E6) and to local law or regulations.

The sponsor or other owner like investigators of the data shall retain all other documentation pertaining to the study for at least 10 years according to the §13 of the German GCP-Ordinance.

Any change of data ownership shall be documented. All data shall be made available if requested by relevant authorities.

TMF (Trial Master File) will be organized by KKS and archived by the coordinating investigator (LKP).

10 ETHICAL AND LEGAL ASPECTS

10.1 Good Clinical Practice

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that all persons involved in the study abide by ICH harmonized tripartite guideline on Good Clinical Practice (ICH-GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki. The study will be carried out in keeping with local legal and regulatory requirements.

10.2 Legal bases

The study has to be conducted in compliance with the protocol, ICH-GCP and the applicable regulatory requirements.

10.2.1 Declaration of Helsinki
The study will be carried out in conformity with the "Ethical principles for medical research involving human subjects" of the 18th World Medical Association General Assembly in Helsinki (1964), and amended by the 29th, 35th, 41st, 48th, 52nd and 59th, World Medical Association General Assemblies (Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh 2000, Seoul 2008, and Fortaleza 2013) and the Note of Clarification on Paragraph 29 added by the World Medical Association General Assembly, Washington 2002 and the Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004. The applicable version for the respective country will be taken into consideration.

10.2.2 Other Legal Bases
The other legal bases of this clinical study are as follows:

- ICH Topic E6, Guideline for Good Clinical Practice, including post Step 4 errata, September 1997
- Directive 2001/20/EC (April 4, 2001)
- Commission Directive 2005/28/EC (April 8, 2005)
- National regulatory requirements/guidelines of the participating countries concerning Clinical Studies [e.g. federal drug law (AMG), GCP ordinance (GCP-Verordnung), Medical device law (MPG)]
- General national regulatory requirements, e.g. Bundesdatenschutzgesetz (BDSG)

10.3 Approval of Study Protocol and Amendments

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the independent Ethics Committee (EC) as well as to the competent authority (BfArM).

A written favorable vote of the EC and an (implicit) approval by the competent authority are a prerequisite for initiation of this clinical study. The statement of EC should contain the title of the study, the study code, the study site, and a list of reviewed documents. It must mention the date on which the decision was made and must be officially signed by a committee member. This documentation must also include a list of members of the EC present on the applicable EC meeting and a GCP compliance statement.

The investigator, supported by the KKS Heidelberg, will keep a record of all communication with the EC and the regulatory authorities.

Before the first subject is enrolled in the study, all ethical and legal requirements must be fulfilled.

All planned substantial changes (see §10, [28] of German GCP-Regulation) will be submitted to EC and the competent authority in writing as protocol amendments. They have to be signed by the sponsor and biometrician and approved by the EC and the competent authority.

10.4 Notification of Regulatory Authorities

In addition to the approval by the competent authority (see 10.3) the clinical study must also be notified to the competent authority before recruitment of the first patient (according to AMG §67).

The local regulatory authorities responsible for each particular investigator will be informed before the beginning, during and at the end of the study according to the applicable regulations. Each investigator is obliged to notify his/her local regulatory authority whereas the notification of the competent authority is the responsibility of the sponsor. Both responsibilities have been delegated to the KKS.

Substantial Amendments, interruption or premature end of the study need to be reported, too.

10.5 Information, Informed Assent and Informed Consent

Before being admitted to the clinical study, the persons having care and custody of the child must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. The persons having care and custody of the child must give consent in writing.

Only if the legal guardians have given consent and the disease has been explained to the patient in general, the patient is also informed about the study. The extent and manner of this information depends on the maturity of the child. Signing of the assent form (if the patient is able to write) is considered only as documentation of not having refused study participation. Alternatively, the investigator documents that the child understood the information given and does not refuse participation in the study.

A copy of the signed informed consent document must be given to the persons having care and custody of the child; the original will be filed by the investigator. If the assent form for the child has been signed as well, a copy is given to the patient resp. the legal guardians, too. The documents must specify who informed the patient and the persons having care and custody of the child.

The persons having care and custody of the child will be informed as soon as possible if new information may influence his/her decision to participate in the study. Depending on the maturity of the child, also the child is informed about such news. The communication of this information should be documented.

10.6 Insurance

According to § 40 AMG, the sponsor has to subscribe to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards. The insurance was taken out at Zurich Insurance plc (insurance number: 801.520.894.139).

Any impairment of health which might occur in consequence of study participation must be notified to the insurance company. The subject is responsible for notification. The insured person will agree with all appropriate measures serving for clarification of the cause and the extent of damage as well as the reduction of damage.

During the conduct of the study, the subject must not undergo other clinical treatment except for cases of emergency. The subject is bound to inform the investigator immediately about any

adverse events and additionally drugs taken. The terms and conditions of the insurance should be delivered to the subject.

The insurance company has to be informed about all amendments that could affect subjects' safety.

10.7 Continuous Information to the Ethics Committee and the Competent Authority

Pursuant to the German Drug Law (AMG) and the GCP Ordinance, the responsible EC, the competent authority and all participating investigators will be informed of all suspected serious unexpected adverse reactions (SUSARs) occurring during the study. Both institutions will be informed in case the risk/benefit assessment did change or any others new and significant hazards for subjects' safety or welfare did occur. Furthermore, a report on the subject's safety will be submitted once a year – Development Safety Update Report.

The EC and the regulatory authorities must be informed of the end of the study. They will be provided with a summary of study results within one year after the end of clinical phase (LPO).

11 QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor, the investigators, and all involved study personnel agree to conduct this clinical study in accordance with the ICH Guideline for Good Clinical Practice.

11.1 Data Protection

The data obtained in the course of the study will be treated pursuant to the Federal Data Protection Law (Bundesdatenschutzgesetz, BDSG).

Study findings stored on a computer will be stored in accordance with local data protection law and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of local data legislation will be fulfilled in its entirety.

The persons having care and custody of the child consents in writing to release the investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by health authorities and authorized persons (inspectors, monitors, auditors). Authorized persons (clinical monitors, auditors, and inspectors) may inspect the subject-related data collected during the study ensuring the data protection law.

The investigator will maintain a subject identification list (screening numbers with the corresponding subject names and randomization numbers) to enable records to be identified. If the patient or the persons having care and custody of the child did not assent/consent to circulate their pseudonymized data, they will not be included into the study.

This protocol, the CRFs, other results forms, laboratory data must be handled with strict confidentiality and not be disclosed to third parties except with the express prior consent of Sponsor. In particular, it must be ensured that the study medication is kept out of reach of third parties. Staffs of the investigators involved in this study are also bound by this agreement.

11.2 Monitoring

Monitoring will be done by personal visits from a clinical monitor according to SOPs of the KKS. The monitor will review the entries into the CRFs on the basis of source documents. The investigator must allow the monitor to verify all essential documents and must provide support at all times to the monitor.

By frequent communications (letters, telephone, fax), the site monitor will ensure that the study is conducted according to the protocol and regulatory requirements.

Frequency and details of monitoring will be defined in the monitoring manual.

11.3 Inspections and Audits

Regulatory authorities and/or auditors authorized by the sponsor may request access to all source documents, CRF, and other study documentation. Direct access to these documents must be guaranteed by the investigator who must provide support at all times for these activities.

The investigator will inform the sponsor immediately about a planned inspection.

11.4 Responsibilities of the Investigator

The investigator ensures that all team members are informed adequately about the protocol, all amendments to the protocol, the study procedures und study specific duties and tasks.

The investigator will maintain a list to delegate tasks to the team members.

12 ADMINISTRATIVE AGREEMENTS

12.1 Financing of the Study

The study will be financed using funds of the BMBF.

12.2 Financial Disclosure

Before the start of the study, the investigator will disclose to the sponsor any proprietary or financial interests he or she might hold in the sponsor/a funding company, in the investigational product(s) or any commercial organization being involved in the clinical study. The investigator has also to confirm that he/she has not entered into any financial arrangement, whereby the value of compensation paid could affect the outcome of the clinical study.

The investigator agrees to update this information in case of significant changes.

12.3 Reports

The clinical project management will produce a final integrated clinical study report. The IMBI Heidelberg will provide the biometrical part of this document.

Since 21 July 2014, posting of clinical study summary results in the European Clinical Trials Database (EudraCT) is mandatory for sponsors. In the case of a pediatric study as INTENT, this will have to be done by the sponsor and the clinical project management within 6 months after completion of the study.

Within one year of the completion of the study, the competent federal authority and the ethics committee will be supplied with a summary of the final report on the clinical study containing the main results.

12.4 Registration of the Study

Prior to the beginning of the clinical phase (FPI), the clinical project management will register the study at “GermanCtr.de”. Thus the study will be given a unique registration number, which is a prerequisite for a publication in a peer-review paper.

12.5 Publication

All information concerning the study is confidential before publication.

Publication strategy:

The planned INTENT study has been assigned priority by the German Society for Pediatric Nephrology (GPN). After public study registration, the protocol will be published open-access with e.g. Biomed Central. The results of the study will have substantial impact on health care policy. It will be distributed among the GPN members at regular conferences every six months, and incorporated in current clinical practice guidelines (AWMF Leitlinie). It can reliably be assumed that the study findings will not only be highly recognized on a national, but also on international level.Study results may be of interest not only for pediatric nephrologists, but also for a general medical audience and their journals. In addition to publishing the results in a highly reputed journal, results of this study will be submitted for oral and poster presentations at national and international conferences (e.g. Annual Meeting of the German Society for Pediatrics, European Society for Pediatric Nephrology (ESPN), International Pediatric Nephrology Association (IPNA) and others.

13 SIGNATURES

The present study protocol was subject to critical review and has been approved in the present version by the persons undersigned. The information contained is consistent with:

- the current risk-benefit assessment of the investigational medicinal product,
- the moral, ethical, and scientific principles governing clinical research as set out in the latest relevant version of Declaration of Helsinki, the principles of the guidelines of ICH Good Clinical Practices and the applicable legal and regulatory requirements.

The investigator will be supplied with details of any significant or new finding including AEs relating to treatment with the investigational medicinal product.

Date: 19.12.2018 Signature: _____

Name (block letters): BURKHARD TOUSHOFF

Function: Coordinating investigator (LKP according to §40 AMG)

Date: _____ Signature: _____

Name (block letters): _____

Function: Medical Coordinator (Author)

Date: _____ Signature: _____

Name (block letters): _____

Function: Biometrician

13 SIGNATURES

The present study protocol was subject to critical review and has been approved in the present version by the persons undersigned. The information contained is consistent with:

- the current risk-benefit assessment of the investigational medicinal product,
- the moral, ethical, and scientific principles governing clinical research as set out in the latest relevant version of Declaration of Helsinki, the principles of the guidelines of ICH Good Clinical Practices and the applicable legal and regulatory requirements.

The investigator will be supplied with details of any significant or new finding including AEs relating to treatment with the investigational medicinal product.

Date:	_____	Signature:	_____
		Name (block letters):	_____
		Function:	Coordinating investigator (LKP according to §40 AMG)
Date:	17.12.2018	Signature:	_____
		Name (block letters):	Marcus BENZ
		Function:	Medical Coordinator (Author)
Date:	_____	Signature:	_____
		Name (block letters):	_____
		Function:	Biometrician

13 SIGNATURES

The present study protocol was subject to critical review and has been approved in the present version by the persons undersigned. The information contained is consistent with:

- the current risk-benefit assessment of the investigational medicinal product,
- the moral, ethical, and scientific principles governing clinical research as set out in the latest relevant version of Declaration of Helsinki, the principles of the guidelines of ICH Good Clinical Practices and the applicable legal and regulatory requirements.

The investigator will be supplied with details of any significant or new finding including AEs relating to treatment with the investigational medicinal product.

Date:	_____	Signature:	_____
		Name (block letters):	_____
		Function:	Coordinating investigator (LKP according to §40 AMG)
Date:	_____	Signature:	_____
		Name (block letters):	_____
		Function:	Medical Coordinator (Author)
Date:	17.12.2018	Signature:	
		Name (block letters):	Anja Sander
		Function:	Biometrician

14 DECLARATION OF INVESTIGATOR

I have read the above study protocol and confirm that it contains all information to conduct the clinical study. I pledge to conduct the clinical study according to the protocol.

I will enroll the first subject only after all ethical and regulatory requirements are fulfilled. I pledge to obtain written assent for study participation from all patients, if ≥6 years of age. I pledge to obtain written consent for study participation from all persons having care and custody of the child

I know the requirements for accurate notification of serious adverse events and I pledge to document and notify such events as described in the protocol.

I pledge to retain all study-related documents and source data as described. I will provide a Curriculum Vitae (CV) before study start. I agree that the CV and Financial Disclosure (FD) may be submitted to the responsible EC.

Date: _____ Signature: _____

Name (block letters): _____

Function: Investigator

Investigational Site (address): _____

_____

_____

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16 APPENDICES

Appendix 1: Definitions

Appendix 2: Interpretation of Albustix®

Appendix 1 Definitions

Item	Definition	Literature
Nephrotic syndrome	Criteria: 1. urine protein level of ≥40 mg/m^2 BSA/h (urine collection for a minimum of 12 hours) or urine protein/creatinine (Up/c) ratio ≥ 2 g/g (first or second morning urine) **and** 2. serum albumin concentration ≤ 2.5 g/dL	[4,23,25]
Remission	Remission is denoted by a reduction of urinary protein (concentration or excretion) in the first or second morning urine for 3 consecutive days to: Albustix™ negative or trace or Up/c ≤ 0.2 g/g* or urine protein excretion of ≤ 4 mg/m^2 BSA/h (urine collection for a minimum of 12 hours)* * If the results of Albustix™ are doubtful, first or second morning urine or a specimen of a urine collection (minimum 12-hour urine collection) has to be checked. This can be performed at the study center or at any pediatrician.	[4,23,25]
Albustix™	Albustix™ Bayer VitDiagn. PZN 01266154 Interpretation (first or second morning urine): Negative or trace = ≤4 mg/m² BSA/h 2+ to 4+ = >4 mg/m² BSA/h 1+ = doubtful value → the urine protein/creatinine ratio (Up/c) or a specimen of a urine collection has to be analyzed, if 1+ appears for 3 days or 1+ is combined with ≥2+ within 3 days.	[4,23,25]
Steroid sensitive nephrotic syndrome (SSNS)	Remission within 28 days after beginning of standard therapy for first episode of idiopathic nephrotic syndrome in children Remission is defined as given above.	[4,23,25]
Standard therapy for first episode of idiopathic nephrotic syndrome in children	Prednisone 60 mg/m^2 BSA/d (maximum 80 mg) for a total of 6 weeks (dosage is given in three divided doses per day with the highest dose in the morning) Followed by Prednisone 40 mg/m^2 BSA (maximum 60 mg) given on alternate days for 6 weeks (the entire dosage is given in the morning)	[4,8]

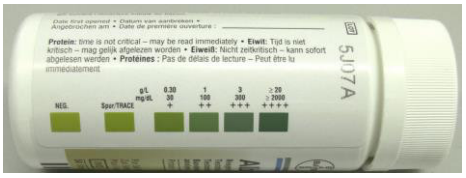
	(alternate day = every second day)	
Relapse	Relapse is denoted by a reappearance of proteinuria for 3 consecutive days: Albustix™ ≥ 2+ (first or second morning urine) (for interpretation see Albustix™) or urine protein/creatinine ratio (Up/c) ratio ≥ 2 g/g (first or second morning urine)* or urine protein excretion of ≥ 40 mg/m^2 BSA/h (urine collection for a minimum of 12 hours)* * If the results of Albustix™ are not clear, first or second morning urine or a specimen of a urine collection has to be checked. This can be performed at the study center or at any pediatrician. A spot urine sample with a protein/creatinine (Up/c) ratio of ≥ 2 g/g or a urine protein excretion of ≥ 40 mg/m² BSA/h (urine collection for a minimum of 12 hours) will define the relapse. In case of a relapse the study center should be informed by the persons having care and custody of the child. After diagnosis of a relapse, a time period of up to 10 days is allowed for a possible spontaneous remission, before standard therapy for relapse is initiated (see below). This decision is at the discretion of the study center. Treatment of the relapse has to be initiated according to the standard therapy of the GPN (see below). Relapses with and without treatment are documented in the eCRF.	[4,8]
Standard therapy for relapse of idiopathic nephrotic syndrome in children	Prednisone 60 mg/m^2 BSA/d (maximum 80 mg) until remission (this dose is given in one dose or in two to three divided dosages per day with highest dosage in the morning), which is denoted by a reduction of urinary protein concentration or excretion in the first or second morning urine for 3 consecutive days to: Albustix™ negative or trace or Up/c ≤ 0.2 g/g* or urine protein excretion of ≤ 4 mg/m^2 BSA/h (urine collection for a minimum of 12 hours)* * If the results of Albustix™ are doubtful, first or second morning urine or a specimen of a urine collection has to be checked. This can be performed at the study center or at any pediatrician. Followed by Prednisone 40 mg/m^2 BSA (maximum 60 mg) on alternate days for 4 weeks	[4,8]

	(entire dosage is given in the morning) (alternate day = every second day)	
Frequently relapsing nephrotic syndrome	Relapses occur 4 or more times in any 12 month period or 2 or more relapses within the first 6 months period after initial response.	[4,23,25]
Steroid-dependent nephrotic syndrome (SDNS)	Relapses occur during the alternate day prednisone treatment period or within 2 weeks after discontinuation of prednisone treatment.	[4,23,25]
Steroid-resistant nephrotic syndrome (SRNS)	No remission within 28 days after initiation of standard prednisone therapy for the first episode of idiopathic nephrotic syndrome in children	[4,23,25]
eGFR	Estimated glomerular filtration rate Formula = (K * height [cm])/serum creatinine [mg/dl] K = constant (determined by regression analysis) depends on the method of creatinine measurement: • Jaffé method (photometric, kinetic measurement with picric acid) constant for age 1-13 years: K = 0.55 • Enzymatic measurement constant K = 0.413	[25,26]
Body surface area (BSA)	$\sqrt[2]{(\text{height [cm]}*\text{weight [kg]})/3600}$	
Alternative immunosuppressive agents in case of glucocorticoid-induced toxicity	In frequently relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS) alternative immunosuppressive agents such as cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil or rituximab may be administered according to center practice.	

Appendix 2: Interpretation of Albustix®

Results of Albustix®

- Negative
- Trace
- 30 mg/dL = +
- 100 mg/dL = ++
- 300 mg/dL = +++
- ≥ 2000 mg/dL = ++++



- If Albustix® is ≥ 30 mg/dL
  - Daily weight with domestic scales [kg]
  - Daily investigation for edema (yes/no)
  - The urine protein/creatinine ratio (Up/c) or a specimen of a urine collection has to be analyzed, if 1+ appears for 3 days or 1+ is combined with ≥2+ within 3 days.
  - In doubt the persons having care and custody of the child are encouraged to contact the study center.
- If Albustix® is ≥ 100 mg/dL
  - The persons having care and custody of the child have to contact the study center.