# FINAL STUDY REPORT ACCORDING TO § 42b AMG

*– Results have not yet been published in a peer-reviewed journal. –*

**Study Title:**

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

**Acronym: INTENT Study**

This is a multicenter clinical trial designed to show that MMF is not inferior to standard high-dose prednisone therapy in the initial treatment of idiopathic steroid-sensitive nephrotic syndrome (SSNS) in children in terms of maintenance of initial remission and subsequent relapse rate.

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| **Version Number/ Date:** | Final report Version 1.0 / 31.01.2024 |
| **EudraCT-Number:** | 2014-001991-76 |
| **Date of Approval by 1st CA:** | 10.03.2015 |
| **Identification (template no.) CA:** | 4040246 |
| **Identification Ethics Committee:** | AFmu-554/2014 |
| **Protocol version:** | Version 6.0 /20181205 |
| **Investigational drugs:** | Mycophenolate mofetil |
| **Reference drug:** | Prednisone |
| **Indication:** | Idiopathic nephrotic syndrome in children |
| **Phase of study:** | Phase III |
| **Registration number** | DRKS 00006547 |

| Sponsor: | Principal Investigator/Coordinating Investigator (Leiter der klinischen Prüfung*): |
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* According to § 40 German Drug Law (AMG)

| Clinical Project Management | Biometrics |
|---|---|
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| Study centers | |
|---|---|
| See Appendix 1 | |
| **Protocol versions** | |
| Study_protocol _INTENT_V2_2015_02_12 | (Votum EC: 2015_03_18) |
| Study_protocol _INTENT_V3_2015_03_11 | (Votum EC: 2015_05_06) |
| Study_protocol_INTENT_V4_2015_03_25 | (Votum EC: 2015_05_06) |
| Study_protocol_INTENT_V5_2016_04_26 | (Votum EC: 2016_06_01) |
| Study_protocol _INTENT_V6_2018_12_05 | (Votum EC: 2019_01_08) |
| Addendum_Study_protocol_INTENT_V6_2018_12_05 | (Votum EC: 2020_12_23) |

| **Publication** (reference) |
|---|
| Ehren R, Benz MR, Doetsch J, Fichtner A, Gellermann J, Haffner D, Höcker B, Hoyer PF, Kästner B, Kemper MJ, Konrad M, Luntz S, Querfeld U, Sander A, Toenshoff B, Weber LT; Gesellschaft für Pädiatrische Nephrologie (GPN). Initial treatment of steroid-sensitive idiopathic nephrotic syndrome in children with mycophenolate mofetil versus prednisone: protocol for a randomised, controlled, multicentre trial (INTENT study). BMJ Open, 2018. 8(10): p. e024882. |
| **Study period** |
| Date of first enrolment: 12.10.2015<br>Date of last enrolment: 23.04.2021<br>Date of early termination: 27.04.2021<br>Date of last completed: 27.07.2023<br><br>Early termination of the study after inclusion of 272 patients due to the recommendation of the data safety monitoring board, which had commissioned a futility analysis. |
| **Duration of study for each patient** |
| The patient is recruited individually after achieving remission in the manifestation of nephrotic syndrome and randomized into the treatment groups. The patient is treated until total initial treatment duration of 12 weeks is reached (induction of remission with prednisone + maintenance of remission with prednisone (control) or with MMF (experimental intervention)). After the end of the treatment phase, a follow-up period of 24 months follows. |
| **Indication** |
| First episode of steroid-sensitive nephrotic syndrome (SSNS) in children in remission (N04.9)<br>Nephrotic syndrome: MedDRA term 10029164 (version: 16.2, LLT) |
| **Phase of development** |
| Phase III |
| **Objectives** |
| To demonstrate that mycophenolate mofetil as initial treatment is not inferior to standard treatment with prednisone related to relapse rate within 24 months<br>**Primary efficacy endpoint:**<br>Occurrence of treated relapse within 24 months after end of initial treatment<br>**Key secondary endpoint(s):**<br>• Course of the disease: Time from remission to first treated relapse; number of relapses; mean relapse rate per patient and year; incidence of frequent relapsers<br>• 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<br>• MMF-associated toxicity: diarrhea; blood cell count disturbances, infections |
| **Investigational medical product** |
| INN: Mycophenolate mofetil (MMF)<br>ATC-code: L04AA06<br>MMF is administered in liquid form (CellCept suspension, Roche AG).<br>Dosing: Mycophenolate mofetil (MMF) 1200 mg/m2 body surface area (BSA) per day, until a |

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| total initial treatment duration of 12 weeks is reached (induction of remission with prednisone + maintenance of remission with MMF (intervention)).<br>MMF is administered in conjunction with alternate day prednisone 40 mg/m2 BSA for the first 2 weeks. |
| **Reference drug** |
| INN: Prednisone<br>ATC-code: H02AB07<br>Prednisone is administered as tablet.<br>Dosing: Continuing the standard protocol for children with first episode of SSNS according to GPN guidelines: 60 mg prednisone/m2 BSA per day for 6 weeks followed by alternate day prednisone 40 mg/m2 BSA for another 6 weeks. |
| **Study design** |
| Prospective, randomized, multicenter, controlled, open, parallel group study |
| **Study population** |
| Inclusion Criteria<br>• First episode of steroid-sensitive nephrotic syndrome (SSNS)<br>• In remission induced by daily glucocorticoids within 28 days<br>• Male and female children aged ≥ 1 year and ≤ 10 years at beginning of study (typical age range of patients with SSNS)<br>• Ability of the persons having care and custody of the child to understand character and individual consequences of clinical study<br>• Written informed consent of the persons having care and custody of the child.<br>Exclusion Criteria<br>• Secondary nephrotic syndrome<br>• estimated glomerular filtration rate (eGFR) <90 ml/min x 1.73 m2 BSA<br>• Ongoing treatment with systematically administered glucocorticoids or other immunosuppressive drugs at time of first episode of nephrotic syndrome<br>• Hemoglobin concentration of ≤9 g/dL<br>• Leucocyte count of ≤2.500/µl<br>• Severe chronic gastrointestinal disease<br>• 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)<br>• Refusal of subject (please see also chapter 10.5)<br>• Participation in other clinical studies or observation period of competing studies, respectively |
| **Sample size** |
| Number of patients planned: 340<br>Number of patients analyzed: 272 |
| **Statistical analysis** |
| The non-inferiority of the experimental group (MMF) versus the control group (Pred) was evaluated using the test according to Farrington and Manning with a one-sided significance level of 5%. The hypothesis to be assessed was as follows: |

$$H_0: p_{MMF} - p_{Predn} \geq \delta \text{ vs. } H_1: p_{MMF} - p_{Pred} < \delta,$$

where $\delta$=0.15 denotes the non-inferiority margin and $p_{MMF}$ and $p_{Pred}$ the rate of the primary endpoint in the MMF and Pred group, respectively. Confirmatory analysis was done based on the modified intention to treat (mITT) and per-protocol (PP) set.
If no treated relapse in the FU phase was observed but follow-up data after a specific visit were missing (e.g. due to drop-out, withdrawal), the primary endpoint was imputed in the following way: a logistic regression model was used to estimate the probability of occurrence of a treated relapse after loss to FU/withdrawal. The model included treatment group, age (continuous), gender, center (grouped, number of recruited patients <10 vs. ≥10), relapse (treated or untreated) in treatment phase (y/n), and patient in PP set (y/n). As the time being relapse-free may influence the probability of occurrence of a treated relapse in the future, this information was taken into consideration by fitting separate models. Subsequently, occurrence of treated relapse in FU phase (y/n) were randomly drawn with relapse probability as calculated. The imputation was done for the mITT set. In the PP analysis, the values as imputed for the mITT set were used.

Secondary endpoints:
Descriptive p-values of the corresponding statistical tests comparing the treatment groups and associated 95% confidence intervals will be given.

Safety:
The total number of adverse events (AE) and serious adverse events (SAE) during the observation period (starting with first administration of the investigational medicinal product and ending with visit 4 [i.e. 6 months after the first treatment with standard therapy]) were reported by group. The rates of patients experiencing at least one AE or SAE during the observation period were calculated per group.

Statistical analyses were performed using the software package SAS version 9.4.

## SUMMARY – CONCLUSIONS

### Efficacy results

Three patients are not considered in the mITT set as they did not meet the criteria for being in remission at start of therapy (after randomization). The PP set consists of 101 patients in the MMF and 112 patients in the Prednisone group. For further information please compare Appendix 2.

In the mITT set, the primary endpoint occurred in 79,1% of patients in the MMF group and in 74.8% in the Pred group. The risk difference is 0.043 (p-value 0.019, corresponding 90% CI: -0.042; 0.127). In the PP set, the rates are 79.2% and 77.7%, respectively. The risk difference is 0.015 (p-value 0.008, corresponding 90% CI: -0.077;0.108). As both, the primary analysis in the mTT and the PP set show a significant p-value, non-inferiority is (statistically) proven. Corresponding to this, the upper limit of the 90% CI (5% one-sided) does not include the non-inferiority margin.

The disease status frequently relapsing nephrotic syndrome (FRNS) (≥4 relapses within 12 months or ≥2 relapses within 6 months after initial manifestation) was 45.2% in the Prednisone group and 47.2% in the MMF group, with missings in the Pred group being 9 patients and in the MMF group 7 patients (due to incomplete FU time).

**Safety results**

All patients received at least one dose of study medication and are therefore in the safety set. One patient randomized in the MMF group did not take MMF and withdrew consent directly after randomization. However, this patient received prednisone and is therefore analyzed in the Pred group (see Appendix 2).

(S)AEs observed in the control group as wells as in the experimental group were in accordance with published data. Only preferred terms (PT) that have occurred at least 10 times in total are shown in the table below. (S)AEs can be categorized into more than one PT. The number and rate of patients in each group experiencing at least one AE or SAE of the respective type were reported. A total of 258 patients experienced at least one AE in the observation period (128 in the MMF group, 130 in the Pred group). While mild AEs happened almost equally frequently in both groups (127 patients in the MMF group, 127 in the Pred group), AEs with grade moderate or severe were more common in the Pred group (moderate: 47 patients in the MMF group, 79 patients in the Pred group, severe: 3 patients in the MMF group, 11 patients in the Pred group). SAEs occurred rarely overall (7 patients in the MMF group, 8 in the Pred group experienced at least one SAE) and were all resolved; SAEs were more frequent in the control group (7 SAEs in MMF group, 11 in Pred group).

**Summary of adverse events**

| AE | MMF (N= 135) | | Pred (N=137) | | Total (N=272) | |
|---|---|---|---|---|---|---|
| **Grade** | | | | | | |
| -mild | 127 | (94.1%) | 127 | (92.7%) | 254 | (93.4%) |
| -moderate | 47 | (34.8%) | 79 | (57.7%) | 126 | (46.3%) |
| -severe | 3 | (2.2%) | 11 | (8.0%) | 14 | (5.1%) |
| **Causality to Prednisone** | | | | | | |
| -Definitely related | 25 | (18.5%) | 99 | (72.3%) | 124 | (45.6%) |
| -Possible | 64 | (47.4%) | 101 | (73.7%) | 165 | (60.7%) |
| -Unlikely | 59 | (43.7%) | 61 | (44.5%) | 120 | (44.1%) |
| -Not related | 55 | (40.7%) | 60 | (43.8%) | 115 | (42.3%) |
| **Causality to MMF** | | | | | | |
| -Definitely related | 5 | (3.7%) | 0 | (0.0%) | 5 | (1.8%) |
| -Possible | 72 | (53.3%) | 2 | (1.5%) | 74 | (27.2%) |
| -Unlikely | 77 | (57.0%) | 0 | (0.0%) | 77 | (28.3%) |

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|---|---|---|---|---|---|---|
| -Not related | 74 | (54.8%) | 0 | (0.0%) | 74 | (27.2%) |
| **PT** | | | | | | |
| - Abdominal pain | 7 | (5.2%) | 3 | (2.2%) | 10 | (3.7%) |
| - Abdominal pain upper | 19 | (14.1%) | 11 | (8.0%) | 30 | (11.0%) |
| - Aggression | 15 | (11.1%) | 25 | (18.2%) | 40 | (14.7%) |
| - Alopecia | 8 | (5.9%) | 4 | (2.9%) | 12 | (4.4%) |
| - Bronchitis | 10 | (7.4%) | 7 | (5.1%) | 17 | (6.3%) |
| - Cough | 22 | (16.3%) | 19 | (13.9%) | 41 | (15.1%) |
| - Cushingoid | 30 | (22.2%) | 97 | (70.8%) | 127 | (46.7%) |
| - Depressed mood | 6 | (4.4%) | 15 | (10.9%) | 21 | (7.7%) |
| - Diarrhoea | 23 | (17.0%) | 12 | (8.8%) | 35 | (12.9%) |
| - Euphoric mood | 5 | (3.7%) | 7 | (5.1%) | 12 | (4.4%) |
| - Gastroenteritis | 13 | (9.6%) | 13 | (9.5%) | 26 | (9.6%) |
| - Headache | 20 | (14.8%) | 23 | (16.8%) | 43 | (15.8%) |
| - Hypertension | 4 | (3.0%) | 7 | (5.1%) | 11 | (4.0%) |
| - Hypertrichosis | 13 | (9.6%) | 39 | (28.5%) | 52 | (19.1%) |
| - Infection | 7 | (5.2%) | 7 | (5.1%) | 14 | (5.1%) |
| - Irritability | 6 | (4.4%) | 15 | (10.9%) | 21 | (7.7%) |
| - Muscular weakness | 0 | (0.0%) | 10 | (7.3%) | 10 | (3.7%) |
| - Nasopharyngitis | 26 | (19.3%) | 32 | (23.4%) | 58 | (21.3%) |
| - Nausea | 7 | (5.2%) | 6 | (4.4%) | 13 | (4.8%) |
| - Otitis media | 7 | (5.2%) | 6 | (4.4%) | 13 | (4.8%) |
| - Pain in extremity | 5 | (3.7%) | 7 | (5.1%) | 12 | (4.4%) |
| - Pharyngitis | 7 | (5.2%) | 7 | (5.1%) | 14 | (5.1%) |
| - Pyrexia | 30 | (22.2%) | 18 | (13.1%) | 48 | (17.6%) |
| - Rash | 11 | (8.1%) | 4 | (2.9%) | 15 | (5.5%) |
| - Respiratory tract infection | 38 | (28.1%) | 31 | (22.6%) | 69 | (25.4%) |
| - Rhinitis | 25 | (18.5%) | 19 | (13.9%) | 44 | (16.2%) |
| - Rhinorrhoea | 4 | (3.0%) | 6 | (4.4%) | 10 | (3.7%) |
| - Upper respiratory tract infection | 19 | (14.1%) | 7 | (5.1%) | 26 | (9.6%) |
| - Vitamin D deficiency | 7 | (5.2%) | 10 | (7.3%) | 17 | (6.3%) |
| - Vomiting | 14 | (10.4%) | 11 | (8.0%) | 25 | (9.2%) |
| - Weight increased | 6 | (4.4%) | 74 | (54.0%) | 80 | (29.4%) |

| SAE | MMF (N= 135) | | Pred (N=137) | | Total (N=272) | |
|---|---|---|---|---|---|---|
| **Grade** | | | | | | |
| -mild | 1 | (0.7%) | 2 | (1.5%) | 3 | (1.1%) |
| -moderate | 4 | (3.0%) | 0 | (0.0%) | 4 | (1.5%) |
| -severe | 2 | (1.5%) | 7 | (5.1%) | 9 | (3.3%) |
| **Causality to Prednisone** | | | | | | |
| -Definitely related | 1 | (0.7%) | 0 | (0.0%) | 1 | (0.4%) |
| -Possible | 2 | (1.5%) | 3 | (2.2%) | 5 | (1.8%) |
| -Unlikely | 2 | (1.5%) | 5 | (3.6%) | 7 | (2.6%) |
| -Not related | 1 | (0.7%) | 1 | (0.7%) | 2 | (0.7%) |
| **Causality to MMF** | | | | | | |
| -Definitely related | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| -Possible | 2 | (1.5%) | 0 | (0.0%) | 2 | (0.7%) |
| -Unlikely | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| -Not related | 5 | (3.7%) | 0 | (0.0%) | 5 | (1.8%) |
| **PT** | | | | | | |
| - Bronchitis | 0 | (0.0%) | 1 | (0.7%) | 1 | (0.4%) |
| - Gastroenteritis | 0 | (0.0%) | 3 | (2.2%) | 3 | (1.1%) |
| - Headache | 0 | (0.0%) | 2 | (1.5%) | 2 | (0.7%) |
| - Hyperglycaemia | 1 | (0.7%) | 0 | (0.0%) | 1 | (0.4%) |
| - Influenza | 0 | (0.0%) | 1 | (0.7%) | 1 | (0.4%) |
| - Injury | 1 | (0.7%) | 0 | (0.0%) | 1 | (0.4%) |
| - Nephrotic syndrome | 1 | (0.7%) | 0 | (0.0%) | 1 | (0.4%) |
| - Oedema | 0 | (0.0%) | 1 | (0.7%) | 1 | (0.4%) |
| - Pharyngitis | 0 | (0.0%) | 1 | (0.7%) | 1 | (0.4%) |
| - Pyrexia | 0 | (0.0%) | 2 | (1.5%) | 2 | (0.7%) |
| - Renal disorder | 1 | (0.7%) | 1 | (0.7%) | 2 | (0.7%) |
| - Respiratory failure | 1 | (0.7%) | 0 | (0.0%) | 1 | (0.4%) |
| - Respiratory tract infection | 0 | (0.0%) | 1 | (0.7%) | 1 | (0.4%) |
| - Upper respiratory tract infection | 0 | (0.0%) | 1 | (0.7%) | 1 | (0.4%) |
| - Urinary tract disorder | 0 | (0.0%) | 1 | (0.7%) | 1 | (0.4%) |
| - Urinary tract infection | 1 | (0.7%) | 0 | (0.0%) | 1 | (0.4%) |
| - Varicella zoster virus infection | 1 | (0.7%) | 0 | (0.0%) | 1 | (0.4%) |
| - Vomiting | 0 | (0.0%) | 2 | (1.5%) | 2 | (0.7%) |

| **Conclusions** |
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| In this clinical trial, children with a first episode of nephrotic syndrome that had gone into remission under standard glucocorticoid therapy, i.e. who had steroid-sensitive nephrotic syndrome (SSNS), were randomized into two groups with regard to further remission-maintaining therapy. The control group received standard therapy with high-dose prednisone, so that the total duration of therapy was 12 weeks. The experimental group received MMF at a fixed dose of 1200 mg/m² BSA per day for the same duration of treatment.<br><br>The primary analyses based on the mITT and PP sets prove non-inferiority. However, as the trial was prematurely stopped due to futility this result is surprising and requires further investigation. However, the bias associated with the premature stopping of recruitment due to the open-label nature of the study is considered to be low.<br><br>Glucocorticoid-related adverse events were higher in the control group than in the experimental group. At the same time, MMF-associated adverse events were hardly increased in the MMF group compared to the Pred group, especially not to the extent described in the literature when MMF is used in combination with other immunosuppressants, for example in the post-transplant setting.<br><br>Nephrotic syndrome in children is a chronic relapsing disease. Many patients fulfill the definition of a frequently relapsing nephrotic syndrome (FRNS). Disease status FRNS was similar in the Prednisone and MMF groups. This result is consistent with other reports that the composition and duration of initial therapy do not have a major impact on the medium-term course of the disease. It also underlines the non-inferiority of the experimental group (MMF) compared to standard therapy (Pred) in terms of medium-term prognosis.<br><br>The presented results of the INTENT study show non-inferiority of the MMF arm to the standard prednisone arm with no safety concerns and fewer glucocorticoid-related adverse events, providing an excellent extension of the evidence base for future patient-centered shared decision making. |
| **Date of report** |
| 31.01.2024 |

**Signatures**

Date: 31.1.2024 Signature: [redacted]

Name (block letters): Prof. Dr. med. Burkhard Tönshoff

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

Date: 30.01.2024 Signature:

Name (block letters): Prof. Dr. med. Lutz Weber

Function: Medical Coordinator (Author)

Date: 30.01.2024 Signature:

Name (block letters): Dr. med. Marcus Benz

Function: Medical Coordinator (Author)

Date: 30.01.2024 Signature:

Name (block letters): Dr. Anja Sander

Function: Biometrician

| **Appendices** |
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| Appendix 1: List of Study centers<br>Appendix 2: CONSORT Flow Diagram |

**Appendix 1 List of study centers**

| No. | Study center | Name of Principle Investigator | Date of initiation | Date of closing |
|---|---|---|---|---|
| 001 | Universitätsklinikum Heidelberg<br>Zentrum für Kinder- und Jugendmedizin<br>Im Neuenheimer Feld 410<br>69120 Heidelberg | Prof. Dr. med. Burkhart Tönshoff | 16.05.2015 | 21.02.2023 |
| 002 | Klinik für Pädiatrie mit Schwerpunkt Nephrologie<br>Charité Campus Virchow Klinikum<br>Mittelallee 8<br>13353 Berlin | Dr. med. Jutta Gellermann | 07.07.2015 | 04.05.2023 |
| 003 | Klinik für Kinder- und Jugendmedizin/KinderZentrum<br>Grenzweg 10<br>D33617 Bielefeld | Dr. med. Norbert Jorch | 25.08.2015 | 26.07.2023 |
| 004 | Klinisches Studienzentrum<br>Pädiatrische Nephrologie<br>Universitätsklinikum Bonn<br>Venusberg-Campus 1<br>53127 Bonn | Dr. Indra Schulte | 26.05.2015 | 03.02.2022 |
| 005 | Klinikum Bremen-Mitte<br>Eltern-Kind-Zentrum Prof.Hess<br>St. Jürgen-Straße 1<br>28177 Bremen | Dr. Kristina Möller | 21.08.2015 | 09.02.2022 |
| 007 | Universität Klinikum Dresden<br>Klinik und Poliklinik für Kinder- und Jugendmedizin<br>Fetscherstraße 74<br>01307 Dresden | Dr. med. Brigitte Mayer | 17.08.2015 | 15.02.2023 |
| 008 | Universitätsklinikum Erlangen<br>Kinder- und Jugendklinik<br>Maximiliansplatz 2<br>91054 Erlangen | Dr. med. Katja Sauerstein | 01.10.2015 | 29.11.2022 |
| 009 | Universitätsklinikum<br>Zentrum für Kinder- und Jugendmedizin<br>Hufelandstr. 55<br>45122 Essen | Dr. Anja Büscher | 26.05.2015 | 22.11.2022 |

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|---|---|---|---|---|
| 010 | Universitätsmedizin Göttingen<br>Zentrum für Kinderheilkunde und Jugendmedizin<br>Robert-Koch-Str. 40<br>37075 Göttingen | Dr. Matthias Kettwig | 15.01.2016 | 17.03.2022 |
| 011 | Krankenhaus St. Elisabeth und St. Barbara<br>Klinik für Kinder- und Jugendmedizin<br>Mauerstraße 5<br>06110 Halle (Saale) | Dr. med. Ludwig Patzer | 21.09.2015 | 08.08.2023 |
| 012 | Universitätsklinikum Hamburg-Eppendorf<br>Klinik für Kinder- und Jugendmedizin<br>Martinistr. 52<br>20246 Hamburg | Dr. med. Jun Oh | 21.08.2015 | 21.06.2023 |
| 013 | MH Hannover<br>Zentrum für Kinderheilkunde und Jugendmedizin<br>Carl-Neuberg-Str. 1<br>30625 Hannover | Dr. med. Jens Drube | 10.09.2015 | 21.03.2023 |
| 014 | Universitätsklinikum Jena<br>Klinik für Kinder- und Jugendmedizin<br>Sektion Pädiatrische Nephrologie<br>und KfH- Nierenzentrum<br>und KfH Kinderdialyse<br>Am Klinikum 1<br>07747 Jena | PD Dr. med. Ulrike John-Kroegel | 17.08.2015 | 14.12.2022 |
| 015 | Universitätsklinik Köln<br>Klinik und Poliklinik für Kinder- und Jugendmedizin<br>Kerpener Str. 62<br>50937 Köln | Prof. Dr. med. Lutz Weber | 26.05.2015 | 29.06.2023 |
| 016 | Zentrum für Kinder- und Jugendmedizin<br>Sektion Pädiatrische Nephrologie<br>Universitätmedizin der Universität Mainz<br>Langenbeckstraße 1<br>55101 Mainz | PD Dr. med. Rolf Beetz | 20.07.2015 | 11.11.2020 |
| 017 | Klinikum Memmingen<br>Klinik für Kinderheilkunde und Jugendmedizin<br>Bismarckstr. 23<br>87700 Memmingen | Dr. med. Henry Fehrenbach | 27.07.2015 | 01.03.2023 |

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| 018 | Krankenhaus Bethanien Moers<br>Klinik für Kinder-und Jugendmedizin<br>Bethanienstraße 21<br>47441 Moers | Dr. med. Michael Wallot | 26.05.2015 | 19.10.2022 |
| 019 | LMU München<br>Kinderklinik und Kinderpoliklinik<br>im Dr. von Haunerschen Kinderspital<br>Lindwurmstr. 4<br>80337 München | PD Dr. med. Bärbel Lange-Sperando | 23.09.2015 | 25.01.2023 |
| 020 | Christliches Kinderhospital Osnabrück<br>Johannisfreiheit 1<br>49074 Osnabrück | Dr. med. Michael van Husen | 25.08.2015 | 26.10.2022 |
| 021 | KfH-Nierenzentrum für Kinder und Jugendliche<br>in der Kinder- und Jugendklinik der Universität Rostock<br>Ernst-Heydemann-Str. 8<br>18057 Rostock | Dr. med. Hagen Staude | 07.07.2015 | 25.05.2023 |
| 022 | Universitätsklinikum Ulm<br>Klinik für Kinder- und Jugendmedizin<br>Eythstraße 24<br>89075 Ulm | Dr. med. Ortraud Beringer | 29.07.2015 | 03.05.2023 |
| 023 | Klinik für Allgemeine Kinder- und Jugendmedizinmedizin,<br>Kindernephrologie, Mathildenstraße 1<br>79106 Freiburg | Prof. Dr. Martin Pohl | 15.10.2015 | 16.08.2023 |
| 024 | Klinik und Poliklinik für Kinder und Jugendliche<br>Liebigstraße 20 a<br>04103 Leipzig | Zum Zeitpunkt der Schließung vom Zentrum wurde kein Prüfer gemeldet, Stellvertreter: Dr. med. Corinna Gebauer | 24.11.2015 | 27.01.2022 |
| 025 | Universitätsklinikum Gießen und Marburg Zentrum für Kinder- und Jugendmedizin Koordinierungsstelle für Klinische Forschung in der Pädiatrie<br>Baldingerstraße<br>35033 Marburg | Prof. Dr. med. Stefanie Weber | 22.10.2015 | 19.05.2022 |
| 026 | Universitätskinderklinik<br>Allgemeine Pädiatrie, Pädiatrische Nephrologie<br>Waldeyerstr.22 | Prof. Dr. med. Martin Konrad | 13.11.2015 | 26.04.2023 |

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| | 48149 Münster | | | |
| 027 | Marienhausklinik St. Josef Kohlhof<br>Klinik für Kinder- und Jugendmedizin<br>Klinikweg 1<br>66539 Neunkirchen | Prof. Dr. Otto Schofer verstorben, deshalb Schließung vom Zentrum | 17.11.2015 | 22.02.2017 |
| 028 | HELIOS Kliniken Schwerin, Kinder- und Jugendmedizin<br>Wismarsche Straße Nr. 393-397<br>19049 Schwerin | Dr. med. Matthias Kasbohm | 11.11.2015 | 02.11.2022 |
| 029 | Klinikum Augsburg<br>2. Klinik für Kinder und Jugendliche<br>Mutter-Kind-Zentrum Schwaben<br>Stenglinstr. 2<br>86156 Augsburg | Prof. Dr. med. Gernot Buheitel | 28.04.2016 | 31.05.2023 |
| 030 | Kinderklinik, Klinikum Dritter Orden<br>Menzingerstr. 44<br>80638 München | Dr. med. Marcus Benz | 11.05.2016 | 24.05.2023 |
| 031 | Krankenhaus Barmherzige Brüder Regensburg - Klinik St. Hedwig<br>Steinmetzstraße 1-3<br>93049 Regensburg | Dr. med. Jochen Kittel | 19.07.2016 | 06.07.2023 |
| 032 | Pädiatrische Nephrologie<br>Klinik für Kinder- und Jugendmedizin<br>Universitätsklinikum Tübingen<br>Hoppe-Seylerstr. 1<br>72076 Tübingen | Dr. med. Matthias Zirngibl | 09.05.2016 | 21.07.2023 |
| 033 | Universitätsklinikum Schleswig-Holstein<br>Klinik für Kinder- und Jugendmedizin I<br>Arnold-Heller-Str. 3, Haus C<br>D-24105 Kiel | Dr. med. Simon Vieth | 06.04.2016 | 08.12.2022 |
| 034 | Klinikum Coburg<br>Ketschendorfer Str. 33<br>96450 Coburg | PD Dr. Dr. med Peter Dahlem | 11.05.2017 | 18.01.2023 |
| 035 | Clementine Kinderhospital<br>Theobald- Christ-Str. 16<br>60316 Frankfurt am Main | Dr. med. Kay Latta | 19.01.2017 | 15.02.2022 |
| 036 | Olgahospital Stuttgart<br>Klinikum Stuttgart, Klinik Pädiatrie 2<br>Kriegsbergstr. 62<br>70174 Stuttgart | Dr. med. Martin Bald | 22.03.2017 | 12.04.2022 |
| 037 | Städtisches Klinikum Dresden- | Dr. med. Geord Heubner | 30.08.2017 | 20.07.2022 |

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| | Neustadt<br>Industriestraße 40<br>01129 Dresden | | | |
| 038 | Klinikum Dortmund gGmbH –<br>Westfälisches Kinderzentrum<br>Klinik für Kinder- und Jugendmedizin<br>Beurhausstraße 40<br>44137 Dortmund | Prof. Dr. med. Dominik Schneider | 29.03.2018 | 18.01.2022 |

**Appendix 2 CONSORT Flow Diagram**