Application to the Ethics-Committee
of the Medical Faculty Carl Gustav Carus at the Technische Universitaet Dresden
for the execution of clinical investigations in humans

Beantragung einer Beratung gemäß:

☒ **§ 15 der Berufsordnung für Ärzte in Sachsen**

☐ **§ 1 Abs. 3 Satz 1 der Satzung der Ethikkommission an der Technischen Universität Dresden (gilt für Zahnmediziner, Psychologen, Nichtmediziner etc.)**

Applicant:

Title/Name:	Prof. Dr. med. Hohenstein
Vorname:	Bernd
Clinik/Instituet:	Medizinische Klinik III, Bereich Nephrologie
Street:	Fetscherstr. 74
City:	01307 Dresden
e-Mail-adress:	bernd.hohenstein@uniklinikum-dresden.de
Phone	0351 458 18639

1. Study title:

Registry on epidemiology, diagnosis and therapy of C3 glomerulopathies and immune-complex mediated MPGN

Check if applicable
yes no

2. Has this or an similar study been submitted to any other ethics committee? ☐☒

3. Questions and aims of the study:

Based upon the grown knowledge that the term membranoproliferativen glomerulonephritis (MPGN) rather defines an disease entity than similar histopathological forms of different underlying renal diseases [1], a new classification into immune-complex mediated and complement mediated forms was introduced in 2010 [2].
According to an international consensus report, complement-mediated forms should be summarized as glomerulonephritis with dominant C3 [3].
Now, the central diagnostic criterion is the sole or dominant (defined as more than 2 times more intense than Ig deposits) deposition of complement C3 as detected by immunohistochemistry or immune-fluorescence on renal biopsies. Besides less well-defined other types and postinfectious glomerulonephritis (GN), C3 glomerulopathy (c3G) comprises the most prominent form of this diseases, which can be further defined by their histological appearance as membranoproliferativen C3G, mesangial C3G, membranous C3G= dense deposit disease) [4]. If histological assessment fails to show a predominant C3 staining but rather demonstrates predominant IgG deposition a diagnosis of immune-complex mediated GN (for instance MPGN) should be made.

Central prerequisite for the development of C3Gs is the dysregulation of the alternative complement pathway, leading to persistent overactivation. The disturbed regulation leads to increased production and activation of C3 and/or C5 convertase. Both, the lack of single or several regulatory components as well as the stabilization of activated C3 or C5 convertase can be initiating mechanisms. Mutations of single components as well as autoantibodies represent relevant underlying pathogenetic mechanisms leading to dysregulation of the alternative complement pathway [5-8].
Mutation in various complement encoding genes can be detected in 20-25% of all C3G cases [9-13]. Autoantibodies can be detected in 50-80% of patients with C3G [3].
Knowledge of the underlying pathophysiology guides the subsequent diagnostic evaluation of patients with C3G. Comprehensive complement analysis, antibody screening and genetic analysis should be performed. Following the improved understanding of C3G pathophysiology, a variety of therapeutic options have been report in patients with C3G. However, no systematic data or therapeutic trials exist. Robust epidemiologic data and follow up of the clinical time course, especially in Germany and many other European countries, are not existent
Due to the orphan type of disease (approx. 1-3 per million per year), reliable epidemiologic data can only be collected via central registry databases. Therefore, the applicant in collaboration with the coordinating center for clinical studies at the TU Dresden has developed an internet-based registry system to collect and document diagnostic findings and clinical follow up data in patients with C3G and immune-complex mediated MPGN to allow subsequent design of therapeutic trials. Registry data will undergo explorative data analysis to describe frequent diagnostic findings and clinical time courses. In parallel, we will also collect blood samples from each patient in order to perform subsequent analysis of currently unknown pathogenetically relevant factors. This registry is available in German and English.

4. Principal investigator in our area of responsibility (only PI allowed!):

Prof. Dr. med. Bernd Hohenstein, Bereich Nephrologie, Medizinische Klinik III

Coordinating investigator (for multicenter studies):

Prof. Dr. med. Bernd Hohenstein
Bereich Nephrologie, Medizinische Klinik III
Universitätsklinikum Carl Gustav Carus
Fetscherstrasse 74, 01307 Dresden
Phone: +49 351 458 18639
Fax: +49 351 458 5333
email: bernd.hohenstein@uniklinikum-dresden.de

5. Investigators in our area of responsibility:

Prof. Dr. med. Bernd Hohenstein
Prof. Dr. med. Christian Hugo
PD Dr. med. Jens Passauer
Dr. med. Mirian Opgenoorth

6. Funding of the study:

	check if applicable yes	no
This study has no third party funding.	☒	☐

☒ Application for release from committee's fee attached

check if applicable
yes no

7. Type of study:

This is an

- Open study ☒ ☐
- controlled study
  - ➢ against Placebo ☐ ☐
  - ➢ against comparator ☐ ☐

Was a biometrical analysis performed? ☐ ☒

This is an open registry study without necessity for a biometrical plan. Registry data will undergo explorative data analysis to describe frequency of diagnostic findings and clinical time courses as epidemiologic data base for subsequent interventional trials.

8. Study subjects

- Healthy subjects ☐ ☒
- symptomatic subjects ☒ ☐
- patients ☒ ☐

Are all persons contractually capable? ☐ ☒

Wenn **nein**: nähere Angaben (z.B. Minderjährige; eingeschränkt geschäftsfähige Personen; geschäftsunfähige Personen; Personen, für die ein Betreuer bestellt wurde)

9. Study subjects under 8. are treated:

- In outpatient centers ☒ ☐
- In hospital ☒ ☐

10. Estimated duration for each participant:

Informed consent for the study, approx. 15 to 30 minutes per patient.

yes no

11. Do patients receive payments/honorary? ☐ ☒

12. Used compounds or machines – not applicable-

yes no

check if applicable
yes no

13. Study related procedures in patients/ subjects

- In hospital treatment ☐ ☒
- Blood drawing ☒ ☐
- Bladder catheter ☐ ☒
- endoscopy ☐ ☒

- biopsies ☐ ☒
- radioaktive compounds ☐ ☒
- therapy breaks ☐ ☒
- others: NONE

***Mandatory!* Information on possible application of radiation**

☒ **A:** This study will not pre-/include any application of radiation covered by the German StrlSchV or RöV, or use of radiation will only be applied with justifying indication of a physician with competencies according to § 80 StrlSchV or § 23 RöV. The subject will receive the same application of radiation (type, dose) if he/she would not participate in this registry.

	Check if applicable yes	no
14. Aim of the study		
- in direct interest of the patient?	☐	☒
- primarily scientific interest without direct diagnostic or therapeutic value?	☒	☐

15. **Evaluation of study approach by PI with respect to risk to benefit distribution**:

This is a registry study.
There will be no predefined diagnostic of therapeutic procedure. Diagnosis as well as subsequent therapy are under full responsibility of the individual investigator. Blood samples will be collect with inclusion into the registry, but are no prerequisite for inclusion. This incorporates a low risk of local infection, injury to blood vessels and nerves.

Welche Nebenwirkungen sind im Rahmen der Studie zu erwarten?

Blood samples incorporate a low risk of local infection, injury to blood vessels and nerves and will be drawn during routine labwork for subject's follow up.

	Check if applicable yes	no
16. With respect to this study exist		
- literature?	☒	☐
- Lab- (in vitro-) experiments?	☒	☐
- Animal experiments?	☒	☐
- Investigations in humans as **case reports**	☒	☐
➢ über die Verträglichkeit (Phase I)?	☐	☐
➢ Wirksamkeit (Phase II)?	☐	☐
➢ Klinische Prüfung (Phase III)? (gemäß den Richtlinien über die Prüfung von Arzneimitteln)	☐	☐

siehe Anlage Nr.:

17. Existing insurances:		
- for patients	☐	☒
Art des Versicherungsschutzes	ja	nein
- verschuldensabhängig (Haftpflichtversicherung)	☐	☐
- ereignisabhängig (Unfallversicherung)	☐	☐
- Wegeunfallversicherung	☐	☐

→ wenn **nein**, muss in der Patienten/Probandeninformation darüber aufgeklärt werden

This study will exclusively be executed during necessary medical follow up, this is also true fort he not mandatory blood samples. The local liability insurance will therefore provide coverage.

18. Summary of the experimental plan (protocol attachement 1)

Data will be collected and evaluated after pseudonymisation. Publications will only contain anonymized data. By no means, data will be forwarded to third parties and persons not participating in this study. As appropriate, authorized and sworn to secrecy inspectors of the ethics committee will be allowed to review data.
Data collection and evaluation of this registry do not contain any guidelines with respect to diagnostic or therapeutic measures, but will cover any established diagnostic and therapeutic procedure being used to diagnose and treat patients with C3 glomerulopathy and immune-complex mediated MPGN. In addition, follow up data of patients will be assessed in quarterly to yearly intervals.
Eligible patients will be recruited either via a local specialized center or after referral via the division of nephrology at the university hospital Carl Gustav Carus in Dresden.
All physicians and patients will be asked to provide 4 blood samples (2x serum, 2x EDTA, both centrifuged and frozen, total sample volume approx.. 30ml) and one spot urine sample, which will be assigned to the Registry.

The following parameters will be collected:
At diagnosis: eGFR (ml/min/1,73m^2), proteinuria (g/g creatinine or g/24h), presence of nephrotic syndrome, presence of aterial hypertension, family history of this disease, presence of secondary causes, current medication, histopathological findings (MPGN type 1 or 2 or 3, dense deposit disease, C3 glomerulonephritis, C3 glomerulopathy, immunecomplex-mediated MPGN, evaluating pathologist, written final report.
Complement diagnostics after diagnosis: Presence of functional complement analysis including findings, presence of genetic diagnostics of known, pathophysiologically relevant genes including findings, pathophysiologically relevant autoantibodies (c3NeF, anti-C3, anti-CFB, anti-CFH).
Clinical course: Change of renal function over time since diagnosis, time until 50% decline of renal function or doubling of serum creatinine, current medication, initiation of dialysis therapy, time until dialysis, renal transplantation (yes/no), if yes: recurrence after transplantation (yes/no), after how many months, remarks (free text field)
Therapy: Was any therapy initiated (yes/no), is yes supportive and/or immunomodulation using XY, efficacy of therapy.

Check if applicable
yes no

19. Informed consent**:**
((aims, study plan, individual benefit, risks, voluntariness, tight of withdrawal, insurance)
- Oral and written ☒ ☐

Attachement no.: 2

20. Documentation of consent of the patient**:**

Attachement no.: 2

21. Patient's data documentation**:**

Not applicable, electronic database system

Dresden, May 04th 2015

....

Principal investigator Director of the Clinic

References:

1. Walker, P.D., et al., *Dense deposit disease is not a membranoproliferative glomerulonephritis.* Mod Pathol, 2007. **20**(6): p. 605-16.
2. Fakhouri, F., et al., *C3 glomerulopathy: a new classification.* Nat Rev Nephrol, 2010. **6**(8): p. 494-9.
3. Pickering, M.C., et al., *C3 glomerulopathy: consensus report.* Kidney Int, 2013. **84**(6): p. 1079-89.
4. Cook, H.T. and M.C. Pickering, *Histopathology of MPGN and C3 glomerulopathies.* Nat Rev Nephrol, 2015. **11**(1): p. 14-22.
5. Jozsi, M., et al., *Autoantibodies to complement components in C3 glomerulopathy and atypical hemolytic uremic syndrome.* Immunol Lett, 2014. **160**(2): p. 163-71.
6. Chen, Q., et al., *Combined C3b and factor B autoantibodies and MPGN type II.* N Engl J Med, 2011. **365**(24): p. 2340-2.
7. Ohi, H. and T. Yasugi, *Occurrence of C3 nephritic factor and C4 nephritic factor in membranoproliferative glomerulonephritis (MPGN).* Clin Exp Immunol, 1994. **95**(2): p. 316-21.
8. Licht, C., et al., *MPGN II--genetically determined by defective complement regulation?* Pediatr Nephrol, 2007. **22**(1): p. 2-9.
9. Sethi, S., et al., *C3 Glomerulonephritis Associated With Complement Factor B Mutation.* Am J Kidney Dis, 2014.
10. Tortajada, A., et al., *C3 glomerulopathy-associated CFHR1 mutation alters FHR oligomerization and complement regulation.* J Clin Invest, 2013. **123**(6): p. 2434-46.
11. Deltas, C., et al., *C3 glomerulonephritis/CFHR5 nephropathy is an endemic disease in Cyprus: clinical and molecular findings in 21 families.* Adv Exp Med Biol, 2013. **735**: p. 189-96.
12. Lesher, A.M., B. Nilsson, and W.C. Song, *Properdin in complement activation and tissue injury.* Mol Immunol, 2013. **56**(3): p. 191-8.
13. Martinez-Barricarte, R., et al., *Human C3 mutation reveals a mechanism of dense deposit disease pathogenesis and provides insights into complement activation and regulation.* J Clin Invest, 2010. **120**(10): p. 3702-12.

Attachement 1:

Study design

Web based registry: www.C3Gnet.de or www.c3g.website

Database development and hosting: Koordinierungszentrum fuer Klinische Studien, Technische Universitaet Dresden

Inclusion criteria:

- male/ female
- age 18-99 years
- written informed consent of patient
- one of the following diagnoses
    - MPGN type 1
    - MPGN type 2
    - MPGN type 3
    - dense deposit disease
    - C3 glomerulonephritis
    - C3 glomerulopathy
    - Immune-complex mediated MPGN

The following pseudonymised data will be collected:

Findings at diagnosis:
eGFR (ml/min/1,73m^2), proteinuria (g/g creatinine or g/24h), presence of nephrotic syndrome, presence of aterial hypertension, family history of this disease, presence of secondary causes, current medication, histopathological findings, evaluating pathologist, written final report.
2x serum samples, (after centrifugation, frozen), not mandatory
2x EDTA samples, (after centrifugation, frozen), not mandatory
1 urine sample, not mandatory
Complement diagnostics after diagnosis:
Presence of functional complement analysis including findings, presence of genetic diagnostics of known, pathophysiologically relevant genes including findings, pathophysiologically relevant autoantibodies (c3NeF, anti-C3, anti-CFB, anti-CFH).
Clinical course:
Change of renal function over time since diagnosis, time until 50% decline of renal function or doubling of serum creatinine, current medication, initiation of dialysis therapy, time until dialysis, renal transplantation (yes/no), if yes: recurrence after transplantation (yes/no), after how many months, remarks (free text field)
Therapy:
Was any therapy initiated (yes/no), is yes supportive and/or immunomodulation using XY, efficacy of therapy.

Follow-up data every 3-12 months