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Supplementary material is linked to the online version of the paper at www.kireports.org

1) Supplementary Methods

Study Design: ClopiD4FSGS is a single-arm multi-center proof-of-concept phase 2 trial over 24 weeks (EudraCT Nr: 2022-003313-11). There will be study visits every 6 weeks, with a screening assessment, a baseline and four follow-up visits (Figure 2). After the first ten patients, an interim analysis will be performed to assess a predefined futility threshold for early detection of lack of efficacy (Figure 1). The threshold for continuation is that more than one patient reaches the FSGS partial remission end point (FPRE) defined as urinary protein-to-creatinine ratio (UPCR) < 1.5 g/g and a > 40% reduction in UPCR from baseline after 12 weeks of treatment.[S1]

A total of up to 22 patients will be recruited from up to 9 Austrian centers, including participants of the ARREST NEPHROSIS registry[S2] who had agreed on being invited to diagnostic and therapeutic studies. It is assumed that 2 – 5 patients can be recruited per center per year; thus, recruitment of 22 patients is anticipated to be completed within one year. Registry data will continue to be independently collected during and after completion of the ClopiD4FSGS trial. The trial will be conducted in accordance with the Declaration of Helsinki and patients will provide written informed consent before enrollment. The study protocol has been approved by the local ethics committee of the Medical University of Vienna (EK 2046/2022) and is currently prepared to be submitted at the local ethics committees of each participating study site (Ethics committee of the Medical University of Innsbruck, Medical University of Graz, Johannes Kepler University Linz, Karl Landsteiner University of Health Sciences St Poelten, Ethic committee of Vorarlberg, Ethics committee of the city of Vienna).

Agent and Dose Selection: Film-coated tablets containing 75 mg clopidogrel are widely used for the prevention of atherothrombotic events. It was initially registered in 1997 in the US and in 1998 in the EU for the treatment of atherothrombotic events in the context of myocardial infarction, stroke and vascular death in patients with documented atherosclerosis or established peripheral arterial disease.[S3,S4] The safety profile has been assessed in multiple clinical trials,[5,6] which allows the investigators to focus on specific safety issues (such as

exclusion of patients with increased risk of bleeding), and to avoid concurrent medications with known interactions. Pre-clinical studies underlying this protocol suggest that this dose is sufficient to achieve the desired therapeutic effect.[S7] Therefore, study patients will take clopidogrel 75 mg daily. In order to optimize the comparability with previous studies, which used predominantly clopidogrel marketed as Plavix®, the IMP (investigational medicinal product) in this study will be Plavix®.

Inclusion and Exclusion Criteria: The ClopiD4FSGS-trial will enroll female and male patients between 18 and 75 years of age with a diagnosis of FSGS confirmed by biopsy or genetic testing. Patients with secondary FSGS are not eligible. Additional inclusion and exclusion criteria are listed in Supplementary Table S1 and S2. Eligible patients will be screened and identified in the ARREST NEPHROSIS registry or during routine clinical visits. Informed consent is retrieved during a screening visit by the local investigator. (Supplementary Table S3) The dosage of immunosuppressive medication must be stable within the last 6 months before enrollment. The dosage of antiproteinuric medication must be stable within the last 3 months before enrollment. Prior use of rituximab or cyclophosphamide is permitted if not administered within 3 months before enrollment. Patients currently taking inhibitors of platelet aggregation or treated with oral anticoagulants are not eligible, due to increased bleeding risk.

Outcomes: UPCR as assessed by 24-hour-urine collection will be collected at baseline and each study visit. The primary endpoint is defined as the percent proteinuria change from baseline in UPCR to visit 4 (week 24). Individual patient trajectories will be reported. The secondary endpoint is the proportion of patients who achieve the FPRE at visit 4 (week 24). This endpoint will also be used to assess the futility threshold after 12 weeks. As tertiary endpoints, the core outcomes “Mortality”, “Life Participation”, “Cardiovascular Disease” as defined by the “Standardized Outcomes in Nephrology” (SONG) initiative will be assessed.[S8] (Figure 2) In addition, changes from baseline in systolic and diastolic blood pressure (BP), eGFR and selected laboratory parameters will be assessed (Supplementary Table S3). GFR will be estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)

formula.[S9] Blood and urine samples will be analyzed at the center's respective laboratory via standard procedures. Since only intra-patient effects are assessed and tested, variations between different laboratories will not affect the results. Tolerability and safety endpoints (incidence and severity of treatment-emergent adverse events [TEAE]; incidence and severity of serious adverse events [SAE]; laboratory findings [clinically significant yes *vs*. no]) will be collected throughout the active study period. All other parameters are obtained at study visits (every 6 weeks) for the treatment duration (total 24 weeks).

Statistical Analyses: The aim of this early proof-of-concept clinical trial is to determine whether clopidogrel is a suitable candidate for further clinical development as treatment for FSGS. Sample size estimation is based on assumptions based on two previous studies that aimed to lower UPCR in FSGS.[S10,S11] Although these studies failed to achieve the desired reduction of UPCR, their results allow for an estimation of the expected variability of UPCR after treatment. Standard deviations for UPCR change (%) were 72.7% and 48%, respectively (combined 58.2%). A sample of 18 participants is therefore able to detect a mean reduction in UPCR of 50% with a power of 90% (two-sided alpha of 0.05 in paired *t*-test). Assuming a conservative dropout rate of less than 20% after the 12 week visit (Figure 2), 22 patients are required. In 22 patients, events with a real incidence rate of 7.1% can be observed at least once with a probability of 80%. All data are summarized by appropriate descriptive statistics (arithmetic or geometric mean, SD, median, minimum, maximum, N, relative and absolute frequencies). Additional pretreatment data are obtained from the ARREST NEPHROSIS registry and may be used for sensitivity analyses. Demography and baseline characteristics are analyzed in the Intent-To-Treat (ITT) population, AE data in the safety population, and efficacy data are additionally analyzed in the per protocol population. Differences between baseline and treatment periods are tested for significance in an exploratory manner. Missing values at week 24 will be inputed by Last Value Carried Forward (LOCF). Additional sensitivity analysis will be performed using the average of the last two and three visits, respectively.

Reporting: Upon completion of the study, a clinical study report including statistical analyses is submitted in accordance with the guidelines of the European Medicines Agency within twelve months.[S12,S13] The investigator will retain all records and documents related to the study for at least 15 years. Significant changes in the study procedure are documented in new versions of the protocol and reviewed by the respective Ethics Committees. In addition to preparing a clinical study report that meets regulatory requirements, the results of the clinical trial will be made available to the scientific community through publication in peer-reviewed journals. The publication process will involve close coordination between the sponsor and the local principal investigators, and authorship will follow applicable guidelines.[S14] All publications will only contain anonymized data that cannot be linked to individuals.

Contract Research Organization (CRO): This study will be conducted by a contract research organization (CRO), following a process of collecting data on paper-based case report forms (CRFs) and transferring it to a study database through double data entry. To ensure data quality, repeated monitoring visits are conducted. The data manager also reviews the data and compares serious adverse event reports (SAEs) with the sponsor's pharmacovigilance database. Medical patient history and adverse events are coded using the MedDRA (Medical Dictionary for Regulatory Activities), and concomitant therapies are classified using the ATC (Anatomic-Therapeutic Classification System) system. Coding and assigning patients to analysis sets are important steps in locking the database and preparing for subsequent analysis.

2) Supplementary References

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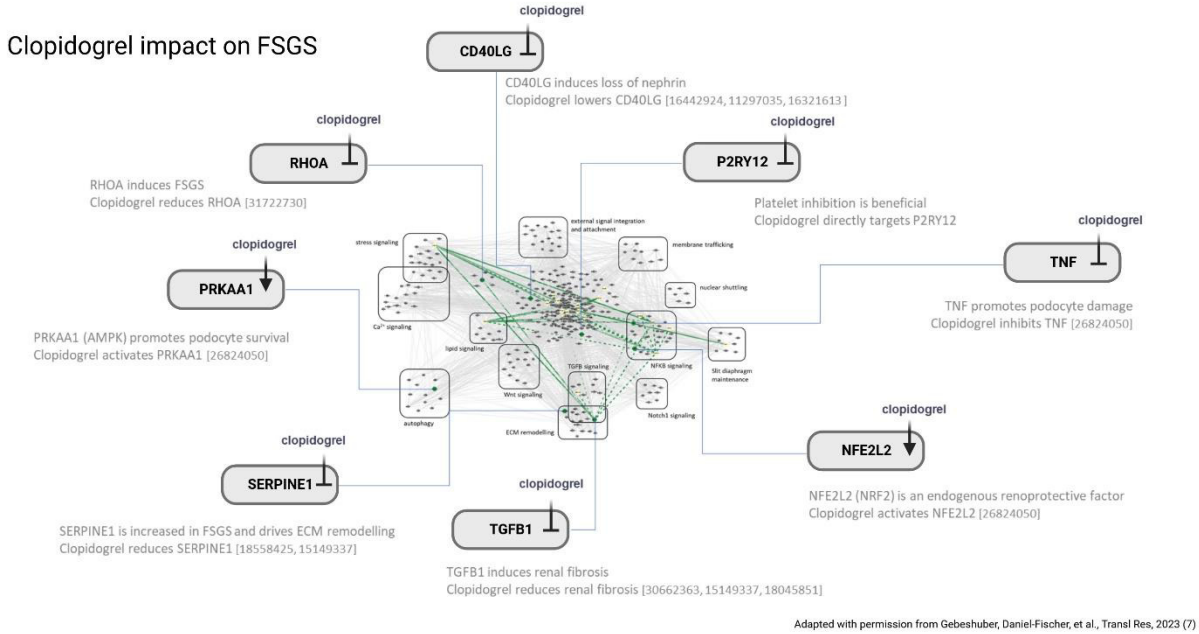
3) Supplementary Figure S1 Modeled impact of clopidogrel on FSGS pathophysiology.



Graphical representation of the FSGS molecular model and its interference with the clopidogrel mechanism of action molecular model and their respective clusters. For each cluster of proteins, the interference signatures are depicted in the context of FSGS pathophysiological mechanisms. One selected protein is annotated by its gene symbol for each cluster. Under the respective gene symbol, the involvement into the FSGS pathomechanisms as well as the assumed effect of clopidogrel is described. Within the brackets the PMID number of the respective literature sources is documented. Adapted with permission from Gebeshuber, Daniel-Fischer, et al., *Translational Research*, 2023[S7].

4) Supplementary Table S1 ClopiD4FSGS inclusion criteria[a]

Biopsy-proven FSGS or a disease-causing genetic mutation associated with FSGS
18 - 75 years of age
Estimated glomerular filtration rate (eGFR) > 30 ml/min·1.73 m² at baseline (assessed via CKD-EPI formula)
Written informed consent (ICF)
At least one UPCR > 1.0 g/g within the previous year at least 6 weeks before screening visit is available in the patient's medical records, e.g., by participation in the ARREST NEPHROSIS registry.
Mean UPCR of the 24h urine sample from screening visit (sample available at or collected within 2 days after screening) and of the 24 h urine sample collected for baseline is > 1.0 g/g
Ability and willingness to co-operate with the investigator and to comply with the requirements of the entire study, including the ability to swallow the clopidogrel capsules and to conduct collection of 24 h urine samples within 2 days before or following each visit starting from baseline visit on, according to the clinical routine of the site
Use of medically acceptable contraception throughout the study in females of childbearing potential or sexual abstinence

ICF = informed consent form; UPCR = urinary protein-to-creatinine ratio; eGFR = estimated glomerular filtration rate

[a]Patients must meet all inclusion criteria to be eligible for the study.

5) Supplementary Table S2 ClopiD4FSGS exclusion criteria[b]

FSGS secondary to another condition
History of type 1 diabetes mellitus, uncontrolled type 2 diabetes mellitus (HBA1c > 8%), or non-fasting blood glucose > 180 mg/dL at screening
Body mass index (BMI) > 40 kg/m²
Any organ transplant
Contraindication or known or suspected allergy to Clopidogrel or related products, or to any constituents of the study medication
Antiplatelet therapy or systemic anticoagulation treatment at screening
Requirement for any of the medications indicated on the list of excluded medications for Clopidogrel according to the SmPC
Clinically relevant findings in physical examination, vital signs, and laboratory parameters at screening, which are designated by the PI as clinically significant, except for findings related to the underlying disease
Current pregnancy or breastfeeding
Rituximab or cyclophosphamide during last six months prior to baseline. Other immunosuppressive medications and/or medications targeting the Renin-Angiotensin-Aldosterone-System and/or Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors are permitted if dosing was stable for three months before baseline.
Ongoing medical history or symptoms of a clinically relevant illness in the three weeks before baseline
Participation in another investigational drug study within 28 days prior to screening, or during the course of this study
Scheduled or foreseeable change of immunosuppressive medications and/or medications targeting the Renin-Angiotensin-Aldosterone-System and/or Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors during the treatment period

HbA1c=glycated hemoglobin, BMI=body mass index; SmPC= summary of product characteristics, HIV = Human immune deficiency virus

[b]A patient who meets any of the criteria will be excluded from the study.

6) Supplementary Table S3 ClopiD4FSGS study assessment schedule

	Screening	Baseline	Active Study Period			
Time [Days]	-42 (-49 - -35)	0 (/)	42 (35 - 49)	84 (77 - 91)	126 (119 - 133)	168 (161 - 175)
Informed consent[1]	●					
Eligibility	●	●[3]				
Physical examination	●	●	●	●	●	●
Demography	●	●[2]				
Medical History	●[4]	●[2]				
Vital Signs	●	●	●	●	●	●
24 h Urine Samples[5,6]	●	●	●	●	●	●
Life Participation Questionnaire		●				●
Safety Laboratory[6]	●	●	●	●	●	●
Hemoccult Test			●	●	●	●
ECG		●				●
Pregnancy Test	●	●	●	●	●	●
Drug Administration[7]		Day 3 ± 1[7] to Visit 4				
Assessment of Compliance[8]		●	●	●	●	●
Protocol Deviations	●	●	●	●	●	●
Adverse Events			●	●	●	●
Previous and Concomitant Treatments	●[4]	●	●	●	●	●

[1] Signed and stored by local investigator

[2] Only changes since screening are recorded

[3] Recheck and assessment of those criteria, which are determined only at baseline

[4] Data can be retrieved from the ARREST NEPHROSIS registry or other medical history

[5] Collected by the patient at home before visit for timed urinary protein and creatinine measurements and UPCR

[6] Analyzed by local laboratory

[7] Clopidogrel is started after eligibility of the subject has been confirmed at baseline.

[8] Assessment of remaining IMPs in handed out blister at each study visit and interview on compliance

7) Supplementary Patient Information and Informed Consent

for participation in the clinical trial

Efficacy of clopidogrel in reducing proteinuria in patients with focal segmental glomerulosclerosis (FSGS): a multicenter single-arm proof-of-concept phase 2 study.

Patient Number:

Dear Participant.

We invite you to participate in the above clinical trial. You will be informed about this in a detailed medical consultation.

Your participation in this clinical trial is voluntary. You may withdraw from the study at any time without giving reasons. Refusal to participate or early withdrawal from this study will not adversely affect your medical care.

Clinical trials are necessary to obtain reliable new medical research results. However, an indispensable prerequisite for conducting a clinical trial is that you give your written consent to participate in this clinical trial. Please read the following text carefully as a supplement to the informational interview with your investigator and do not hesitate to ask questions.

Please sign the consent form only

- if you fully understand the nature and procedure of the clinical trial,

- if you are willing to consent to participate, and

- If you are aware of your rights as a participant in this clinical trial.

The responsible ethics committee has issued a favorable opinion on this clinical trial, as well as on the patient information and consent form.

The clinical trial will be conducted at XXX and financed by the company Delta 4 GmbH.

1. What is the purpose of the clinical trial?

The purpose of this clinical trial is to determine the change in proteinuria in FSGS patients receiving daily clopidogrel (75 mg) compared to proteinuria before clopidogrel.

For this clinical trial, it is planned that affected participants (=patients) aged at least 18 years or older participate in this clinical trial. This is a so-called phase 2 trial, which means that the drug to be tested will be tested for the first time in patients suffering from the disease for whose treatment the drug is intended.

In this clinical trial, clopidogrel (clopidogrel 75 mg) will be used to reduce proteinuria in patients with focal segmental glomerulosclerosis (FSGS).

You are asked to support the study by your voluntary participation.

2. What other treatment options are available?

Currently, therapy for FSGS is limited to immunosuppressants (substances that reduce the functions of the immune system) and non-specific renal protective drugs, e.g. antihypertensives.

If FSGS is not genetic, treatment of the disease that led to FSGS (= underlying disease) is necessary and may include other medications e.g. insulin. Measures such as weight loss or a salt- and protein-reduced diet may also be necessary in addition.

3. How does the clinical trial take place?

This clinical trial will be conducted at our clinic (XXX) and approximately 2 - 5 patients will participate on site. This clinical trial will also be conducted at other clinics in Austria and a total of 22 people will participate in the whole study.

Their participation in this clinical trial is expected to last 31 weeks. The whole study is expected to be conducted for a duration of less than 3 year.

Prior to enrollment in this clinical trial, you will undergo a comprehensive medical examination. As part of your participation, you will undergo a pre-examination, baseline visit, visit 1, visit 2, visit 3, and visit 4.

Your participation in this clinical trial is only possible if your FSGS disease is confirmed by a kidney biopsy or genetic testing for genes that may cause FSGS. The results of each test will be taken from your patient records.

A number of tests and procedures will also be performed as part of your treatment, whether or not you participate in this clinical trial. These will be discussed with you by your investigator as part of the usual medical information session.

The following measures will be performed solely for study reasons:

A number of tests will be performed at the pre-study and throughout the study, as described below. These tests are necessary, among other things, to verify that you are able to participate in the study and to ensure your safety and progress in the clinical trial.

- At the pre-trial visit and all subsequent visits, you will undergo a physical examination. The physical examination may include evaluation of the following areas: Head and neck, eyes and ears, nose and mouth, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin and nervous system. In addition, there will be a survey of your vital signs.
- Vital signs: Your blood pressure, heart rate, and body temperature will be measured at your pre-exam and each visit.
- For female participants of childbearing age, a pregnancy test will be performed at the pre-exam and at all subsequent appointments. If you are pregnant, you will not be able to participate in the study. For further information see section 11 Information for women of childbearing age and men of reproductive age - Pregnancy test.
- ECG: A total of two ECG measurements (also called "electrocardiography") will be performed on you. This is to monitor your heart and will be done at the Baseline visit and at Visit 4.
- Patient questionnaire: at the baseline visit and at visit 4, you will be asked to complete a short questionnaire about your health status. Each will take approximately 5 minutes to complete.
- Blood draws: You will have blood drawn at the pre-visit, baseline visit, visit 1, visit 2, visit 3 and visit 4. A maximum of approximately 36ml (approximately 8 blood tubes, approximately 4.5ml per tube) will be drawn. You will receive the final decision whether you can participate in the study (even if your blood values at the beginning do not suggest a study exclusion) 3-4 days after your baseline visit. You will be notified by telephone by our clinic. From this point on, you will be able to take the study medication.
- Urinalysis: You will be asked to provide several urine samples. From the time of the pre-visit, you will be given collection tubes for 24-hour urine collection. You will be asked to collect your urine for 24 h the day before each visit appointment. In addition, you will be given collection jars to collect your morning urine 1x a week between visits. We ask you to store these weekly urine samples in the freezer at your home. You will also receive a suitable freezer box for this purpose, which will allow the samples to be stored cleanly. The exact procedure for the 24-hour urine collection and the weekly

morning urine collection will be explained to you by your doctor. In total, you will have to do 5 24-hour urine collections and 24 weekly morning urine collections.

- Administration of study medication: If you participate in the clinical trial, you will receive the investigational product clopidogrel 75 mg to take home. The investigational product will be taken 1x daily. You can also find more information in Section 4 What is clopidogrel (clopidogrel 75 mg)?
- Throughout the study, you will also be asked questions about your general health and any changes in your health.
- Throughout the study, study staff will collect information about all medicines you are taking and how long you have been taking them.

You will be asked to come to the clinic each time for this.

There will be a total of 6 visits. Pre-examination and baseline visit will take approximately 3-4 hours. Visits 1 to 4 will take about 1-2 hours.

Adherence to the visit schedule, including the investigator's instructions, is critical to the success of this clinical trial.

4. What is Clopidogrel (Clopidogrel 75 mg)?

Clopidogrel is an already approved drug that prevents the formation of blood clots (thrombi) in "calcified" blood vessels (arteries), and is used to treat or prevent diseases such as atherothrombosis, stroke, or heart attack.

In the context of FSGS, there are few drugs available to date that can slow or stop the progression of the disease. The efficacy of currently available therapies is often low, and a significant proportion of FSGS patients eventually require renal replacement therapy. After kidney transplantation, about one-third of patients experience a recurrence of FSGS. This is a major burden for patients and the development of new therapeutic approaches is of utmost importance.

Clopidogrel is a drug that has emerged as a promising candidate for the treatment of FSGS in laboratory or animal studies. Clopidogrel has largely not been tested in patients with FSGS. This study is one of the first applications of clopidogrel in patients with FSGS.Clopidogrel is a pink tablet that is dispensed in a blister pack and taken by you. You will be instructed to take the pack of investigational product to each visit. The investigator will count the remaining investigational product and then ask you about your dosing schedule as needed.

5. What is the benefit of participating in the Clinical Trial?

The use of clopidogrel is intended to test the efficacy of the investigational product in reducing proteinuria in patients with FSGS. It is believed that patients taking clopidogrel may experience an improvement in FSGS or a temporary halt in the progression of the disease.

However, it is also possible that you may not receive any direct health benefit from your participation in this clinical trial.

It is possible that your participation may provide you with new information about your health condition and may educate you about newly diagnosed, previously unknown conditions or risks, if you so choose.

The results of this clinical trial are intended to help find treatments for other patients who have the same condition as you.

6. Are there any risks, complaints and side effects?

Treatment with clopidogrel may cause side effects or discomfort, although not everybody gets them. Clopidogrel has not yet been approved for the treatment of FSGS. As with any new

substance, new, previously unknown side effects may occur with the use of clopidogrel for FSGS.

In the context of the use of clopidogrel according to its previous approval as an antiplatelet agent, the following side effects have been reported:

- The most commonly reported side effects are bleeding. Bleeding may occur as stomach or intestinal bleeding, as well as bruising, hematoma (unusual bleeding and bruising under the skin), nosebleeds, or blood in the urine. In a few cases, bleeding from vessels in the eye, inside the head, in the lungs, or in joints has been reported. If you cut or injure yourself, bleeding may possibly last longer than usual. Minor cuts and injuries, such as those that may occur when you shave or cut yourself, are usually of no consequence. If you are still unsettled, you should contact your treating doctor immediately.
- Common side effects (may affect up to 1 in 10 people treated): Diarrhea, abdominal pain, indigestion, or heartburn.
- Occasional side effects (may affect up to 1 in 100 people treated): Changes in blood count (decrease in platelets, decrease in white blood cells, increase in certain white blood cells), headache, stomach ulcer, vomiting, nausea, constipation, severe bloating, skin rashes, itching, drowsiness/dizziness, tingling, and numbness.
- Rare side effects (may affect up to 1 in 1,000 people treated): Decrease in certain white blood cells (neutrophil granulocytes) with concomitant occurrence of (severe) infections, dizziness/imbalance problems, enlargement of the mammary glands in men.
- Very rare side effects (may affect up to 1 in 10,000 people treated): Jaundice, severe abdominal pain with or without back pain, fever, difficulty breathing, sometimes associated with cough, general allergic reactions (e.g., general feeling of heat with sudden general malaise up to fainting), swelling around the mouth, blistering of the skin, allergic skin reactions, inflammation of the mucous membrane of the mouth (stomatitis), low blood pressure, states of confusion, hallucinations, joint pain, muscle pain, taste changes or loss of taste.
- Side effects with unknown frequency (frequency cannot be estimated based on available data): Hypersensitivity reactions with chest or abdominal pain, signs of persistent low blood sugar.

Your investigator will monitor you closely for possible side effects. Please inform the staff at the study site of any unexpected medical occurrences and of any illnesses, even if you think they are not directly related to the study medication.

In addition, the procedures performed as part of this clinical trial may cause you discomfort. The blood draw may cause you to have pain or swelling at the injection site, bruising, or bleeding. There is also a very small risk of infection at the site where the needle is inserted into the vein.

7. Additional intake of medicines?

If it is necessary for you to take other medications during the course of the study, or if physicians other than your investigator prescribe medications for you, you will be asked to take them only after consulting with your investigator.

8. Does participation in the clinical trial have any other lifestyle implications and what are the obligations?

From the preliminary examination onwards, you will be expected to provide several urine samples throughout the duration of the study. You will be asked to collect your morning urine 1x a week each week. The weekly urine samples are to be stored in the freezer at your home until the next visit. Before each visit, you will also be asked to perform a 24-hour urine collection.

Urine specimens will be collected according to local clinical routine. They will be provided with the necessary materials and containers at each visit, except the last visit, and will be instructed in detail as needed.

9. What should be done if symptoms, concomitants and/or injuries occur?

If any symptoms, concomitants, or injuries occur during the course of the clinical trial, you must report them to your investigator, immediately in the case of serious concomitants, by telephone if necessary (see below for telephone numbers, etc.).

Contact your investigator immediately if you notice the following about yourself:

- fever, signs of infection, or marked fatigue. This may be due to a rare reduction in certain blood cells.
- Signs of liver problems, such as yellowing of the skin and/or eyes (jaundice), possibly associated with bleeding that appears as red spots under the skin and/or confusion.
- swelling around the mouth or skin conditions such as rashes and itching, blistering of the skin. These may be signs of an allergic reaction.

10. Insurance

As a participant in this clinical trial, you have the legally required no-fault insurance coverage (personal injury insurance according to Section 32 of the German Medicines Act, which covers all damage that may be caused to your life or health by the clinical trial procedures performed on you, with the exception of damage due to changes in the genetic material in cells of the germ line).

The insurance has been taken out for you with HDI Versicherung AG, Edelsinnstraße 7-11, 1120 Vienna, Austria under policy number 5282685. You may inspect the insurance documents upon request.

In the event of a claim, you can contact the insurer directly (telephone number: +43 (0) 509 05-0 and assert your claims independently. Austrian law is applicable to the insurance contract, and insurance claims are enforceable in Austria.

For support, you can also contact the Patients' Ombudsman's Office, Patients' Representation or Patients' Ombudsman's Office.

In order not to jeopardize the insurance coverage

- you may undergo other medical treatment during the duration of the clinical trial only in agreement with your treating investigator (except in emergencies). This also applies to the additional intake of medication or participation in another study.
- You must immediately inform the investigator in charge - or the above-mentioned insurance company - of any damage to your health that may have occurred as a result of the clinical trial.
- You must do everything reasonable to clarify the cause, course and consequences of the insured event and to minimize the damage incurred. This may also include authorizing your attending physicians to provide information requested by the insurer.

11. Information for women of childbearing age and men of procreative age - pregnancy test

Pregnant and breastfeeding women may NOT participate in this clinical trial.

Information for Childbearing Females - Pregnancy Test: Female patients of childbearing potential must use a medically acceptable method of contraception. They are encouraged to inform the investigator of any suspected or confirmed pregnancy. Administration of the

investigational product will be discontinued in the event of pregnancy. Study-related safety assessments will continue in the event of pregnancy.

In addition, pregnancy tests will be performed at each visit.

Information procreative men: As a procreative man, you may participate in the clinical trial,

- if you agree to inform your partner about study participation. If your partner becomes pregnant during your participation in the study, please inform your investigator immediately.
- if you agree to provide safe contraception (until 3 months after the last dose of investigational product to ensure that all sperm produced during treatment have been replaced by newly formed sperm).

12. When will the clinical trial be terminated prematurely?

You may withdraw your willingness to participate and withdraw from the clinical trial at any time, without giving any reason, and without any disadvantage to your continued medical care.

Your investigator will inform you immediately about any new findings that become known in relation to this clinical trial and that could become significant for you. On this basis, you may then reconsider your decision to continue participation in this clinical trial.

However, it is also possible that your investigator (or the sponsor of this clinical trial, if applicable) may decide to terminate your participation in the clinical trial early without first obtaining your consent. The reasons for this may be:

a) You cannot meet the requirements of the clinical trial;
b) your investigator feels that continued participation in the clinical trial is not in your best interest;
c) the Principal Investigator makes the decision to terminate the entire Clinical Trial, or only to terminate your participation early.

If you decide to withdraw from the clinical trial prematurely, or if your participation is terminated prematurely for any of the above reasons, it is important for your own safety that you undergo a normal follow-up examination. This usually consists of a physical examination as well as laboratory tests.

13. Data protection

In the course of this clinical trial, data about you will be collected and processed. A basic distinction must be made between

1) those personal data by which a person is directly identifiable (e.g. name, date of birth, address, social security number, photographs...),

2) pseudonymized personal data, i.e. data in which all information that allows direct conclusions to be drawn about the specific person is either removed, replaced by a code (e.g. a number) or (e.g. in the case of image recordings) rendered unrecognizable. However, despite compliance with these measures, it cannot be completely ruled out that unauthorized re-identification may occur.

3) anonymized data for which a traceability to the specific person can be excluded.

Access to the data by which you are directly identifiable (see point 1) is given to the investigator and other staff of the trial site who are involved in the clinical trial or your medical care. In addition, authorized representatives of the sponsor Delta 4 GmbH, who are bound to secrecy, as well as representatives of domestic and/or foreign health authorities and ethics committees

responsible in each case may inspect this data, insofar as this is necessary to verify the proper conduct of the clinical trial.

All persons who have access to this data are subject to the applicable national data protection regulations and/or the EU General Data Protection Regulation (GDPR) when handling the data.

The code that enables the pseudonymized data to be assigned to your person is only kept at your trial site.

Data will only be passed on, in particular to the sponsor and its contractual partners, in pseudonymized or anonymized form.

Only the pseudonymized or anonymized data will be used for any publications.

In the context of this clinical trial, no transfer of pseudonymized data to countries outside the EU (third country) is intended.

Your consent forms the legal basis for the processing of your personal data. You may revoke your consent to the collection and processing of your data at any time without giving reasons. After your revocation, no further data will be collected about you. However, the data collected until revocation may continue to be processed in the context of this clinical trial.

According to the GDPR, you are generally entitled to the rights of access, rectification, deletion, restriction of processing, data portability and objection, provided that this does not render the objectives of the clinical trial impossible or seriously compromise them and provided that this is not contradicted by other statutory provisions.

The right to delete your data processed in the context of this clinical trial, as provided for in the GDPR, is not available to you due to regulations under the German Medicines Act and the German Medicinal Products Act. In addition, in the case of a clinical trial under the Medicinal Products Act, the right to data portability is suspended.

The expected duration of the clinical trial is 31 weeks. The duration of storage of your data beyond the end or termination of the clinical trial is regulated by legal provisions.

If you have any questions about the handling of your data in this clinical trial, please contact your investigator first. If necessary, he/she can forward your request to the persons responsible for data protection.

Contact details of the data protection officers of the institutes involved in this clinical trial:

Data protection officer of XXX: XXX

Data protection officer of the AKH: XXX

Data protection officer of the sponsor: XXX

You have the right to lodge a complaint about the handling of your data with the Austrian data protection authority (www.dsb.gv.at; e-mail: dsb@dsb.gv.at).

14. What happens to my samples?

The samples taken from you (blood and urine) are pseudonymized and will be destroyed by the test center after completion of the analysis at the test center.

15. Are there any costs for the participants? Is there any reimbursement or compensation?

For your participation in this clinical trial you will receive an expense allowance of 300 EUR. This will be issued in the form of Sodexo vouchers á 50 EUR per visit.

16. Opportunity to discuss further questions

Your investigator and his or her staff will be happy to answer any further questions you may have in connection with this clinical trial. They will also be happy to answer any questions regarding your rights as a patient in this clinical trial.

Name of contact person: XX

Can be reached at: +XX

Name of contact person: XX

Can be reached at: +XX

For medical emergencies outside normal working hours, a doctor from the clinic can be reached at all times at +XXX (SMS and WhatsApp cannot be received).

17. Where can I obtain further information?

In addition, you can also contact the XXX for further concerns, for example if you have had a bad experience.

Contact the Vienna Patient Advocate (WPPA):

Address: XXX

Telephone/fax number: XX

E-mail: XX

18. Should other treating physicians be informed of participation in the clinical trial?

Would you like your primary care physician to be informed about study participation?

□ yes □ no

19. Informed consent

Name of patient:

Date of Birth:

I agree to participate in the clinical trial "Efficacy of clopidogrel in reducing proteinuria in patients with focal segmental glomerulosclerosis (FSGS): a multicenter single-arm proof-of-concept phase 2 study." I have been informed that I may decline to participate without adverse consequences, particularly to my medical care.

I have been informed by Mrs./Mr. (Dr.med.univ.) ..... in a detailed and comprehensible manner about the clinical trial, possible burdens and risks, as well as about the nature, significance and scope of the clinical trial, the existing insurance and the requirements resulting for me from it. I have also read the text of this patient information and consent form, which comprises a total of 10 pages. Questions that arose were answered by the investigator in a comprehensible and satisfactory manner. I have had sufficient time to make up my mind. I have no further questions at this time.

I will comply with the physician's orders that are necessary for the necessary for the conduct of the clinical trial, but I reserve the right to terminate my voluntary however, reserve the right

to terminate my voluntary participation at any time, without any disadvantages, especially for my medical care,arise.

I expressly agree that my data collected in the course of this clinical trial be processed as described in the section "Data Protection" section of this document.

In the event that I withdraw from the clinical trial, I agree that my samples will continue to be stored and analyzed as described in this be stored and analyzed as described in this information and, if applicable, in the described in the substudy information.

□ yes □no

I have received a copy of this patient information and Informed Consent Form have been given to me. The original will remain with the investigator.

.....

(date and signature of patient)

.....

(Date, name and signature of the responsible investigator)

(The patient will receive a signed copy of the patient information and consent form; the original will remain in the investigator's study folder)

8) SPIRIT Checklist

SPIRIT-Outcomes 2022 Checklist (for combined completion of SPIRIT 2013 and SPIRIT-Outcomes 2022 items)[a]

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	-	p1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	-	p3
	2b	All items from the World Health Organization Trial Registration Data Set	-	not applicable
Protocol version	3	Date and version identifier	-	not applicable
Funding	4	Sources and types of financial, material, and other support	-	p7
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	-	p1, p7
	5b	Name and contact information for the trial sponsor	-	p7
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	-	p7
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	-	p7, pS2
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	-	p3
	6b	Explanation for choice of comparators	-	p5
Objectives	7	Specific objectives or hypotheses	-	p4

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	-	pS2
Methods: Participants, interventions, and outcomes				
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	-	pS2
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	-	Supp Table S1 Supp Table S2 pS3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (for specific guidance see TIDieR checklist and guide)	-	pS2 Figure 1 Figure 2
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	-	pS16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-	Suppl Table S3
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	-	Suppl Table S1, Suppl Table S2, p
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	-	pS3/4, Suppl Table S3, Figure 2

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
	12.1		Provide a rationale for the selection of the domain for the trial's primary outcome	p5
	12.2		If the analysis metric for the primary outcome represents within-participant change, define and justify the minimal important change in individuals	pS4
	12.3		If the outcome data collected are continuous but will be analyzed as categorical (method of aggregation), specify the cutoff values to be used	n.a. for primary outcome, for secondary outcome pS4
	12.4		If outcome assessments will be performed at several time points after randomization, state the time points that will be used for analysis	pS4, Figure 2
	12.5		If a composite outcome is used, define all individual components of the composite outcome	pS2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	-	Figure 2, Suppl Table S3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	-	pS4
	14.1		Define and justify the target difference between treatment groups (eg, the minimal important difference)	pS4
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	-	pS3
Methods: Assignment of interventions (for controlled trials)				
Allocation:				
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	-	not applicable

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	-	not applicable
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-	not applicable
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-	not applicable
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-	not applicable
Methods: Data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	-	Supplementary Table S4
	18a.1		Describe what is known about the responsiveness of the study instruments in a population similar to the study sample	p4, pS4
	18a.2		Describe who will assess the outcome (eg, nurse, parent)	pS2, Supp Table S3
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	-	p5/6, pS2

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	-	pS5
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	-	pS4
	20a.1		Describe any planned methods to account for multiplicity in the analysis or interpretation of the primary and secondary outcomes (eg, coprimary outcomes, same outcome assessed at multiple time points, or subgroup analyses of an outcome)	pS4/5, Figure 1/2
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	-	pS4
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	-	pS4
Methods: Monitoring				
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	-	pS5
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	-	p3, pS4, Figure 1
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	-	Suppl Table S3, pS5

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-	Sp5
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	-	pS2
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	-	pS5
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	-	Supplementary Table S3, pS3
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-	pS18-19
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	-	pS16-17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	-	p7
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-	pS5
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-	pS15
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	-	pS5
	31b	Authorship eligibility guidelines and any intended use of professional writers	-	pS5

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-	Sp5
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-	pS11-19
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-	pS12-13, pS17

[a]It is strongly recommended that this checklist be read in conjunction with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement paper for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license and is reproduced with permission.

[b]Indicates page numbers and/or manuscript location: to be completed by authors.