STUDY PROTOCOL

Vaccine-induced immune thrombotic thrombocytopenia and thrombosis syndrome (VITT/TTS) after vaccination against SARS-CoV-2

Protocol Number:	EMA/2021/17/TDA
Study type:	Patient registry
Indication:	Vaccine-induced immune thrombotic thrombocytopenia and thrombosis syndrome (VITT/TTS) after vaccination against SARS-CoV-2
Phase:	IV
Sponsor:	Universitätsmedizin Greifswald
Principal/Coordinating Investigator	Prof. Dr. med. Andreas Greinacher
Protocol Version and Date:	Version: 4.2; Date: 01. December 2021

The study will be conducted according to the protocol and in compliance with the Declaration of Helsinki, and with other applicable regulatory requirements.

SIGNATURE PAGE

Title: **Vaccine-induced immune thrombotic thrombocytopenia and thrombosis syndrome (VITT/TTS) after vaccination against SARS-CoV-2**

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the guidelines on Good Clinical Practice.

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_____ December 01, 2021

Prof. Dr. med. Andreas Greinacher Date
Coordinating Investigator
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Declaration of the Investigator

Title: **Vaccine-induced immune thrombotic thrombocytopenia and thrombosis syndrome (VITT/TTS) after vaccination against SARS-CoV-2**

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the IRB or IEC, except where necessary to eliminate an immediate hazard to the subjects.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

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Date

PROTOCOL SYNOPSIS

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Time of onset;
persistence of antibodies

Exploratory endpoints:</td><td>- First day of clinical symptoms of VITT/TTS
- Last day of positive anti-PF4 antibody test by EIA
- Last date of a positive functional test for PF4 dependent platelet activating antibodies
- Boostability of PF4-antibodies: to assess anti-PF4 antibody response to second or third dose of Covid-19 vaccine, vaccination with any other vaccine, or surgical interventions or heparin application.</td></tr>
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<tr><td>Design:</td><td colspan="2">This is a patient registry in which patients with laboratory confirmed VITT/TTS are followed prospectively, sequential serum samples are obtained and analysed by tests to detect anti-PF4 antibodies and platelet activating anti-PF4 antibodies. Anti-PF4 antibodies are further investigated for the subclasses and the glycosylation pattern. In addition, the study aims to identify potential genetic characteristics predisposing to VITT/TTS.</td></tr>
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	The genome wide analysis is a cross-sectional study enrolling all VITT/TTS patients identified in the Greifswald laboratory independent whether they are enrolled into the follow-up study or not.
Study Population:	All subjects with clinical diagnosis of VITT/TTS in whom the Greifswald reference laboratory has identified anti-PF4 antibodies and platelet activating PF4-dependent antibodies.
Inclusion Criteria:	Prospective patient registry (Cohort 1): At the time of enrolment subjects are eligible to be included in the study only if all of the following criteria apply: 1. Signed written informed consent by the subject who is able to assess the nature, significance and scope of the patient registry. If the subject is temporarily incapable of consent, the consent of a legal representative or authorized representative will be accepted if permitted under applicable local regulations/ethics committee recommendations. 2. Males or females 3. Subjects with clinically suspected VITT/TTS between day 4 and 30 after vaccination with an adenoviral vector-based COVID-19-vaccine in whom VITT is confirmed by a positive anti-PF4/heparin IgG ELISA and a positive PF4-enhanced platelet activation assay. Genome wide analysis (Cohort 2): All subjects with clinically suspected VITT/TTS after vaccination with an adenoviral vector-based COVID-19-vaccine in whom VITT is confirmed by a positive anti-PF4/heparin IgG ELISA and a positive PF4-enhanced platelet activation assay
Exclusion Criteria:	None
Number of Subjects:	The patient registry aims to include a total number of 66 patients for the follow-up study. For the genome wide analysis all patients of whom DNA is available will be investigated.
Countries/Number of Sites:	Germany, Greifswald laboratory
Concomitant Medications:	All concomitant medications will be allowed according to the discretion of the treating physician.
Duration of Participation:	Patients will be followed for 12 months after the anti-PF4 test becomes negative with a maximal preplanned follow up until 12-2022.
Criteria for Evaluation:	
Efficacy Assessments:	The patient registry data will be analysed descriptively. The genome wide analysis will assess statistically significant differences between the VITT/TTS patient population and the general population (SHIP study population).
Safety Assessments:	Safety will be assessed by reported AEs and SAEs following second or third dose of Covid-19 vaccine, vaccination with any other vaccine, or surgical interventions or heparin application.

Statistical Methods:	Anti-PF4 antibody persistence: Statistical analysis will be performed in R. As follow-up times are right-censored and differ between study participants, anti-PF4/heparin IgG EIAs and functional tests will be analysed using the Kaplan-Meier method. OD-thresholds of 2.0, 1.5, 1.0, and 0.5 will be used to dichotomize the anti-PF4/heparin IgG antigen assay after linear interpolation between measurement time points to handle interval-censoring. Patients that achieved negative and then relapsed to positive functional test results will be considered positive at all times. Confidence intervals for Kaplan-Meier estimates will be computed using Greenwood's method, confidence intervals for the binomial distribution will be computed using Wilson's approximation. A one-sided, paired Wilcoxon's signed rank test will be used to compare optical densities of the first and last anti-PF4/heparin IgG EIA measurement per patient. Genome wide analysis: Whole genome sequencing will be performed at 30x coverage using paired end sequencing on a NoveSeq instrument. Raw data will be bioinformatically analyzed using FASTQC and BWA-Mem for mapping, and Platypus/GATK HaplotypeCaller for variant calling. Assembled genome sequences of VITT patients will be compared to age and sex matched probands of the population-based SHIP study. Chi squared / likelihood ratio tests will be used for association analysis; logistic regression will be further employed controlling for confounders. Correction for multiple testing will be done using a Bonferrone threshold of $5x10^{-8}$.

INTRODUCTION

Background

Vaccination against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an important countermeasure to fight the ongoing COVID-19 pandemic. The European Medicines Agency has approved two adenoviral vector-based vaccines (recombinant chimpanzee adenoviral [ChAdOx1-S] vector encoding the spike glycoprotein of SARS-CoV-2, COVID-19 Vaccine Astra-Zeneca [Vaxzevria]; and recombinant human adenovirus type 26 vector encoding SARS-CoV-2 spike glycoprotein, Covid-19 Vaccine Janssen) and two mRNA-vaccines.

Beginning in March 2021, cerebral venous sinus thrombosis, splanchnic vein thrombosis, or other often severe thrombotic events, in combination with thrombocytopenia, were reported in otherwise healthy individuals beginning 5 to 30 days following ChAdOx1 nCov-19 vaccination. This novel disorder, “vaccine-induced immune thrombotic thrombocytopenia” (VITT; synonym, thrombosis with thrombocytopenia syndrome, TTS), is associated with high-titer immunoglobulin G (IgG) class antibodies directed against the cationic platelet chemokine, platelet factor 4 (PF4). These anti-PF4 antibodies potently activate platelets via platelet FcγIIa receptors, with platelet activation greatly enhanced by PF4.

3.2 Rationale

Currently, it is unresolved whether the anti-PF4 antibodies in VITT/TTS persist or disappear. This has very high relevance for management of patients and for risk assessment of adenoviral vector-based vaccines. It is also unresolved whether these patients can be vaccinated safely with an mRNA-vaccine or another vaccine, e.g. influenza vaccines. It is unclear whether these patients may receive heparin or whether application of heparin is triggering a second anti-PF4 immune response leading potentially to heparin-induced thrombocytopenia.

This information is critical for VITT/TTS patients and information can only be obtained by carefully following these patients during interventions like second or third dose of Covid-19 vaccine, vaccination with any other vaccine, or surgical interventions or heparin application.VITT/TTS might be caused by a genetic predisposition. Whole genome sequencing (WGS) allows comprehensive assessment of the entire genome and thereby might provide a hint towards potential genetic risk factors. Identification of genetic risk factors would allow to develop screening assays to identify individuals at risk for VITT/TTS.

Further characterization of the anti-PF4 antibody characteristics like the glycosylation pattern or differences in qualitative or quantitative characteristics of the anti-PF4 antibodies can lead to further research and measures to mitigate the risk of VITT/TTS after vaccination against COVID-19 or other diseases which require an adenoviral vector-based vaccine.

Use of PF4-EIA tests and PIPA Assay

VITT/TTS and HIT are nearly exclusively caused by anti-PF4 antibodies of the IgG class. Anti-PF4 antibodies of the IgM and the IgA class are of minor, if any, clinical relevance.[1-4] Therefore, an ELISA anti-PF4/heparin IgG test (HIT IgG test) will be performed.

One of the purposes of the current study is to systematically assess the frequency of heparin cross-reactivity during follow-up sero-conversion in order to assess its possible relationship to outcomes. This is not possible with the direct enzyme immunoassay (EIA)/enzyme-linked immunosorbent assay (ELISA) methods. The currently available ELISA methods cannot differentiate between anti-PF4 antibodies inducing VITT/TTS and anti-PF4 antibodies inducing HIT. The PIPA test can differentiate between heparin-cross-reacting and non-crossreacting anti-PF4 antibodies.

The decision to use the PF4-induced platelet activation (PIPA) assay was based on the use of a very similar assay, the heparin-induced platelet activation assay (HIPA) to diagnose heparin-induced thrombocytopenia (HIT) described in the literature. This HIPA assay has the same sensitivity and specificity for heparin-associated anti-PF4 antibodies as the serotonin-release assay, SRA.

Risk-Benefit Assessment

The prospective patient registry has minimal risks for the enrolled individuals.

The theoretical risk for patients is to experience bruising at the site of bloodletting when the regular blood sample is taken. These risks are not different from routine blood assessment for other diseases. As blood sampling for the purpose of this study is performed in conjunction with routine blot analysis indicated for other reasons, this study has very minor if any additional risks for the patient. The total amount of blood obtained from these patients during the study is a small fraction of the amount of blood usually given in a standard blood donation.

Beside physical risks there is the need of data protection, especially in the context of genome wide analysis. Special precautions have been established for the study to prevent even theoretical risk of breach of patient confidentiality. Especially for the genome wide analysis all samples will be pseudonymized before analyses will be performed. The Universitätsmedizin Greifswald is taking advantage of the trusts center infrastructure established during large scale population studies in the region and in Germany (Study of Health in Pomerania, Nationale Kohorte).

Overall, we judge the benefits for the individuals participating in this study outweighing by far the minimal if any potential risk.

STUDY OBJECTIVES AND ENDPOINTS

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OVERALL DESIGN AND PLAN OF THE STUDY

Overview

This is a prospective patient registry in which all subjects with clinically suspected VITT/TTS between day 4 and 30 after vaccination with an adenoviral vector-based COVID-19-vaccine in whom VITT is confirmed by a positive anti-PF4/heparin IgG ELISA and a positive PF4-enhanced platelet activation assay are enrolled. Patients will be followed for 12 months after the anti-PF4 antibody test becomes negative with maximal observation period until 12-2022. Regular blood samples will be obtained to follow the development of anti-PF4 antibodies, to follow the development of platelet activating PF4-dependent antibodies, to assess anti-PF4 antibody response to booster vaccination with an mRNA COVID-19-vaccine, to assess anti-PF4 antibody reactions towards vaccination with another vaccine, e. g. influenza vaccine, and to assess anti-PF4 antibody response to exposure to heparin.

Safety will be assessed by reported AEs and SAEs occurring in close relationship to interventions performed by the treating physician, especially second or third dose of Covid-19 vaccine, vaccination with any other vaccine, or surgical interventions or heparin application.

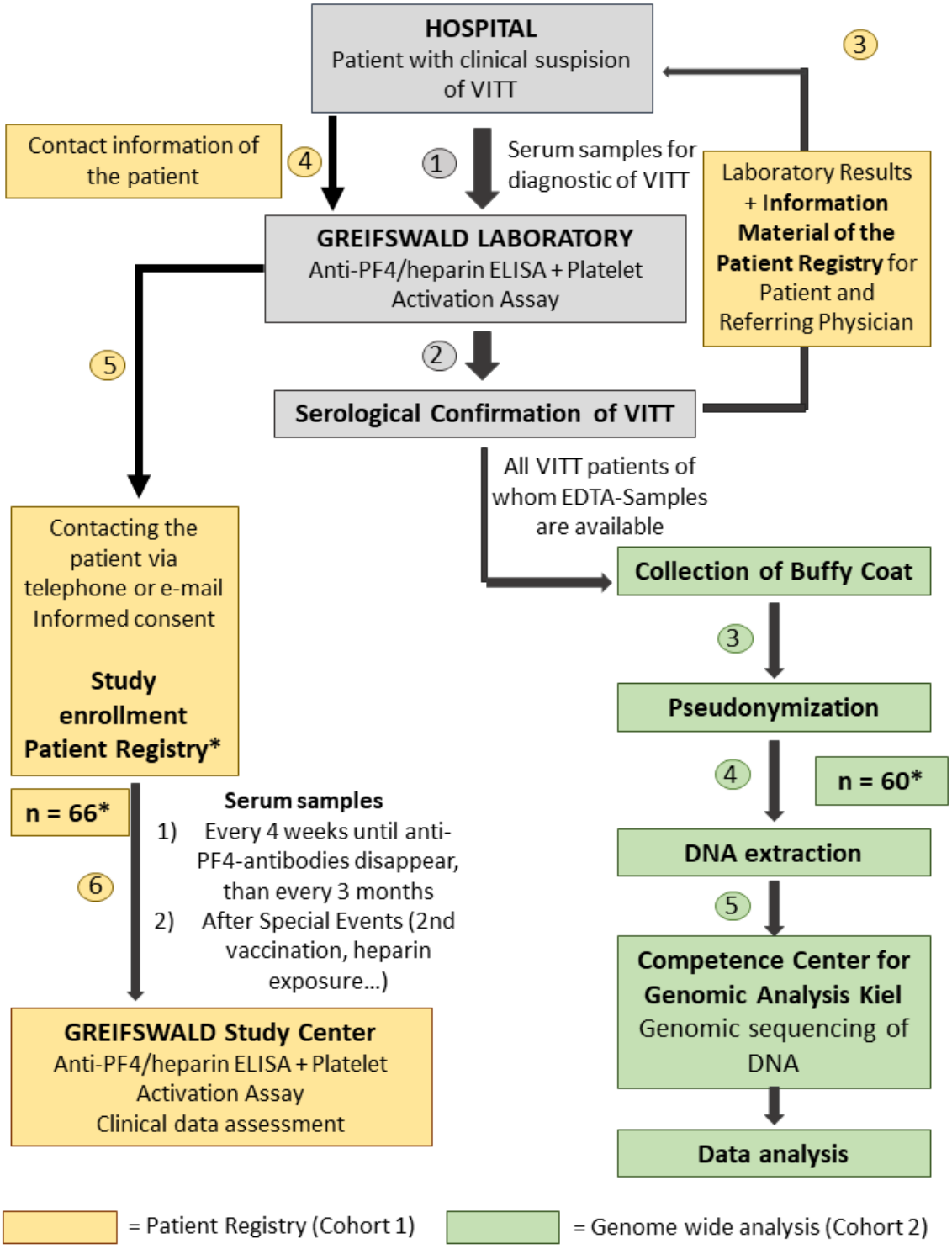
In addition to the development of titers in anti-PF4 antibodies and platelet-activating PF4-dependent antibodies three explorative analyses will be performed:

1. Characterization of the anti-PF4 antibodies, especially the anti-PF4 antibody concentration required to induce platelet activation and the glycosylation pattern of anti-PF4 antibodies.
2. The IgG subclass of anti-PF4 antibodies in VITT/TTS patients.
3. Whole genome wide analysis of VITT/TTS patients and comparison of their genome with the genome characteristics of the general population in a Northeast German cohort.

Discussion of Study Design

The study design of the two different substudies is shown in **Figure 1**.

Figure 1 – Flowchart of the study design of the two different cohorts



Cohort 1 + 2 are two separate cohorts. However, nearly all patients of Cohort 1 are also part of the genome wide analysis (Cohort 2), but not all patients of Cohort 2 are part of the Patient Registry (Cohort 1), because informed consent is needed for Cohort 1

* number may increase if more patients are identified

Prospective patient registry (Cohort 1): Patients are not randomized to any treatment. The study is not an interventional trial but will observe the effects of medical interventions, which are deemed necessary by the treating physician, who is not a member of the study group. These interventions include specifically second or third dose of Covid-19 vaccine, vaccination with any other vaccine, or surgical interventions or heparin application. During the regular patient contacts, patients are asked whether any of these interventions were performed and if performed, the treating physician will be contacted to provide the respective information. As no information is available on the long-term course of VITT/TTS, the patient registry is the only possibility to comprehensively follow all individuals without interfering with their standard medical treatment. The study design will allow to identify the main characteristics of the anti-PF4 antibody course and the anti-PF4 antibody response towards different interventions in patients with VITT/TTS. This will provide the basis for future prospective trials.

Genome wide analysis (Cohort 2): The genome wide analysis will be performed with all samples for which we can isolate sufficient DNA for whole genome sequencing (WGS). Due to the extensive genetic variation identified in whole genome sequencing studies sufficient numbers of enrolled individuals are crucial to obtain a significant signal. We therefore aim to enroll all individuals in whom the diagnosis of VITT/TTS has been objectively confirmed. Still the number will most likely not exceed 100 individuals. Given the high relevance of potential identification of genetic risk markers the analysis will be performed despite the relatively small number. In parallel, all efforts are made to collaborate with other ongoing studies on genetic analysis of VITT/TTS patients to potentially combine results for a combined analysis. There are ongoing negotiations with the UK GEL Consortium and with CEPI.

The small number of individuals with confirmed VITT/TTS will require special biometrical considerations which are outlined in detail in the section on statistical analysis. The investigators are well aware of the limitations of the small sample size. The study will only be informative for individuals with Caucasian origin as the vast majority of VITT/TTS patients diagnosed by the Greifswald laboratory are Caucasians.

STUDY POPULATION

All subjects with clinical diagnosis of VITT/TTS in whom the Greifswald reference laboratory has identified platelet activating PF4-dependent antibodies.

Inclusion Criteria

Prospective patient registry (Cohort 1): At the time of enrolment subjects are eligible to be included in the study only if all of the following criteria apply:

1. Signed written informed consent by the subject who is able to assess the nature, significance and scope of the patient registry. If the subject is temporarily incapable of

consent, the consent of a legal representative or authorized representative will be accepted if permitted under applicable local regulations/ethics committee recommendations.

2. Males or females

3. Subjects with clinically suspected VITT/TTS between day 4 and 30 after vaccination with an adenoviral vector-based COVID-19-vaccine in whom VITT is confirmed by a positive anti-PF4/heparin IgG ELISA and a positive PF4-enhanced platelet activation assay

Genome wide analysis (Cohort 2): All subjects with clinically suspected VITT/TTS after vaccination with an adenoviral vector-based COVID-19-vaccine in whom VITT is confirmed by a positive anti-PF4/heparin IgG ELISA and a positive PF4-enhanced platelet activation.

Exclusion Criteria

There are no exclusion criteria.

Enrollment procedure prospective patient follow-up

1. Patient identification: Patients are identified using the laboratory documentation of the platelet laboratory of the department of transfusion medicine of the Universitätsmedizin Greifswald. Patient identification is performed by a physician involved in performing laboratory diagnosis of VITT/TTS. All patients who fulfil the criteria of clinically suspected VITT/TTS between day 4 and 30 after vaccination with an adenoviral vector-based COVID-19-vaccine in whom VITT is confirmed by a positive anti-PF4/heparin IgG ELISA and a positive PF4-enhanced platelet activation assay are listed in the primary patient log. This patient log is kept under confidential conditions in the department of transfusion medicine as it contains patient identifiers and personal patient data.
2. The treating physician/hospital who has referred the original blood sample for laboratory diagnosis of VITT/TTS is contacted in written form. The contact letter contains an explanatory letter to the referral physician, an explanatory letter to the family doctor of the patient, and an explanatory letter to the patient. The referral physician is asked to forward the information material to the family doctor or/and the patient. (**Appendix 1** shows the information letters for the referral physician, for the family physician and for the patient. These documents are in German language)
3. The patient is asked in the information letter to contact the study center in Greifswald. By contacting the study center in Greifswald the patient actively establishes the interaction with the study center. This procedure has been approved by the ethics board of the Universitätsmedizin Greifswald (**Appendix 2**).
4. The study center in Greifswald provides the patient with the study specific patient information material and the informed consent form and offers a telephone-based information meeting. Thereafter the patient returns the signed informed consent to the

study center in Greifswald. (**Appendix 3**, patient information material and informed consent form). Due to the rarity of VITT, study participants are distributed throughout entire Germany. In person meeting with the study participants is not practicable.

Subject Withdrawal and Replacement

The participation of an individual subject may be discontinued prematurely for reasons such as:

- Withdrawal of written informed consent
- A subject may discontinue participation in the clinical study at his/her own request at any time without stating a reason.

The reason for withdrawal of the subject is documented by the investigator together with all data collected until the day of premature study discontinuation including laboratory results and assessment of AEs.

All efforts will be made that the subject allows using the data obtained until the withdrawal from the study for further analysis. As some study results will be published as interim results it will not be possible to retrieve this information from the publications.

Participants who withdrawal participation will not be replaced.

Enrollment into genome wide analysis

Patients are identified using the laboratory documentation of the platelet laboratory of the department of transfusion medicine of the Universitätsmedizin Greifswald. Patient identification is performed by a physician involved in performing laboratory diagnosis of VITT/TTS. All patients who fulfil the criteria of clinically suspected VITT/TTS after vaccination with an adenoviral vector-based COVID-19-vaccine in whom VITT is confirmed by a positive anti-PF4/heparin IgG ELISA and a positive PF4-enhanced platelet activation assay are listed in the primary patient log. This patient log is kept on the confidential conditions in the department of transfusion medicine as it contains patient identifiers and personal patient data.

As several patients did not survive VITT/TTS it will not be possible to obtain the informed consent for a genome wide analysis. The ethics board of Universitätsmedizin Greifswald has approved that all objectively diagnosed VITT/TTS patients (anti-PF4/heparin ELISA and PIPA test positive) may be enrolled into the genome wide analysis. The DNA of these patients will be purified from EDTA blood and then the samples will be pseudonymized.

Subject Identification

Subject Identification

Each subject in whom the diagnosis of VITT/TTS is objectively confirmed by the Greifswald laboratory receives a 3-digit screening number in sequential order at the date of positive result of the functional assay at the Greifswald Laboratory (e.g. 001, 002, 003), regardless of the site at which the subject is enrolled.

Enrolled subjects who fail screening or discontinue study participation early, will retain their screening number and a sequential number will be assigned to the next enrolled subject.

Data acquisition

1. By a structured telephone interview key data on onset of VITT/TTS, onset of symptoms etc. is obtained from the patient. (**Appendix 4,** data acquisition form)

2. After obtaining the patient's informed consent, the family physician and the original referring physician are asked to provide the study center with case summaries of the patient. These are used to complete the patient data base.

3. Concomitant medications will be allowed according to the discretion of the treating physician.

Following concomitant medications will be recorded in the database:

- Intravenous IgG (IVIG)
- Steroids
- Other immunosuppression (e.g. Rituximab)
- Platelet transfusions
- Anticoagulation (oral and intravenous)
- ASA, ADP-receptor-antagonists

4. Patients will be contacted by the study physician at Universitätsmedizin Greifswald on a regular basis every four to eight weeks until the anti-PF4 antibody tests become negative. Thereafter the patient is contacted every three months. Patients can contact the study center in case of specific questions. Family physicians can contact the study center in case of specific questions regarding management of the VITT/TTS patient. All information provided by the patient or the family physician will be documented in the patient database (**Appendix 5**, example of the database).

Blood sample acquisition

The original blood sample for diagnosis of VITT/TTS is obtained by the laboratory on the discretion of the treating physician who is sending the first blood sample for exclusion or confirmation of VITT/TTS. Only patients in whom VITT/TTS is objectively confirmed by a positive anti-PF4/heparin IgG ELISA and a positive PIPA test will be considered for enrolment into the prospective patient registry. All patients of whom EDTA blood sample is obtained will be considered for enrolment into the genome wide analysis.

The follow-up samples are obtained by referral of non-anticoagulated blood and EDTA anticoagulated blood from the patient by the family physician. The study center provides the family physician with blood tubes and mailing material. The family physician may use the blood tubes provided by the study center or by the blood tubes used in his own practice for ease of handling. The following blood samples will be obtained: non-anticoagulated blood (serum), EDTA anticoagulated blood.

All serum/EDTA blood, which is not required for immediate analyses will be stored at -80°C labelled with the laboratory number of the respective blood sample of the individual. The laboratory number for each blood sample will be transferred into the study patient database.

A timetable of data and blood sample acquisition is presented in **Table 1**.

Table 1: Schedule of Events

Procedure	Confirming Diagnosis[a] (Day 0)	Telephone-based information meeting and study inclusion[b]	Follow-Up First Period (Weeks +/-2)[c]							Follow-up Second Period (Month +/-1)[e]			Special events[f]
			4	8	12	16	20	24	-"-[d]	3	6	12	Variable time point of blood sampling
Informed consent		X											
anti-PF4/heparin IgG ELISA	X		X	X	X	X	X	X	X	X	X	X	X
Platelet activation Assay (HIPA+PIPA)	X		X	X	X	X	X	X	X	X	X	X	X
Demography	(X)	X											
Previous Medical history	(X)	(X)											
Date of vaccination	(X)	X											
Date of onset of symptoms	(X)	X											X[g]
Symptoms (of VITT)	(X)	X											X[g]
Clinical diagnosis	(X)	(X)											X[g]
Initial Treatment[h]	(X)	(X)											X[g]

Procedure	Confirming Diagnosis[a] (Day 0)	Telephone-based information meeting and study inclusion[b]	Follow-Up First Period (Weeks +/-2)[c]							Follow-up Second Period (Month +/-1)[e]			Special events[f]
			4	8	12	16	20	24	-"-[d]	3	6	12	Variable time point of blood sampling
Platelet count	(X)		X	X	X	X	X	X	X	X	X	X	X[g]

Note: Day 0 is defined as the day of confirmation of VITT/TTS with a positive VITT/TTS test including the anti-PF4/heparin IgG ELISA and the PIPA test

The table outlines the minimum frequencies required for each parameter. If clinically necessary, they may be performed more frequently on an individual subject basis.

[a] ( )= The completeness of data is depending on how many clinical information were delivered with the initial blood sample.

[b] ( )= Not all patients are able to provide sufficient information according to their medical condition and treatment. In this case patients will be asked for sending their summarizing discharge letter of their VITT/TTS hospital treatment to complete the data or will be asked for their consent to obtain these data directly from the initial treating physicians/hospitals.

[c] First Period: Patients with positive anti-PF4/heparin IgG ELISA. Blood sampling for the purpose of this study is performed in conjunction with routine blot analysis indicated by the treating physician for other reasons, therefore timepoints can vary. We recommend blood sampling every 4 weeks.

[d] Blood sampling every 4 weeks will be continued until the anti-PF4/heparin IgG ELISA is negative (OD<0.5; =first follow-up period).

[e] Second Period: Patients with negative anti-PF4/heparin IgG ELISA (OD<0.5). After anti-PF4antibodies are no longer detectable in the anti-PF4/heparin IgG ELISA the laboratory analysis will be routinely performed every 3 months until end of study period.

[f] Special events are defined as 1) second or booster vaccination against SARS-CoV-2, 2) other vaccinations (e.g. influenza), 3) heparin exposure, 4) surgery 5) clinical signs of recurrent thrombosis or thrombocytopenia (analysis usually initiated by the treating physician). The aim is to obtain the blood sample between days 7 and 14 after second or third dose of Covid-19 vaccine, vaccination with any other vaccine, or surgical interventions or heparin application.

[g] in case of recurrent thrombosis or thrombocytopenia

[h] Including intravenous IgG (IVIG), steroids, other immunosuppression (e.g. rituximab), plasmapheresis, platelet transfusion, anticoagulation, ASA, ADP-receptor-antagonists

Laboratory methods

Anti-PF4/heparin IgG ELISA

Binding of immunoglobulin G anti-PF4 antibodies from sera of VITT patients to PF4/heparin complexes will be measured by a solid phase PF4/heparin ELISA performed in flat-bottomed microwell plates (Cat. No. 478042 Thermo Scientific, CovaLink). PF4/heparin complexes of 0.5 IU/mL unfractionated heparin (UFH; Heparin-Natrium 25000 IE/ 5 mL, Ratiopharm) and 20 μg/mL PF4 will be formed in coating buffer (50 mM NaH_2PO_4, 0.1% NaN_3) at RT for 1 h and will incubate for seven days at 4°C. Prior to use, complexes will be washed five times with washing buffer (150 mM NaCl, 1% Tween20 pH 7.5). 100 μL/microwell of serum samples (diluted to 1:200 if not indicated otherwise), in sample diluent (0.05 M NaH_2PO_4, 0.15 M NaCl, 7.5% goat normal serum, pH 7.5) will be incubated for 60 min, at RT and then washed five times. Horseradish peroxidase-conjugated goat antihuman IgG (Jackson ImmunoResearch Europe Ltd, Ely, UK) will be added (1:15,000 dilution in sample diluent). Binding of human IgG will be detected by adding chromogenic tetramethylbenzidine substrate (100 μL/microwell; Kementec, Taastrup, Denmark). At 60 min post-incubation, the chromogenic substrate reaction will be stopped with 1 M H_2SO_4 (100 μL/microwell) for 10 min at RT, and optical absorbance will be measured at 450 nm (reference: 620 nm, Tecan, Männedorf, Switzerland) within 10 min. Blank measurements will be subtracted from each sample measurement.

For quality control each lot of PF4 is tested with a panel of 20 different antibodies containing anti-PF4/heparin antibodies with known reactivity. Each lot of PF4/heparin complex coated plates is controlled with the same quality panel of known anti-PF4/heparin antibodies for sufficient reactivity. Each ELISA test is controlled with a known weak positive control and a known negative control.

Platelet activation assay with washed platelets (PIPA test)

Platelet preparation

Platelets will be purified from ACD-A anticoagulated whole blood obtained from healthy donors who did not take antiplatelet medications or non-steroidal anti-inflammatory drugs (NSAIDs) during the previous 10 days as demonstrated in the video tutorial available at: https://www.youtube.com/watch?v=hFs-_85YJX4

Platelet-rich plasma (PRP) will be centrifuged (7 minutes at 650 g, without brake) and the platelet pellet washed with Tyrode's buffer containing 0.35% BSA (albumin bovine Fraction V, Serva, Germany), 0.1% glucose (B. Braun, Germany), 2.5 U/mL apyrase (Sigma Aldrich, Germany), 1 U/mL hirudin (Canyon Pharmaceuticals, Switzerland), pH 6.3. After a further centrifugation (7 minutes at 650 g, without brake), the final platelet pellet will be resuspended in a bicarbonate-based suspension buffer consisting of 0.137 M NaCl, 0.027 M KCl, 0.012 M

NaHCO3, 0.42 mM NaH2PO4, 0.35% BSA, 0.1% glucose, 0.212 M MgCl2, 0.196 M CaCl2, pH 7.2 and adjusted to 300,000 platelets/µL.

PIPA test assessment and interpretation

Heat-inactivated (56 °C, 30 min) patient serum (20 µL) and washed platelets (75 µL) will be incubated in a microtiter plate (Greiner, Austria) with either buffer, 0.2 aFX U/mL low-molecular-weight heparin, reviparin (Abbott, Germany; if reviparin is not available enoxaparin can be used), 100 IU/mL unfractionated heparin (ratiopharm, Germany), or 10 µL platelet factor 4 solution (10 µg/mL, final conc., Chromatec, Germany) in the presence and absence of the FcγIIa receptor- blocking antibody, IV.3 (5 µL added to 75 µL platelets, obtained by cell supernatant, cell line ATCCHB-217, Biometec GmbH). To avoid any effect of thrombin, to all conditions (with the exception of the 100 IU/mL heparin reaction well) hirudin (5 U/mL) will be added.

The microtiter plate will be incubated (45 min, RT) on a magnetic stirrer (1000 rpm) with two steel spheres (2 mm diameter, SKF, Mercateo). The transparency of the suspension will be assessed using an indirect light source every 5 min. The PIPA test will be considered positive in the presence of platelet aggregation shown by clearance of the solution and visible aggregates – obtained within 30 min in at least 2 of 3 (or 2 of 4) test cells - in the presence of PF4 alone (or in buffer as well).

For quality control each platelet preparation is incubated with low concentrations of collagen to secure sufficient platelet reactivity. Each test is controlled by a known serum containing anti-PF4 antibodies causing platelet activation within 15 to 25 minutes.

IgG subclasses

PF4/heparin IgG ELISA

Binding of immunoglobulin G anti-PF4 antibodies of different subclasses IgG1, IgG2, IgG3, IgG4 from sera of VITT patients to PF4/heparin complexes will be measured by a solid phase PF4/heparin ELISA performed in flat-bottomed microwell plates (Cat. No. 478042 Thermo Scientific, CovaLink). PF4/heparin complexes of 0.5 IU/mL unfractionated heparin (UFH; Heparin-Natrium 25000 IE/ 5 mL, Ratiopharm) and 20 µg/mL PF4, in the absence or presence of 20 µM FeCl3, will be formed in coating buffer (50 mM NaH2PO4, 0.1% NaN3) at RT for 1 h and incubated for seven days at 4°C. Prior to use, complexes will be washed five times with washing buffer (150 mM NaCl, 1% Tween20 pH 7.5). 100 µL/microwell of serum samples (diluted to 1:200 if not indicated otherwise), in sample diluent (0.05 M NaH2PO4, 0.15 M NaCl, 7.5% goat normal serum, pH 7.5) will be incubated for 60 min, at RT and then washed five times. Horseradish peroxidase-conjugated anti-human IgG1, or anti-human IgG2, or anti-human IgG3, or anti-human IgG4 will be added. Binding of human IgG is then detected by adding chromogenic tetramethylbenzidine substrate (100 µL/microwell; Kementec, Taastrup, Denmark). At 60 min post-incubation, the chromogenic substrate reaction will be stopped with 1 M H2SO4

(100 µL/microwell) for 10 min at RT, and optical absorbance will be measured at 450 nm (reference: 620 nm, Tecan, Männedorf, Switzerland) within 10 min. Blank measurements will be subtracted from each sample measurement.

For quality control currently, only serum with known anti-PF4 antibodies of the IgG 1 class is available. When anti-PF4 antibodies of the other IgG classes are identified they will be used as positive control.

Glycosylation pattern of IgG

1. Affinity purification of anti-PF4 antibodies

Biotinylated PF4 (Cat.-No. 006/16, Chromatec, Greifswald, Germany) will be commercially obtained. It is produced to protect the polyanion binding site from biotynilation. Briefly, heparin sepharose (GE Healthcare, Uppsala, Sweden) will be washed 3 times with PBS pH 7.4, mixed with PF4 (Chromatec, Greifswald, Germany) from human platelets for 15 min, and then kept at 4°C overnight. The PF4-heparin-sepharose suspension will be mixed and incubated with biotin-XX SE (6-((6-((Biotinoyl)Amino)Hexanoyl)Amino)Hexanoic Acid, Succinimidyl Ester) (Molecular Probes, Eugene, OR, USA) for 1h at RT. Samples will be washed (0.8 M NaCl, 20 mM Hepes, 2 mM EDTA, pH 7.4), and biotinylated PF4 will be eluted with high salt buffer (2 M NaCl, 20 mM Hepes, 2 mM EDTA, pH 7.4). The concentration of biotinylated PF4 will be determined by a bicinchoninic acid protein assay kit using bovine serum albumin as standard (Sigma-Aldrich, Taufkirchen, Germany). Binding of heparin to biotinylated PF4 is not affected since the polyanion binding site of PF4 is protected from alteration by biotin.

For quality control biotinylated PF4 will be tested with VITT sera in the washed platelet functional test. Anti-PF4 antibodies induced platelet activation in the presence of biotinylated PF4 for the same way as in the presence of native PF4 (n=16).

Coupling of biotinylated PF4 (biotin-PF4) (Cat. No. 006/16; Chromatec, Greifswald, Germany) to streptavidin-conjugated paramagnetic microbeads (Dynabeads-SA) (Cat. No. 65601, Dynabeads MyOne Streptavidin T1, Invitrogen) will be performed according to the manufacturer's instructions. Briefly, 250 µL Dynabeads-SA will be washed four times with 1 mL PBS (pH 7.4) and resuspended in 250 µL biotin-PF4 (400 µg/mL PBS). For each sample, 250 µL biotin-PF4 and Dynabeads-SA will be coincubated for 30 min at room temperature with gentle rotation and washed four times with 500 µL washing-buffer (PBS pH 7.4 supplemented with 0.1% BSA). 200 µL of serum will be added and incubated for 90 min at 37°C under gentle rotation. Beads will be then washed four times in 500 µL washing-buffer. 400 µL acidic elution-buffer (0.1 M glycine, pH 2.7) will be added for 1 min. The eluate will be subjected immediately to a 100k-centrifugal filter device (Amicon Ultra-2, Merck Millipore, Darmstadt, Germany) and centrifuged for 5 min, 4000xg. Samples will be washed with an additional 400 µL elution-buffer, centrifuged again, and the remaining 100-130 µL supernatant immediately neutralized with 10 µL Tris-HCl-buffer (1 M, pH 9.0). The protein concentration of each sample will be measured at 280 nm on a NanoDrop2000 photo spectrometer (ThermoFisher, Waltham, USA) against the respective blank (TRIS-neutralized glycine-buffer).

For affinity purification of anti-PF4 IgG from biotin-PF4/heparin coupled Dynabeads-SA, PF4/heparin complexes of 1.0 IU/mL unfractionated heparin (Heparin-Natrium 25000 IE/5mL; Ratiopharm) with 40 µg/mL PF4 (30% biotin-PF4) will be formed in 12.5 mL PBS at room

temperature for 1 h. The coupling to washed Dynabeads-Streptavidin (250 µL per sample) will be performed consecutively in two steps with 2500 µL of the complex-solution (2x 1250 µL) for 30 min each and with subsequent steps performed as described above.

2. Glycosylation analysis

Glycosylation analysis of the affinity purified anti-PF4 IgG will be performed by mass spectrometry in the laboratory of Prof. Gestur Viddarson in a joint collaboration. In brief:

Eluates of purified IgG will be collected in low-binding PCR plates (Eppendorf, Hamburg, Germany) and dried by vacuum centrifugation (50 °C). The dried samples will be dissolved in a reduction and alkylation buffer containing sodium deoxycholate (0.4%), tris(2-carboxyethyl)phosphine (10 mM), 2-chloroacetamide (40 mM), and TRIS (pH 8.5; 100 mM), or ammonium bicarbonate (50 mM). After boiling the samples (10 min; 95 °C), trypsin (5 µg/mL) in ammonium bicarbonate (50 mM) will be added. The digestion will be terminated after overnight incubation (37 °C) by acidifying to a final concentration of 2% formic acid. Prior to mass spectrometry injection, sodium deoxycholate precipitates, in samples where this is added, will be removed by centrifugation (3000 × g; 30 min), and filtering through 0.65 µm low protein binding filter plates (Millipore, Burlington, USA).

Analysis of IgG Fc glycosylation will be performed with nanoLC reverse phase-electrospray mass spectrometry on an Impact HD quadrupole-time-of-flight mass spectrometer (Bruker Daltonics, Bremen, Germany), and data will be processed with Skyline software (version 4.2.0.19107). Distinct samples will be measured once. Samples will be considered seropositive if the intensity of antigen-specific IgG1 glycopeptides will be at least higher than the mean plus 10× the standard deviation of Dutch seronegative control samples. The level of fucosylation and bisection will be calculated as the sum of the relative intensities of glycoforms containing the respective glycotraits. Galactosylation and sialylation levels will be calculated as antenna occupancy. The relative intensities of the glycoforms will be summed with mono-galactosylated/sialylated species only contributing with 50% of their relative intensity

Genomic sequencing

For genomic sequencing DNA is extracted from EDTA anticoagulated blood by standard DNA purification methods. Sequencing will be performed in the Competence Center for Genomic Analysis of the subcontractor University Kiel using standard methods (30x coverage by paired end Illumina sequencing on a NovaSeq instrument). The whole genome sequencing will be performed by the Illumina DNA Prep protocol.[5] Sequencing will be performed on Illumina NovaSeq™ S4 with 2x150bp configuration.

Raw data will be provided by the sequencing center of the University Kiel to the study center Greifswald, where they will be processed bioinformatically and statistically, as described in *Statistical Methods* below.

The assembled genome sequences of the VITT patients will be compared to age and sex matched probands of the population-based Study of Health in Pomerania (SHIP study) representing the normal population in North-East Germany. The study will only include participants of Caucasian origin because only those are available in this region. SHIP is a population-based project in Northeast Germany.[6] It consists of two independent cohorts, SHIP-START and SHIP-Trend, that include adult men and women living in the cities Greifswald, Stralsund, Anklam, and the

surrounding communities. For both cohorts, representative samples of the 20-79 year old inhabitants of the study region were drawn from the local population registries. From these samples, 4308 subjects participated in the baseline SHIP-START examinations, that were conducted between 1997 and 2001, and 4420 subjects participated in the baseline SHIP-Trend examinations, that were conducted between 2008 and 2012. Further details on study design, sampling procedures and rationale are given elsewhere.[6] The study follows the recommendations of the Declaration of Helsinki and was approved by the ethics committee of the University of Greifswald. All participants provided informed written consent.

Adverse events

We aim to assess all AEs and SAEs, which occur during the observation period in close time relationship to the interventions second or third dose of Covid-19 vaccine, vaccination with any other vaccine, or surgical interventions or heparin application. This is a non-interventional study. All interventions are initiated and carried out by the treating physician and are not part of the study design.

Serious adverse event

Serious adverse events will be checked at each interview starting from October 2021 (start of study contract with EMA) and obtained retrospectively for the time since enrolment.

Serious Adverse Event

An SAE is defined as any untoward medical occurrence or effect:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is medically important event

An important medical event is an AE which may not be immediately life-threatening or result in death or hospitalization, but which may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether a case is serious.

Severity of Adverse Event

The severity of an AE refers to the extent to which an AE affects the subject's daily activities. Severity will be categorized according to the following criteria:

Mild: The AE does not interfere with the subject’s routine activities.

Moderate:	The AE interferes with the subject's daily routine, but usual routine activities can still be carried out.
Severe:	The AE results in the inability to perform routine activities.

The term "severity" is used to describe the intensity of an event. This is not the same as "serious." Seriousness, not severity, serves as the guide for defining regulatory reporting obligations. The highest severity grade attained should be reported, for AEs with divergent severities.

Causality of Adverse Event

The causality of an AE refers to the relationship of the AE to any intervention carried out by the treating physician and will be based upon the Investigators clinical judgement in close communication with the subject and the respective treating physician. Causality will be categorized according to the criteria below, taking into account all relevant information available at the time, including subject's age, laboratory test data, temporal relationship of the event to the intervention, presence of co-morbid conditions, medical history, clinical course of the presenting condition, concomitant drugs or chemicals. The relationship will be classified as follows:

Not Related:	A causal relationship between the intervention and the AE is not a reasonable possibility
Related:	A causal relationship between the intervention and the AE is a reasonable possibility, and there are no other obvious causes for the AE

Outcome of Adverse Events

The Investigator will assess the outcome of each AE as:

- Unresolved
- Resolving
- Resolved
- Resolved with sequelae
- Death
- Unknown

Every effort should be made to determine the outcome of any AE that occurs at any point in the study.

STATISTICAL METHODS

Disposition of Subjects

The following subject data will be summarized overall:

- Number of subjects enrolled into the prospective patient follow-up
- Number of subjects enrolled into the genome wide analysis
- Type and number of vaccines which caused VITT
- Number of subjects who received other vaccines during the follow-up period
- Number of subjects who received heparin during the follow-up period

Analysis Populations

Subjects enrolled into the prospective patient follow-up study will be analysed separately from subjects enrolled into the genome wide analysis.

Demographics, Baseline Characteristics and Concomitant Medications

Descriptive statistics for demographic data such as age (in years) will be presented. Frequency distributions will be presented for sex.

Other baseline characteristics will also be summarized according to their scaling type (continuous or categorical).

Comorbidities of the patients will be described.

Endpoints

Anti-PF4 Antibody persistence:

Time of onset will be given descriptively.

Persistence of anti-PF4 antibodies: Statistical analysis will be performed in R. As follow-up times are right-censored and differ between study participants, anti-PF4/heparin IgG ELISAs and functional tests will be analyzed using the Kaplan-Meier method. OD-thresholds of 2.0, 1.5, 1.0, and 0.5 will be used to dichotomize the anti-PF4/heparin IgG antigen assay after linear interpolation between measurement time points to handle interval-censoring. Patients that achieved negative and then relapsed to positive functional test results will be considered positive at all times. Confidence intervals for Kaplan-Meier estimates will be computed using Greenwood's method, confidence intervals for the binomial distribution will be computed using Wilson's approximation. A one-sided, paired Wilcoxon's signed rank test will be used to compare optical densities of the first and last anti-PF4/heparin IgG ELISA measurement per patient.

Evaluation of the Brighton Collaboration interim case definition of TTS

Sensitivity for the clinical diagnosis of VITT/TTS according to the Brighton collaboration case definition will be calculated for the combined results of the anti-PF4/heparin IgG ELISA and the washed platelet assay for PF4-dependent platelet activating antibodies (either both positive or

both negative; a result of ELISA positive and PF4-dependent platelet activating antibodies negative will be considered "negative")

Whole genome analysis:

Raw sequencing data obtained with 30x coverage by paired end Illumina sequencing on a NovaSeq instrument will be provided by the sequencing center of the University Kiel. Raw reads will be analyzed by FASTQC for sequencing metrics and reference based mapped on the human genome (GRCh38) via BWA-Mem.[7] Afterwards the BAM file is analyzed for "PCR duplicates" via Picard tools and pre-processed for GATK performing a base quality score recalibration (BSQR) and a local realignment around indels due to alignment artifacts. Due to sensitivity advantage the combination of two orthogonal SNV/indel callers namely Platypus[8] and GATK HaplotypeCaller[9] will be combined via BCFtools. Copy number variants (CNVs) based on read-depth will be analyzed using CNVnator[10] and for discordant read-pair analysis as well as structural variants (SVs) compared to matched SHIP probands LUMPY[11] will be used. Processed data will be subjected to careful quality control, e.g. checking for rare or monomorphic variants or variants that are not in Hardy-Weinberg equilibrium. PCA will be used to assess relatedness between samples.

Further statistical analysis will be performed in R. Assembled genome sequences of the VITT patients will be compared to age and sex matched probands of the population-based Study of Health in Pomerania. Chi-squared / likelihood ratio tests will be used to perform univariate tests of association between variants and cases/controls. Logistic regression will be performed when indicated, controlling for additional confounders. Correction for multiple testing will be done using a Bonferroni threshold of $5x10^{-8}$.

Distribution of the IgG subclasses of anti-PF4 antibodies will be provided descriptively.

Determination of anti-PF4 antibody amount required to activate platelets will be provided descriptively.

Determination of Sample Size

As no data on VITT/TTS are available, no reference data can be used for calculating a meaningful sample sizes for genetic analysis. We will therefore enroll as many subjects as possible to provide the basis for future prospective studies by our patient registry.

The inclusion of 66 VITT/TTS patients allows the sensitivity estimation of the Brighton Collaboration interim case definition with +/- 12.5% precision using conservative 95%-Clopper-Pearson confidence intervals, which is sufficient for a first evaluation of an interims definition.

DATA MANAGEMENT

Data Collection

Data collection will be performed by structured telephone interview of the patient and the treating physician by the investigators and by obtaining case summaries provided by the referral physician who treated the acute phase of VITT/TTS.
Data will be paper documented and for each subject a data file will be generated. Information documented on the patient file will be transcribed into a database which contains key numerical data of each individual. An example of the database is given in **Appendix 5**.

Data Correction

If new information occurs, the consistency will be double checked with the database by a second investigator and if necessary data will be corrected. Only the investigators have access to the database.

Data Handling

Data will be stored in an analog form in written patient files as well as in electronic form in an Excel database.

Data Quality Assurance

All received data available as paper documentation is transferred to the patient database by one investigator and double-checked by a second investigator.
Information obtained by the structured interview will be checked with the case reports sent by the treating physicians if existing.

QUALITY CONTROL AND QUALITY ASSURANCE

Study Initiation Activities

The Investigator(s) are informed about study objectives and methods, the inclusion and exclusion criteria, the time-schedule, and study procedures.

Training of Site Staff

The Investigator will ensure that everyone assisting with the clinical study is adequately informed about the protocol, their study-related duties and functions.

Documentation and Filing

Documentation System

This study will use paper documentation and an Excel file for documentation.

The Investigator must verify that all data entries in the electronic database are accurate and correct. Entries will be checked against appropriate source documentation by a second investigator. Due to the nature of the study no external monitoring system will be established.

List of Subjects (subject identification log)

The Investigator will keep a confidential list of names of all subjects participating in the study, so that the subjects' records can be identified if necessary.

In addition, the Investigator will keep a list of all subjects screened on a Screening log to document identification of subjects who entered pre-study Screening.

In parallel to the study documentation, the physicians, who are involved in direct patient contact will keep a document list with the names of the patient that allow direct access to all data for medical counselling. This document containing patient names will not be used for research purposes.

Source Data

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents which comprise clinical documentation, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

ETHICAL ASPECTS AND INSURANCE

Institutional Review Board/Independent Ethics Committee

The regulatory permission to perform the trial will be obtained in accordance with applicable regulatory requirements. The IRB/IEC will approve this protocol, the subject information sheet, the informed consent form, and any updates to these documents. The regulatory and ethical approvals must be available before a subject is exposed to any trial-related procedure, including Screening tests for eligibility.

Informed Consent

Before each subject is admitted to the study, informed consent will be obtained from the subject or their legally acceptable representative according to the regulatory and legal requirements of the participating country and the current version of the Declaration of Helsinki. Consent will be obtained from parents or legal guardians for any subjects under the age of consent. Subjects under the age of consent will be provided with assent documents detailing the study in age appropriate terms. This consent form must be dated and retained by the Investigator as part of the study records. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained.

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IRB/IEC and signed by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

Confidentiality of Subject and Sponsor Data

The Investigator(s) will respect and protect the confidentiality of the subject in all possible ways. Subject identification, other than subject number, will not appear in any documents given to the EMA. Only the Investigator and the persons authorized to verify the quality and integrity of the trial will have access to subject records where the subject can be identified.

Upon the subject’s permission, medical information may be given to their personal physician or other appropriate medical personnel responsible for their welfare. The source documentation for data generated by this study must be available for inspection by designees of health authorities, and the IEC/IRB.

Liability and Insurance

Due to the nature of the study no insurance is required.

ADMINISTRATIVE REQUIREMENTS

Protocol Modifications

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB/IEC/Competent Authorities, in accordance with local legal requirements.

To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate).

Administrative changes (not affecting the subject benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

The IRB/IEC must be informed of all amendments and must give approval for any amendments likely to affect the safety of the subjects or the conduct of the trial.

Records Availability and Retention

Investigators maintain all study documentation, including informed consent forms.

Subject identity information will be maintained for 15 years unless a longer period is required by applicable law or regulation.

The Investigator will archive the Study Master File.

Use of Information and Publication

The final clinical study report will be used for the further understanding of VITT/TTS. Data must not be published without written approval by the investigators.

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Datum: 01.12.2021

Mögliche Rezidive bei Patienten mit Vakzin-induzierter thrombotischer Thrombozytopenie (VITT)

Sehr geehrte Frau Kollegin, sehr geehrter Herr Kollege,

Sie haben uns kürzlich Proben eines Patienten bzw. einer Patientin (_____) mit thrombotischer Komplikation nach Impfung mit dem Impfstoff von AstraZeneca (Vaxzevria®) bzw. Johnson&Johnson (Janssen®) zur Diagnostik einer Vakzin-induzierten thrombotischen Thrombopenie (VITT) zugesandt. Diese Diagnose hat sich in unserem Labor bestätigt.
Wir wissen inzwischen, dass es Patienten mit VITT gibt, bei denen trotz initial erfolgreicher Therapie und Genesung noch nach Wochen die Antikörper wieder ansteigen können und die Patienten eventuell ein erhöhtes Risiko für ein Rezidiv haben. Aus diesem Grund möchten wir den Patienten und Patientinnen anbieten, diese Antikörper in regelmäßigen Abständen bei uns zu kontrollieren, um eine Abschätzung des Rezidivrisikos vornehmen zu können und im besten Fall eine weitere thrombotische Komplikation zu verhindern. Dieses ist eine Vorsichtsmaßnahme, Patienten sollten keine Angst haben.

Wir bitten Sie, Ihre Patientin/Ihren Patienten oder die Angehörigen über dieses Schreiben zu informieren und um das Einverständnis einer Kontaktaufnahme unsererseits zu bitten, damit wir die weitere Diagnostik über die aktuell behandelnden Ärzte in die Wege leiten können.
Wir haben ein Anschreiben sowie ein Schreiben an die Patienten und den aktuell behandelnden Arzt vorbereitet, in dem wir eine Wortwahl vorschlagen, die nicht zur völligen Verunsicherung führt. Beides finden Sie anbei. Für die Weiterleitung an Ihre Patienten nutzen Sie bitte gern den vorfrankierten Umschlag.
Sollte Ihr*e Patient*in in der Zwischenzeit verstorben sein, betrachten Sie dieses Schreiben bitte als gegenstandslos. Dennoch bitten wir Sie um eine kurze Rückinformation auf dem beigelegten Antwortschreiben, damit wir keine weiteren Anstrengungen unternehmen, um Kontakt zu Ihrem Patienten herzustellen, beispielsweise über das Paul-Ehrlich-Institut.
Bei Rückfragen wenden Sie sich bitte gern telefonisch oder per E-Mail an Frau Dr. med. Schönborn (Kontakt Briefkopf). Wir möchten Sie zusätzlich bitten, uns das beigefügte Einsender-Antwortschreiben kurz per Fax oder E-Mail zurückzusenden, damit wir wissen, welche Patienten bereits informiert worden sind.
Wir bedanken uns sehr für Ihre Unterstützung.

Mit freundlichen Grüßen

Prof. Dr. med. Andreas Greinacher
Leiter Abteilung Transfusionsmedizin

Universitätsmedizin Greifswald
Institut für Immunologie und Transfusionsmedizin
Abteilung Transfusionsmedizin
Dr. med. Linda Schönborn
Ferdinand-Sauerbruch-Straße
17475 Greifswald

Institut für Immunologie und Transfusionsmedizin
Abteilung Transfusionsmedizin

Kontakt
Dr. med. Linda Schönborn (Assistenzärztin)

Tel: +49 3834 865496
+49 3834 865479 (Sekretariat)
Fax:+49 3834 865489
E-Mail: Linda.Schoenborn@med.uni-greifswald.de

Datum:

Antwortschreiben Einsender – Nachverfolgung VITT-Patienten

Antwortschreiben bitte zurück per Post, Fax 03834 / 865489 oder per E-Mail

Befundnummer: [_____]

Ansprechpartner: _____
_____
_____

1. Wir
   - □ haben den Patienten / die Patientin über Ihr Schreiben informiert.
   - □ möchten / können den Patienten nicht informieren.

2. Der Patient / die Patientin
   - □ hat einer Kontaktaufnahme bereits zugestimmt.
     Kontaktdaten: _____
     _____
     _____
     Tel.: _____
   - □ wünscht keine Kontaktaufnahme.
   - □ wurde informiert und wird sich mit Ihnen in Verbindung setzen.
   - □ ist verstorben.

_____ _____
Ort, Datum Unterschrift

Transfusionsmedizin . Universitätsmedizin Greifswald . Sauerbruchstr . 17475 Greifswald

Institut für Immunologie und Transfusionsmedizin
Abteilung Transfusionsmedizin

Kontakt
Dr. med. Linda Schönborn (Assistenzärztin)

Tel: +49 3834 865496
+49 3834 865479 (Sekretariat)
Fax:+49 3834 865489
E-Mail: Linda.Schoenborn@med.uni-greifswald.de

An die Patientin / an den Patienten

Datum: 01.12.2021

Kontrolluntersuchungen nach Impfstoff-assoziierten Thrombosen

Sehr geehrte*r Patient*in,

bei Ihnen sind nach der Impfung mit AstraZeneca (Vaxzevria®) bzw. Johnson&Johnson (Janssen®) Komplikationen in Form einer Thrombozytopenie (niedrige Blutplättchen) und Thrombosen (Blutgerinnsel) aufgetreten. Diese Komplikationen wurden durch Antikörper verursacht. Die Antikörper wurden an der Universitätsmedizin Greifswald nachgewiesen.
Wir wissen im Moment nicht, wie lange diese Antikörper im Blut nachweisbar sind. Es besteht die Möglichkeit, dass die Antikörper relativ schnell aus Ihrem Blut verschwinden und nicht mehr nachweisbar sind. Wir wissen aktuell auch nicht, ob diese Antikörper vielleicht noch einmal wiederkommen können.
Die Universitätsmedizin Greifswald bietet Ihnen an, Ihr Blut innerhalb der nächsten Monate mehrfach zu untersuchen, um nachzuweisen, ob diese Antikörper wirklich verschwinden. Die Ergebnisse dieser Untersuchungen können wichtig sein, falls bei Ihnen nochmals gesundheitliche Probleme auftreten.
Die Untersuchung der Antikörper kann mit eingeschicktem Blut erfolgen. Die Blutentnahme kann ihr Hausarzt durchführen. Wir benötigen 1 Röhrchen Nativblut (ohne Gerinnungszusätze) und 1 kleines Röhrchen EDTA-Blut. Das Blut kann mit der normalen Post verschickt werden. Ihre Hausärztin/Ihr Hausarzt wird dann umgehend über die Ergebnisse informiert. Ihnen entstehen keine zusätzlichen Kosten.
Wenn Sie Interesse haben, dieses Angebot anzunehmen, schicken Sie bitte das beiliegende Antwortschreiben direkt nach Greifswald an folgende Adresse, oder alternativ per E-Mail oder Fax (Adresse und Nummer siehe oben):

Universitätsmedizin Greifswald
Abteilung Transfusionsmedizin
Dr. med. Linda Schönborn
Ferdinand-Sauerbruchstraße
17475 Greifswald

Wir haben auch ein Schreiben an Ihre*n Hausärztin/Hausarzt beigelegt, mit dem Sie sich auch direkt bei Ihrem Hausarzt vorstellen können.
Mit freundlichen Grüßen

Prof. Dr. med. Andreas Greinacher
Leiter Abteilung Transfusionsmedizin

Transfusionsmedizin . Universitätsmedizin Greifswald . Sauerbruchstr . 17475 Greifswald

Universitätsmedizin Greifswald
Institut für Immunologie und Transfusionsmedizin
Abteilung Transfusionsmedizin
Dr. med. Linda Schönborn
Ferdinand-Sauerbruch-Straße
17475 Greifswald

Institut für Immunologie und Transfusionsmedizin
Abteilung Transfusionsmedizin

Kontakt
Dr. med. Linda Schönborn (Assistenzärztin)

Tel: +49 3834 865496
+49 3834 865479 (Sekretariat)
Fax:+49 3834 865489
E-Mail: Linda.Schoenborn@med.uni-greifswald.de

Datum:

Patienten-Antwortschreiben

Antwortschreiben bitte zurück per Post, Fax 03834 / 865489 oder per E-Mail

Befundnummer: [_____]
Name, Vorname: _____
Geburtsdatum: _____

1. Ich

□ möchte gern in regelmäßigen Abständen an den Kontrolluntersuchungen teilnehmen.

oder

□ möchte keine Kontrolluntersuchungen wahrnehmen.

Falls Teilnahme gewünscht:

2. Sie erreichen mich am besten wie folgt (telefonische Erreichbarkeit, E-Mail).

□ Kontaktdaten: _____
_____
_____
Tel.: _____

_____ _____
Ort, Datum Unterschrift

Transfusionsmedizin . Universitätsmedizin Greifswald . Sauerbruchstr . 17475 Greifswald

An die behandelnde Ärztin / den behandelnden Arzt

Institut für Immunologie und Transfusionsmedizin
Abteilung Transfusionsmedizin

Kontakt
Dr. med. Linda Schönborn (Assistenzärztin)

Tel: +49 3834 865496
+49 3834 865479 (Sekretariat)
Fax:+49 3834 865489
E-Mail: Linda.Schoenborn@med.uni-greifswald.de

Datum: 01.12.2021

Mögliche Rezidive bei Patienten mit Vakzin-induzierter thrombotischer Thrombozytopenie (VITT)

Sehr geehrte Frau Kollegin, sehr geehrter Herr Kollege,

bei Ihrem Patienten bzw. Ihrer Patientin (_____) mit thrombotischer Komplikation nach Impfung mit dem Impfstoff von AstraZeneca (Vaxzevria®) bzw. Johnson&Johnson (Janssen®) haben wir in unserem Labor Antikörper, die eine Vakzin-induzierte thrombotische Thrombopenie (VITT) auslösen, bestätigt.

Wir wissen nicht genau, wie sich diese Antikörper längerfristig verhalten. Es besteht die große Wahrscheinlichkeit, dass bei den meisten Patienten die Antikörper innerhalb von 3 Monaten wieder verschwinden. Falls die Antikörper bestehen bleiben, wäre das eine wichtige Information, falls nochmals gesundheitliche Probleme auftreten.

Aus diesem Grund möchten wir den Patienten und Patientinnen anbieten, diese Antikörper in regelmäßigen Abständen bei uns zu kontrollieren. Dieses ist eine reine Vorsichtsmaßnahme. Wir wollen Ihre Patientin/Ihren Patienten keinesfalls verunsichern, sondern ganz im Gegenteil alles dafür tun, dass sich die Patienten möglichst sicher fühlen.

Wir haben über die akut behandelnde Klinik Ihre Patientin/ Ihren Patienten kontaktiert und die Wiedervorstellung bei Ihnen empfohlen.
Würden Sie bitte alle 4 Wochen je 1 Röhrchen Nativblut (ohne Gerinnungszusätze) und ein Röhrchen EDTA-Blut abnehmen und uns mit der regulären Post zusenden, bis zweimal ein negatives Ergebnis nachgewiesen wird? Es wäre gut, wenn das Blut Anfang der Woche abgenommen wird, damit es nicht über das Wochenende lagert. Nutzen Sie für die Zusendung bitte den beigefügten Anforderungsschein.
Die Kosten werden wir aus unserem Budget tragen. Ihnen werden keine Kosten für die Laboruntersuchung entstehen.
Für Rückfragen stehen wir gern unter 03834 /86 5496 (Frau Dr. med. Schönborn) zur Verfügung.

Mit freundlichen Grüßen

Prof. Dr. med. Andreas Greinacher
Leiter Abteilung Transfusionsmedizin

Universitätsmedizin Greifswald
Institut für Immunologie und Transfusionsmedizin
Abteilung Transfusionsmedizin
Thrombozytenlabor
Dr. med. Linda Schönborn
Ferdinand-Sauerbruch-Straße
17475 Greifswald

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Kontakt
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Tel: +49 3834 865496
+49 3834 865479 (Sekretariat)
Fax:+49 3834 865489
E-Mail: Linda.Schoenborn@med.uni-greifswald.de

Datum: 01.12.2021

Anforderungsschein Verlaufskontrolle – VITT

Für die Diagnostik benötigen wir bitte **6ml Serum-Blut** + **6ml EDTA-Blut**
(geplant ist eine Kontrolle alle 4 Wochen, bis zweimalig ein negatives Ergebnis vorliegt)

Name des Patienten: _____

Geburtsdatum: _____

Datum der Blutentnahme: _____

Ist in der Zwischenzeit eine **Zweitimpfung** gegen SARS-CoV-2 erfolgt O ja O nein

Falls ja, wann und mit welchem Impfstoff? _____, Datum: _____

War der Patient zum Zeitpunkt der 2. Impfung **antikoaguliert**? O ja, mit _____
O nein

Bitte vollständige Adresse des Absenders (falls diese nicht aus dem Stempel hervorgeht):

_____
_____
_____

Fax-Nummer oder E-Mail-Adresse für Befundübermittlung:
(Mit meiner Unterschrift bestätige ich, dass für alle auf das Faxgerät eingehenden Dokumente, die Datenschutzbestimmungen nach DSVGO eingehalten werden.)

_____

_____ _____
Ort, Datum Unterschrift des Abnehmenden
und Praxisstempel

Universitätsmedizin Greifswald • Fleischmannstraße 8 • D-17475 Greifswald

Universitätsmedizin Greifswald
Institut für Immunologie und Transfusionsmedizin
Abteilung Transfusionsmedizin
Herr Prof. Dr. Andreas Greinacher
Ferdinand-Sauerbruch-Straße

D-17475 Greifswald

Ethikkommission

GESCHÄFTSSTELLE
Universitätsmedizin Greifswald
Ethikkommission
Institut für Pharmakologie
Felix-Hausdorff-Str.3
D-17487 Greifswald

BEARBEITER
Frau Dr. K. Saljé

DATUM
02.06.2021

Studientitel: Verwendung von Restmaterial von Patienten mit seltenen schwerwiegenden Nebenwirkungen einer COVID-19-Impfung
Interne Reg.Nr.: BB 052/21a

Stellungnahme der Ethikkommission
(hier: Studienprotokoll, Version 2.0 vom 17.05.2021)

Sehr geehrter Herr Prof. Greinacher,

die Ethikkommission der Universitätsmedizin Greifswald hat sich mit dem o.g. Amendment in ihrer Sitzung am 01.06.2021 befasst.

Die Kommission stellte mehrheitlich fest, dass gegen die Fortführung der Studie in der veränderten Form keine ethischen und rechtlichen Bedenken bestehen.

Die Ethikkommission erlaubt sich aber folgende Hinweise.

Im Studienprotokoll (Version 2.0 vom 17.05.2021) sollte der Zeitraum, über den in regelmäßigen Abständen Verlaufskontrollen durchgeführt werden, aufgeführt werden.

Das Anschreiben an die behandelnde Ärztin / den behandelnden Arzt sollte gemäß den in der Sitzung gegebenen Hinweisen überarbeitet werden.

Die Ethikkommission macht darauf aufmerksam, dass die ethische und rechtliche Verantwortung für die Durchführung des Forschungsvorhabens beim Studienleiter und allen beteiligten Ärzten liegt. Zusammensetzung und Arbeitsweise entsprechen den gesetzlichen Bestimmungen. Den Beratungen der Kommission liegt die Deklaration von Helsinki in der aktuellen Fassung zugrunde.

Telefon:
+49 (0)3834 86-5644

Telefax:
+49 (0)3834 86-5631

E-mail:
ethik@uni-greifswald.de

Internet:
www.medizin.uni-greifswald.de

Bankverbindung:
Deutsche Bundesbank Rostock
Konto-Nr. 130 015 30
BLZ 130 000 00

USt ID:
DE137584813

Die Mitglieder der Kommission wünschen Ihnen auch weiterhin viel Erfolg bei der Durchführung des Vorhabens.

Mit freundlichen Grüßen

PD Dr. M. Gründling
Vorsitzender der Ethikkommission

UNIVERSITÄTSMEDIZIN GREIFSWALD · KÖRPERSCHAFT DES ÖFFENTLICHEN RECHTS
VORSTAND: Prof. Dr. Uwe Reuter (VV/ÄV) · Toralf Giebe (KV) · Prof. Dr. Karlhans Endlich (komm. WV)
AUFSICHTSRATSVORSITZENDER: Mathias Brodkorb
Fleischmannstraße 8 · 17475 Greifswald · Tel.: +49(0)3834 86-0 · www.medizin.uni-greifswald.de

Allgemeine Hinweise:

- Die Zusammensetzung und Arbeitsweise der Ethikkommission an der Universitätsmedizin Greifswald entsprechen den nationalen gesetzlichen Bestimmungen und der ICH-GCP-Leitlinie. Den Beratungen der Ethikkommission liegt die Deklaration von Helsinki in der aktuellen Fassung zugrunde.
- Bei Änderungen oder Erweiterungen des Forschungsvorhabens vor oder während der Durchführung bedarf es einer Anzeige der Änderungen/Erweiterungen und ggf. einer erneuten Beratung. Die Ethikkommission bittet die Änderungen und/oder Erweiterungen der Studienunterlagen deutlich zu kennzeichnen.
- Die Ethikkommission bittet um Mitteilung des Studienendes und die Zusendung einer Synopse des Abschlussberichtes.
- Die Ethikkommission empfiehlt die Eintragung des Forschungsvorhabens in ein öffentliches Studienregister.

Zur Bewertung haben der Kommission vorgelegen:

- Begleitschreiben vom 18.05.2021
- Amendment zum Studienprotokoll, Version 2.0 vom 17.05.2021
- Anschreiben an Einsender von Proben mit bestätigter VITT, Patient*innen und behandelnder Ärzt*innen inklusive Antwortschreiben
- Anforderungsschein Verlaufskontrolle
- Studieninformation und Einverständniserklärung Patient*in

Der Ethikkommission gehören an:

reguläre Mitglieder	*ständige Stellvertretung*
PD Dr. A. Aghdassi* Klinik für Innere Medizin A	*PD Dr. L. Bossaller* *Klinik für Innere Medizin A*
Prof. Dr. B. Kordaß Zentrum für Zahn-, Mund- und Kieferheilkunde	*Prof. Dr. R. Biffar* *Zentrum für Zahn-, Mund- und Kieferheilkunde*
Prof. Dr. S. Engeli* Institut für Pharmakologie	*Prof. Dr. M. Dörr* *Klinik für Innere Medizin B*
PD Dr. M. Gründling* Klinik für Anästhesiologie und Intensivmedizin	*OA Dr. P. Abel* *Klinik für Innere Medizin B*
PD Dr. F. von Podewils Klinik und Poliklinik für Neurologie	*Dr. R. Bülow* *Institut für Diagnostische Radiologie und Neuroradiologie*
Prof. Dr. Th. Kohlmann* Institut für Community Medicine	*Prof. Dr. W. Hoffmann* *Institut für Community Medicine*
OÄ Dr. K. Grass Klinik und Poliklinik für Allgemeine Chirurgie	Prof. Dr. B. Bockholdt Institut für Rechtsmedizin
Prof. Dr. H. Lang* Fakultät für Rechts- und Staatswissenschaft	*Prof. Dr. C. Sowada und Prof. Dr. H. Lege* *Fakultät für Rechts- und Staatswissenschaft*
Sebastian Laacke, M.A.* Institut für Ethik und Geschichte der Medizin	*Prof. Dr. M. Werner* *Institut für Philosophie*
PD Dr. S. Schmidt* Klinik und Poliklinik für Kinder- und Jugendmedizin	*Prof. Dr. A. Meyer-Bahlburg* *Klinik und Poliklinik für Kinder- und Jugendmedizin*
CA Dr. F. Ruhland* Fachabteilung für Gynäkologie und Geburtshilfe, HELIOS Hanseklinikum Stralsund	*OA Dr. Z. Alwafai* *Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe*
Prof. Dr. H.-C. Schober Klinik für Innere Medizin, Klinikum Südstadt Rostock	*Dr. Dr. M. Gillner* *Fachabteilung für Forensische Psychiatrie, HELIOS Hanseklinikum Stralsund*
Selma Pohlmann, Medizinstudentin	*Philipp Schweikhard, Medizinstudent**

*bei der Sitzung am 01.06.2021 anwesend

UNIVERSITÄTSMEDIZIN GREIFSWALD · KÖRPERSCHAFT DES ÖFFENTLICHEN RECHTS
VORSTAND: Prof. Dr. Uwe Reuter (VV/ÄV) · Toralf Giebe (KV) · Prof. Dr. Karlhans Endlich (komm. WV)
AUFSICHTSRATSVORSITZENDER: Mathias Brodkorb
Fleischmannstraße 8 · 17475 Greifswald · Tel.: +49(0)3834 86-0 · www.medizin.uni-greifswald.de

Studieninformation – Verlaufskontrolle nach seltener Impfnebenwirkung

Sehr geehrte Patientin, sehr geehrter Patient,

nachdem bei Ihnen nach einer Impfung gegen COVID-19 eine seltene Nebenwirkung aufgetreten ist (Blutgerinnsel und/oder niedrige Blutplättchen), wurden an der Universitätsmedizin Greifswald Antikörper nachgewiesen, welche für diese Nebenwirkung verantwortlich sind.
Sie haben bereits eingewilligt, dass wir mit Ihnen Kontakt aufnehmen und in regelmäßigen Abständen Ihr Blut auf das Vorhandensein dieser Antikörper zur gesundheitlichen Vorsorge untersuchen können. Für Sie persönlich kann diese Untersuchung wichtig sein, falls bei Ihnen nochmals gesundheitliche Probleme im Zusammenhang mit den nachgewiesenen Antikörpern auftreten.

Bisher wissen wir nicht, wie lange diese Antikörper nachweisbar sind. Wir möchten Sie daher um Ihr Einverständnis bitten, die Ergebnisse Ihrer Blutuntersuchung und die erhobenen Daten zum Krankheitsverlauf wissenschaftlich auswerten zu können.

Ablauf und Umfang der Datenerhebung
Wir möchten Sie bitten, uns ca. alle 4 Wochen eine Blutprobe (ca. 12mL) zuzusenden (Details entnehmen Sie bitte dem separat beigefügtem Anforderungsschein). Diese können Sie bei Ihrem Hausarzt / Ihrer Hausärztin abnehmen lassen und uns per Post zusenden. Wenn Sie dies wünschen, senden wir Ihnen gern die entsprechenden Röhrchen, ein Blutentnahme-Set sowie einen frankierten Rückumschlag zu.
Aktuell ist es geplant, diese Untersuchungen fortzuführen, bis 2x hintereinander keine Antikörper mehr nachweisbar sind.
Bei der durchgeführten Datensammlung handelt es sich um eine pseudonymisierte Datenerhebung. Bei der Pseudonymisierung wird der Name oder ein anderes Identifikationsmerkmal durch ein Pseudonym (Code/ID) ersetzt, um die Feststellung der Identität des Betroffenen auszuschließen oder wesentlich zu erschweren (siehe § 3 Abs. 6a BDSG bzw. entsprechendes Landesrecht).
Die Durchführung der Datenerhebung und die Eingabe der Daten erfolgt durch einen ärztlichen Mitarbeiter der Abteilung Transfusionsmedizin der Universitätsmedizin Greifswald. Die Daten werden nach den Datenschutzbedingungen des Landes für einen Zeitraum von 10 Jahren aufbewahrt.

Nutzen und Risiken der Teilnahme
Unabhängig von Ihrer Studienteilnahme führen wir Ihre Verlaufskontrollen der Antikörper weiter.

Wenn Sie mit der Teilnahme an unserer Studie einverstanden sind, ermöglichen Sie uns durch die Erhebung und Auswertung Ihrer Daten ein besseres Verständnis Ihrer Erkrankung, das ggf. auch anderen Patient*innen von Nutzen sein kann.

Wie werden Ihre Daten genutzt?

Forschungsergebnisse und andere wissenschaftliche Erkenntnisse aus den Untersuchungen werden insbesondere der Fachöffentlichkeit durch Publikationen und andere Veröffentlichungen bekannt gemacht. Die Erkenntnisse werden als Grundlage für die kontinuierliche Verbesserung der Patientenversorgung genutzt. Alle Veröffentlichungen erfolgen immer anonym und beziehen sich niemals auf Sie als konkrete Personen.

Freiwilligkeit der Teilnahme und Widerruf der Einwilligung

Ihre Teilnahme an der Studie ist freiwillig. Bei Ablehnung entstehen Ihnen keine Nachteile. Sie können Ihre Einwilligung jederzeit frei widerrufen, ohne dass Ihnen hierdurch Nachteile entstehen. Ihre Verlaufskontrollen werden weiterhin durchgeführt. Zudem haben Sie jederzeit das Recht Ihre Teilnahme zu widerrufen. Aus bereits publizierten Daten ist ein Entfernen Ihrer Daten jedoch nicht mehr möglich.

Aufgrund des Wirksamwerdens der Europäischen Datenschutz-Grundverordnung = DSGVO zum 25. Mai 2018, ergeben sich folgende Anforderungen und Rechte an die Verarbeitung personenbezogener Daten nach Artikel 12 ff. DSGVO.

Bezüglich Ihrer Daten haben Sie folgende Rechte:

1. Sie haben das Recht auf Auskunft über die Sie betreffenden personenbezogenen Daten, die im Rahmen der Studie erhoben, verarbeitet oder ggf. an Dritte übermittelt werden
2. Sie haben das Recht Sie betreffende unrichtige personenbezogene Daten berichtigen zu lassen
3. Unter bestimmten Voraussetzungen haben Sie das Recht auf Einschränkung der Verarbeitung zu verlangen, d.h. die Daten dürfen nur gespeichert, nicht verarbeitet werden. Dies müssen Sie beantragen. Wenden Sie sich hierzu bitte an ihren Prüfer oder an den Datenschutzbeauftragten des Prüfzentrums
4. Sie haben das Recht, die sie betreffenden personenbezogenen Daten, die sie dem Verantwortlichen für die Studie/ Prüfung bereitgestellt haben, zu erhalten. Damit können Sie beantragen, dass diese Daten entweder Ihnen oder, soweit technisch möglich, einer anderen von Ihnen benannten Stelle übermittelt werden
5. Sie haben das Recht, jederzeit gegen konkrete Entscheidungen oder Maßnahmen zur Verarbeitung der Sie betreffenden personenbezogenen Daten Widerspruch einzulegen

Möchten Sie weiterführende Informationen zur Speicherung und Nutzung der Daten, wenden Sie sich bitte an den verantwortlichen Studienleiter oder an den Datenschutzbeauftragten der Universitätsmedizin Greifswald. Außerdem haben Sie das Recht, Beschwerde bei der/den Aufsichtsbehörde/n einzulegen,

wenn Sie der Ansicht sind, dass die Verarbeitung der Sie betreffenden personenbezogenen Daten gegen die DSGVO verstößt:

Datenschutz Kontaktdaten

Verantwortlicher für die Datenverarbeitung

Name: PD Dr. med. Thomas Thiele

Adresse: Universitätsmedizin Greifswald
Institut für Immunologie und Transfusionsmedizin, Abteilung Transfusionsmedizin
Ferdinand-Sauerbruch-Straße
17475 Greifswald

E-Mail: thomas.thiele@med.uni-greifswald.de

Beauftragter für den Datenschutz Universitätsmedizin Greifswald

Name: Professor Ulf Glende
Universitätsmedizin Greifswald
W. Rathenau Str. 49 Wohnung 2.5
17475 Greifswald

E-Mail: datenschutz-umg@uni-greifswald.de

Einwilligungserklärung

Hiermit willige ich

Name Patient*in: _____,

Geburtsdatum: _____,

ein, dass meine Blutproben für die Aufklärung des zugrundeliegenden Pathomechanismus der Impfkomplikationen sowie zur Entwicklung, Optimierung, Validierung und Qualitätskontrollen von diagnostischen Testverfahren verwendet werden dürfen. Ich habe das Informationsblatt zur Studie gelesen und bin über Zweck und Inhalt der Studie informiert worden. Ich habe verstanden, dass meine Teilnahme freiwillig ist und mir bei Nichtteilnahme keine Nachteile entstehen. Ich bin damit einverstanden, dass daraus entstehende Ergebnisse wissenschaftlich veröffentlicht werden dürfen, wenn daraus keine Rückschlüsse auf meine Person möglich sind.

Ort, Datum: _____

Unterschrift Patient*in: _____

Bei nicht einwilligungsfähigen Patienten
Unterschrift eines gesetzl. Vertreters: _____

Telefonprotokoll Strukturiertes Interview – Verlaufskontrolle VITT

Labor-ID: Datum:

Mündliche Einverständnis zur Studienteilnahme: O ja O nein

Einverständniserklärung verschickt am: _____

Datum 1. Impfung: _____

Symptombeginn: _____

Symptome: _____

Diagnose: _____

Zweite Impfung gegen COVID-19:

O geplant

O nicht geplant

O bereits erfolgt am _____._____.____

mit dem Impfstoff _____

währenddessen erfolgte die Einnahme von Gerinnungshemmern:
O ja O nein

falls ja, Name des Medikaments: _____

Zusätzliche Informationen zu Verlauf und Therapie vorhanden:

_____

_____

_____

_____

Appendix 5 – Database example (No real patient data are shown)

	Labor-ID	Name	age	sex	oral informed consent	written informed consent	Date of vaccination	Type of vaccine	Onset of symptoms	Time of onset of symptoms	Weeks betw onset symptoms + 1. blood sample	Date of 2nd SARS-CoV-2 vaccination	Type of vaccine 2nd vaccin.	Last PIPA before 2nd vacc.	Anticoagulation at 2nd vaccin.	Monitoring of platelet count after 2nd vacc	Influenza vaccination	Symptoms
1																		
2	001	####	43	m	yes	yes	26.02.2021	AstraZeneca	12.03.2021	6	1	14.08.2021	BioNTech/Pfizer	negativ	Xarelto 20mg			Abdominal pain
3	002	####	21	w	yes	yes	09.03.2021	AstraZeneca	15.03.2021	7	1	13.10.2021	BioNTech/Pfizer	negativ	Eliquis 5mg			Dyspnea
4	005	####	43	w	yes	yes	15.03.2021	AstraZeneca	26.03.2021	7	1							Headache, paresis left
5	009	####	63	w	yes	yes	12.03.2021	AstraZeneca	17.03.2021	8	1	14.07.2021	BioNTech/Pfizer	negativ	none		20.10.2021	Pain left leg
6	014	####	25	m	yes	yes	07.04.2021	AstraZeneca	09.04.2021	9	1	30.06.2021	BioNTech/Pfizer	positive	Xarelto 20mg			Emesis, Dyspnea
7																		

	Labor-ID	Clinical Diagnosis	Initial Anticoagulation	Preexisting Condition	ivIgG	Steroide	Platelet Tranfusion	Number of blood sample	Date of 1st Blood sample	Weeks between onset of symptoms and first blood sample	Platelet count	OD anti-PF4/heparin ELISA	HIPA result	HIPA interpretation	PIPA result	PIPA interpretation	Number of 2nd blood sample	Date of second blood sample	.... (Repetition for all existing blood samples)
1																			
2	001	Mesenterial	Argatra					442585	30.03.2021	1	48	3.06	0/4	neg	4/4	pos	7822472	14.06.2021	....
3	002	PE	Xarelto		yes			754257	01.04.2021	1	/	2.17	0/3	neg	3/3	pos	7572147	10.06.2021	....
4	005	CVST + secondary ICB						824554	06.04.2021	1	/	3.00	0/3	neg	4/4	pos	4287282	25.06.2021	....
5	009	DVT + PE			yes	yes		247754	06.04.2021	1	/	3.41	1/3	neg	4/4	pos	8781477	16.06.2021	....
6	014	PE			yes		2 PLT	457274	16.04.2021	1	220	1.27	0/4	neg	3/4	pos	4884215	13.09.2021	....