# Vaccine-induced immune thrombotic thrombocytopenia and thrombosis syndrome (VITT/TTS) after vaccination against SARS-CoV-2 (COVID-19)

**First published:** 14/01/2022

**Last updated:** 23/04/2024

Study   Finalised

## Administrative details

**EU PAS number**

EUPAS45098

**Study ID**

47159

**DARWIN EU® study**

No

**Study countries**

☐ Germany

**Study description**

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.

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**Study status**

Finalised

# Contact details

## Study institution contact

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( Study contact )

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## Primary lead investigator

Andreas Greinacher

( Primary lead investigator )

# Study timelines

## Date when funding contract was signed

Actual: 01/09/2021

## Study start date

Actual: 01/09/2021

## Data analysis start date

Actual: 01/10/2021

## Date of interim report, if expected

Planned: 18/01/2022

Actual: 18/01/2023

## Date of final study report

Planned: 18/01/2023

Actual: 20/03/2023

# Sources of funding

- EMA

# Study protocol

[Study protocol Version 4.2 (002).pdf](1.49 MB)

# Regulatory

**Was the study required by a regulatory body?**

Yes

**Is the study required by a Risk Management Plan (RMP)?**

Not applicable

# Other study registration identification numbers and links

The study is registered at the German Clinical Trials Register: DRKS00025738

# Methodological aspects

# Study type

# Study type list

**Study topic:**

Disease /health condition

**Study type:**

Not applicable

**Scope of the study:**

Other

**If 'other', further details on the scope of the study**

Patient registry

**Data collection methods:**

Primary data collection

**Main study objective:**

What are the characteristics of the immune response against PF4 induced by SARS-CoV-2 vaccine? Evaluation of the Brighton Collaboration interim case definition of TTS Genome wide analysis of patients with VITT/TTS Characterization of the anti-PF4 antibodies in VITT/TTS

# Study drug and medical condition

**Medical condition to be studied**

Vaccination complication

**Additional medical condition(s)**

Vaccine-induced immune thrombotic thrombocytopenia

# Population studied

**Short description of the study population**

The study involved two cohorts: subjects with clinical diagnosis of vaccine-induced immune thrombotic thrombocytopenia and thrombosis syndrome (VITT/TTS) with platelet activating PF4-dependent antibodies identified by Greifswald reference laboratory, and those with clinically suspected VITT/TTS after vaccination with an adenoviral vector-based COVID-19 vaccine, confirmed by positive anti-PF4/heparin IgG ELISA and positive PF4-enhanced platelet activation.

Inclusion Criteria:

Prospective patient registry (Cohort 1):

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.

**Age groups**

Children (2 to < 12 years)

Adolescents (12 to < 18 years)

Adults (18 to < 46 years)

Adults (46 to < 65 years)

Adults (65 to < 75 years)

Adults (75 to < 85 years)

Adults (85 years and over)

**Special population of interest**

Renal impaired

Hepatic impaired

Immunocompromised

Pregnant women

Other

**Special population of interest, other**

Patients with vaccine-induced immune thrombotic thrombocytopenia and thrombosis syndrome

**Estimated number of subjects**

69

# Study design details

**Outcomes**

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. - Reevaluation of TTS patients according to the Brighton collaboration case definition with special emphasis on occurrence of VITT/TTS in the absence of thrombosis. - Sequencing the genome of VITT/TTS patients and comparison with the genomes of the matched probands of the normal population obtained by the Study of Health in Pomerania (SHIP) - Assessment of the IgG subclasses of the anti-PF4 abs

## Data analysis plan

Following laboratory methods are used: - Anti-PF4/heparin IgG ELISA - Platelet activation assay with washed platelets (PIPA) - Glycosylation analysis of the affinity purified anti-PF4 IgG will be performed by mass spectrometry - 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 Statistical analysis - 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.

# Documents

### Study results

Abstract Final Study Report EMA.pdf(38.33 KB)

Final Study Report_uploaded at EUPAS register.pdf(1.06 MB)

### Study publications

Greinacher A, Schönborn L, Siegerist F, Steil L, Palankar R, Handtke S, Reder A…

Schönborn L, Greinacher A. Longitudinal aspects of VITT. InSeminars in Hematolo…

Schönborn L, Seck SE, Thiele T, Warkentin TE, Greinacher A. SARS-CoV-2 infectio…

Schönborn L, Thiele T, Esefeld M et al. Quantitative interpretation of PF4/hepa…

Schönborn L, Thiele T, Kaderali L, Günther A, Hoffmann T, Seck SE, Selleng K, G…

# Data management

## Data sources

**Data sources (types)**

Other

**Data sources (types), other**

Prospective patient-based data collection

## Use of a Common Data Model (CDM)

**CDM mapping**

No

## Data quality specifications

**Check conformance**

Unknown

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**Check completeness**

Unknown

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**Check stability**

Unknown

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**Check logical consistency**

Unknown

# Data characterisation

**Data characterisation conducted**

No