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.

Study status

Finalised

Contact details

Study institution 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

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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

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

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

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No