CLINICAL STUDY PROTOCOL

Intravenous immunoglobulin (IVIG) treatment in children with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS): an open-label trial in South-western Sweden

IVIGPANSOpen

Phase II study

This protocol is confidential

Study code:	IVIGPANSOpen
EudraCT number:	2019-004758-27
Version number:	2
Date:	2020-10-03 rev 20-11-29
Product name/indication:	Privigen (IVIG) / PANS
Sponsor:	Christopher Gillberg
NCT no:	04609761
Principal Investigator	Mats Johnson

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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Signature page

Intravenous immunoglobulin (IVIG) treatment in children with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS): an open-label trial in South-western Sweden

EudraCT number: 2019-004758-27. Protocol v1, 18 Feb 2020

Sponsor

I am responsible for ensuring that this protocol includes all essential information to be able to conduct this study. I will submit the protocol and all other important study-related information to the responsible investigator(s) so that they can conduct the study correctly. I am aware that it is my responsibility to hold the staff members who work with this study informed and trained.

Sponsor's signature Date

Christopher Gillberg, senior professor

Printed name

Coordinating Investigator / Principal Investigator

I have read this protocol and agree that it includes all essential information to be able to conduct the study. By signing my name below, I agree to conduct the study in compliance with this protocol, the Declaration of Helsinki, ICH GCP (Good Clinical Practice) guidelines and the national and international regulations governing the conduct of this clinical study.

I will submit this protocol and all other important study-related information to the staff members and responsible investigators who participate in this study, so that they can conduct the study correctly. I am aware of my responsibility to continuously keep the staff members and responsible investigators who work with this study informed and trained.

I am aware that quality control of this study will be performed in the form of monitoring, possibly audit, and possibly inspection.

Coordinating Investigator / Principal Investigator's signature Date

Mats Johnson, MD, PhD

Printed name

Contact information

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List of used acronyms and abbreviations

Abbreviation	Term/Explanation
ABAS-II	Adaptive Behavior Assessment System-II
AE	Adverse Event = any untoward medical occurrence
AR	Adverse Reaction = adverse event, that is each unfavorable and unexpected reaction to a study treatment, regardless of dose
CGI-S/CGI-I	Clinical Global Impression Severity and Improvement Scales
CHIP-CE	Child Health and Illness Profile- Child Edition (Parent report)
CRF	Case Report Form
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
DSUR	Development Safety Update Report = annual safety report
EPM	Etikprövningsmyndigheten (English: Swedish Ethical Review Authority)
GCP	Good Clinical Practice
ICH	International Council for Harmonization
ITT	Intention-to-treat = including all data from all subjects who have participated in the study
LVFS	Läkemedelsverkets författningssamling (English: Swedish Medical Products Agency's statutes)
MRI	Magnetic Resonance Imaging
OCD	Obsessive Compulsive Disorder
PANS	Pediatric Acute Neuropsychiatric Syndrome
PANDAS	Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections
PP	Per Protocol analysis = including only data from subjects who have completed the study completely in accordance with the protocol, with no deviations from the protocol
SAE	Serious Adverse Event = serious untoward medical occurrence
SPC or SmPC	Summary of Product Characteristics

SUSAR	Suspected Unexpected Serious Adverse Reaction

1. Synopsis

Title: Intravenous immunoglobulin (IVIG) treatment in children with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS): an open-label trial in South-western Sweden
Study code: IVIGPANSOpen
Short background/Rationale/Purpose: Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) is a recently defined research diagnosis describing an abrupt, dramatic onset of neuropsychiatric symptoms including obsessions/compulsions and/or food restriction in children. Immunologic mechanisms are suspected, but treatment trials are few.
Study objectives: Primary objective: The primary objective of this study is to evaluate the efficacy of intravenous immunoglobulin (IVIG), 2 g/kg given every 4 weeks for 6 months, to patients with post-infectious PANS including the subgroup PANDAS, in improving neuropsychiatric symptoms and impairment. Secondary objectives: The secondary objectives of this study are to evaluate: • changes from baseline to follow-up at 3 months, 6 months and 12 months in: • OCD symptoms • adaptive functioning • quality of life • cognitive functioning • for patients with baseline inflammation signs on cerebral Magnetic Resonance Imaging (MRI) to evaluate changes in these measures after IVIG therapy after 6 months. (Spinal tap should be made on clinical indications before study start to rule out encephalitis, and results of spinal fluid examination should be available before screening. MRI should have been performed on clinical indications or can be performed as a baseline measure of inflammation for patients who can tolerate MRI without general anaesthesia). • number of days of work/school/daily activities missed per subject year due to PANS/PANDAS before and after IVIG therapy

- parental care load, e.g. need for sick leave, before and after IVIG therapy
- IgG, IgM and IgA levels at baseline, 3 months, 6 months and 12 months
- sustainability of any improvement at 12 months after initiation of IVIG measured with the PANS scale, CGI-S and CGI-I

To assess the safety and tolerability of high dose IVIG therapy

- Clinical signs and symptoms (nausea, headache, local reactions)
- ALAT
- Hemoglobin, complete blood count including leucocyte differential

Study design:
Open-label prospective trial to study efficacy, safety and tolerability of intravenous immunoglobulin (IVIG) in subjects with PANS.

Study population: Children and adolescents 4- 17 years

Number of subjects: 10

Inclusion criteria:

To be included in the study, subjects must meet the following criteria:

1. The subject and parents/caregivers have given written consent or assent to participate in the study.
2. Children and adolescents between the ages of 4 and 17 years at Baseline.
3. Documented and confirmed pre-existing diagnosis of post-infectious PANS/PANDAS
4. The subject has not been treated with IVIG previously or not been treated for the last 6 months
5. Throat culture for Group A Streptococcus (GAS) should be performed before study start and standard phenoximethyl penicillin treatment given if positive culture. If the patient is on long-term antibiotic prophylaxis, this should be unchanged one month before baseline and during the trial.
6. Infections occurring during the trial should be treated according to standard clinical practice.
7. Treatment with COX-inhibitors or corticosteroids should be discontinued at least one month before baseline and during the trial. Two-three days treatment with corticosteroids during and after IVIG treatment is allowed to reduce IVIG side effects such as headache and nausea.
8. Any psychopharmacological treatment (e.g. SSRI, antipsychotics), if considered essential for the subject, should be kept at a stable and unchanged dose from one month before baseline and during the trial. If not considered essential, it should be discontinued at least one month before baseline.
9. The medical records for all subjects should be available to document diagnosis, previous infections and treatment.

10. For female participants, adequate contraception should be used, see exclusion criteria. A negative pregnancy test can possibly be a requirement, specify requirement/type of pregnancy test. Contraceptive requirements may also apply to male participants.

Exclusion criteria:

Subjects must not be included in the study if any of the following criteria are met:

1. Clinical evidence of any significant acute or chronic disease that, in the opinion of the Investigator, may interfere with successful completion of the trial or place the subject at undue medical risk. If encephalitis cannot be excluded by clinical history alone, spinal tap results are required before study start to rule out encephalitis (which would need to be treated according to encephalitis treatment guidelines). MRI should have been performed if clinically indicated.
2. The subject has had a known serious adverse reaction to immunoglobulin or any severe anaphylactic reaction to blood or any blood-derived product
3. Females of childbearing potential who are pregnant, have a positive pregnancy test at Baseline (human chorionic gonadotropin [HCG]-based assay), are breastfeeding, or unwilling to practice a highly effective method of contraception (oral, injectable or implanted hormonal methods of contraception, placement of an intrauterine device [IUD] or intrauterine system [IUS], condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilization, or true abstinence) throughout the study Note: True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.)
4. The subject has significant proteinuria (dipstick proteinuria ≥ 3+, known urinary protein loss > 1 g/24 hours, or nephrotic syndrome), has a history of acute renal failure, has severe renal impairment (blood urea nitrogen [BUN] or creatinine more than 2.5 times the upper limit of normal [ULN]), and/or is on dialysis
5. The subject has Screening Visit values of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding 2.5 times the ULN for the expected normal range for the testing laboratory.
6. The subject has hemoglobin < 90 g/L at Screening
7. The subject has a known previous infection with or clinical signs and symptoms consistent with current hepatitis B virus (HBV) or hepatitis C virus (HCV) infection
8. The subject has a history of or current diagnosis of deep venous thrombosis or thromboembolism (e.g., myocardial infarction, cerebrovascular accident, or transient ischemic attack); history refers to an incident in the year prior to Baseline or 2 episodes over lifetime.
9. The subject currently has a known hyperviscosity syndrome
10. The subject has an acquired medical condition that is known to cause secondary immune deficiency, such as chronic lymphocytic leukemia, lymphoma, multiple myeloma, chronic or recurrent neutropenia (absolute neutrophil count less than 1.0 x 10^9/L], or HIV infection/acquired immune deficiency syndrome (AIDS).
11. The subject is HIV positive by NAT based on a Screening blood sample.

12. The subject has non-controlled arterial hypertension at a level of greater than or equal to the 90th percentile blood pressure (either systolic or diastolic) for their age and height
13. The subject is receiving any of the following medications: (a) immunosuppressants including chemotherapeutic agents, (b) immunomodulators, (c) long-term systemic corticosteroids defined as daily dose > 1 mg of prednisone equivalent/kg/day for > 30 days. Note: Intermittent courses of corticosteroids of not more than 10 days would not exclude a subject. Inhaled or topical corticosteroids are allowed.
14. The subject has known substance or prescription drug abuse.
15. The subject has participated in another clinical trial within 30 days prior to Baseline (observational studies without investigative treatments [non-interventional] are permitted) or has received any investigational blood product within the previous 3 months
16. The subject/caregiver is unwilling to comply with any aspect of the protocol, including IV infusions, blood sampling
17. Mentally challenged subjects who cannot give independent informed consent
    In the opinion of the Investigator the subject may have compliance problems with the protocol and the procedures of the protocol.

Investigational product(s), dosage, administration:

Intravenous immunoglobulin IVIG (Privigen), 2 g/kg BW every 4th week for 6 months (= 6 infusions).

Primary efficacy variables:

- changes in symptom severity and impairment on the investigator-rated Pediatric Acute Neuropsychiatric Symptom (PANS) scale (Swedo, Leckman et al.). Clinical response is defined as >30% reduction in symptoms and impairment, respectively.
- changes in global symptoms and functioning measured by CGI-S (Clinical Global Impression-Severity) and in global improvement measured by CGI-I (Clinical Global Impression-Improvement). Clinical response is defined as a score of 1-2 on CGI-S and CGI-I, respectively.
- All these variables are considered necessary to achieve the trial objectives

Secondary variable(s): Changes in:

- OCD symptoms measured with the CY-BOCS scale
- Level of functioning in everyday life assessed by the ABAS II scale (rated by parent or other caregiver and from the responsible teacher/preschool teacher)
- Quality of life assessment (CHIP-CE scale - Parent report, rated by parent or other caregiver.
- Neuropsychiatric and neurodevelopmental symptoms assessed by the parent-rated 5-15 scale.
- Motor/neurologic functioning (neurologic assessment of choreiform movements, balance (Rombergs test with extended arms), diadochokinesis, finger-nose tapping, eye movements, muscle tone, reflexes, figure copying, drawing, handwriting).
- Cognitive functioning (auditory working memory subtest from WISC-V. Visual working memory. VMI (visual perception test).

• School-PANS (short version of PANS-scale rated by teacher or school assistant; Murphy, personal communication) • Days absent from school during the study period compared to previous 3 months • Parental situation, e.g. sick leave, reduced working hours • Trough concentrations of total IgG, IgA, IgM • AEs, suspected adverse drug reactions (suspected ADRs), serious AEs (SAEs), and discontinuations due to AEs and SAEs • Vital signs during clinic visits (temperature [T], respiratory rate [RR], heart rate [HR], systolic blood pressure [SBP] and diastolic blood pressure [DBP]). • Physical assessments: physical exams will be recorded as normal or abnormal, according to the physician's judgment criteria, and findings will be recorded. • Laboratory assessments including chemistry, hematology, and urinalysis. • In a subgroup of participants who can tolerate Cerebral Magnetic Resonance Tomography (MRI) without general anesthesia, MRI will be done according to a specific protocol (Hadjikani, personal communication) The secondary variables will be assessed at baseline and after 3, 6 and 12 months
Study period: Q2 2020-Q4 2023

2. Background and rationale

Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) is a research diagnosis defined by an abrupt, dramatic onset of neuropsychiatric symptoms including obsessions/compulsions and/or food restriction. The sudden onset and complexity of neuropsychiatric symptoms separates PANS from obsessive-compulsive disorder (OCD) or eating disorder. The clinical picture includes acute concurrent symptoms of depression, irritability, anxiety, hyperactivity, tics, choreiform movements, insomnia, difficulty with schoolwork and handwriting skills. Diagnostic criteria for PANS were defined in 2010 by the National Institute of Mental Health (NIMH) and published by Swedo et al. (2012). The etiology of PANS is unknown in most cases but is thought to be triggered by infections and other inflammatory reactions (Swedo et al. 1998, 2012).

Like PANS, children with Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections (PANDAS) have an acute onset – within 2 to 3 days – with neuropsychiatric symptoms. However, patients with PANDAS test positive for a recent streptococcal infection. Although PANDAS was identified as a medical entity more than a decade before PANS, it is today classified as a subset of PANS. To date, PANDAS is the only known subset of PANS, but more specific causes underlying PANS may be discovered in the future (Swedo et al. 1998, 2012).

Since PANS is relatively newly described, few treatment trials have been performed to investigate which interventions may be effective. If the diagnostic work-up of PANS reveals an

infectious trigger, treatment of the infection may be useful in reducing symptom severity of OCD and other neuropsychiatric symptoms. The temporal relationship between infections and PANS/PANDAS onset suggest post-infectious immunological mechanisms. OCD symptoms may also benefit from cognitive behavioral therapy (CBT) and/or anti-obsessional medications. (Chang et al. 2015, Thienemann et al. 2017).

A consortium of US clinicians and researchers (PANS Research Consortium) have advocated the use of antibiotics to treat acute symptoms of PANS/PANDAS, even when no streptococcal infection can be proved. They observed significant improvement in the OCD and other neuropsychiatric symptoms following treatment with phenoxymethylpenicillin (penicillin V), azithromycin, amoxicillin/clavulanic acid and other beta-lactam antibiotics. Treatment trials with antibiotics have shown variable results and interpretation is limited by selection differences, small sample sizes and study design problems. These case reports and trials need to be confirmed by larger controlled treatment trials before antibiotics can be recommended to be used in the treatment of PANS/PANDAS (Cooperstock et al. 2017).

It is argued that immune-based therapies should be used only in cases where there is a strong suspicion that the neuropsychiatric symptoms are related to an (auto)immune response (as in PANDAS and most likely also in PANS), after thorough exclusion of other etiologies. In addition, the clinician may utilize laboratory tests to confirm immune dysfunction. Among others, such testing might include anti-streptococcal antibody titers, anti-nuclear antibody titers, and inflammatory markers, such as an erythrocyte sedimentation rate (ESR) or C-reactive protein (Chang et al. 2015, Frankovich et al. 2017).

Intravenous immunoglobulin (IVIG) is approved and used clinically for the treatment of immune deficiencies and autoimmune diseases. The safety of the IVIG product Privigen has been evaluated in several preclinical studies. In studies in young rats where dosage was adjusted to clinical indications no effects on brain development were seen. Relevant studies on safety pharmacology and toxicity did not show risks for humans. The safety and efficacy of Privigen was evaluated in 6 prospective, open multicenter studies in Europe and USA. In the pivotal PID (Primary Immunologic Deficiency) study 80 patients aged 3 to 69 years were treated for 12 months. In the pivotal ITP-study (Immunologic Thromobocytopenic Purpura) 57 patients aged 15 to 69 years were treated with 2 infusions (FASS.se, 2019).

In PANDAS only two controlled studies of the effect of IVIG exist. One compared one dose of IVIG, plasmapheresis and placebo in 29 children (Perlmutter et al. 1999) and found a treatment effect for IVIG vs. placebo. The second study was an IVIG/placebo trial (Williams et al. 2016) which showed no significant difference between the groups. This study also had methodological problems making results inconclusive. Recently, an open study comprising 21 patients with PANS was published (Melamed I et al Abstract ESID, 2019) where, in contrast to the two randomized studies, multiple doses of IVIG were given instead of just one dose, over a 6-month period. All psychometric variables showed significant improvement. Apart from these three studies, only case reports have been published, where the largest comprises 12 patients with a very heterogeneous population; some of the patients were newly diagnosed, other had symptoms since more than 5 years. Thus, overall study results are variable and uncertain. A research review of treatment in PANS/PANDAS by the National Board of Health

and Welfare (Socialstyrelsen, 2017) and a recent Health Technology Report from Sahlgrenska University Hospital both indicate that more research is needed to inform about treatment efficacy and safety.

Regarding intervention studies, randomized controlled trials (RCTs) are often considered the gold standard. However, there are circumstances when this design is problematic, for example when a studied treatment gives rise to specific side effects that reveal blinding to both patients and researchers. IVIG treatment in high dose has such side-effects by giving headache and nausea in virtually all patients.

This study aims to investigate efficacy and safety of IVIG treatment in children and adolescent with PANS in an open-trial design with rigorous monitoring of symptom profiles before and after treatment, with reports from different sources, such as parents and preschool/school staff. The assessments from different sources with a focus on symptoms, everyday functioning, and quality of life is expected to give more reliable and ecologically valid information about treatment effectiveness. The patients will be recruited from those referred to the Child Neuropsychiatric Clinic/Gillberg Neuropsychiatry Center/Gothenburg University, and the Linköping Pediatric Clinic, meeting criteria for PANS and clinically considered for IVIG treatment.

3. Risk-benefit evaluation

Temporary side effects with headache and nausea from IVIG treatment are well known since many years from studies regarding other medical conditions. Other known adverse events such as allergic reactions are rare (see SmPC FASS). During the trial any adverse events will be carefully monitored by clinical examinations and blood tests. The needle punctures for infusion carry a small risk for local bleeding/bruises at the puncture site, and some pain which can be relieved with local anaesthetic. Patients with PANS/PANDAS have a severe medical condition with severely impaired function. Previous clinical experience has shown that the treatment may give robustly reduced symptoms and impairment, and in some cases complete symptom remission. Health economic benefits from such improvement have in such cases been considerable, for instance the child being able to return to school and the parents to work. To participate in a clinical trial gives the patient a treatment according to a reviewed protocol and with careful follow-up. To contribute to the development of knowledge and new treatments is also positively perceived by many patients/families. The risk/benefit-balance in this study is therefore considered to be strongly dominated by benefit.

4. Study objectives

4.1. Primary objective

The primary objective of this study is to evaluate the efficacy of intravenous immunoglobulin (IVIG), 2 g/kg given every 4 weeks for 6 months, to patients with post-infectious PANS including the subgroup PANDAS, in improving neuropsychiatric symptoms and impairment.

Secondary objective(s):

The secondary objectives of this study are to evaluate:

- changes from baseline to follow-up at 3 months, 6 months and 12 months in:
  - OCD symptoms
  - adaptive functioning
  - quality of life
  - cognitive functioning
  - for patients with baseline inflammation signs on cerebral Magnetic Resonance Imaging (MRI) to evaluate changes in these measures after IVIG therapy after 6 months. (Spinal tap should be made on clinical indications before study start to rule out encephalitis, and results of spinal fluid examination should be available before screening. MRI should have been performed on clinical indications or can be performed as a baseline measure of inflammation for patients who can tolerate MRI without general anaesthesia.
  - number of days of work/school/daily activities missed per subject year due to PANS/PANDAS before and after IVIG therapy
  - parental care load, e.g. need for sick leave, before and after IVIG therapy
  - IgG, IgM and IgA levels at baseline, 3 months, 6 months and 12 months
  - sustainability of any improvement at 12 months after initiation of IVIG measured with the PANS scale, CGI-S and CGI-I
- To assess the safety and tolerability of high dose IVIG therapy
  - Clinical signs and symptoms (nausea, headache, local reactions)
  - ALAT
  - Hemoglobin, complete blood count including leucocyte differential

4.2. Primary variable

- Primary efficacy variables:
  - changes in symptom severity and impairment on the investigator-rated Pediatric Acute Neuropsychiatric Symptom (PANS) scale (Swedo, Leckman et al.). Clinical response is defined as >30% reduction in symptoms and impairment, respectively.
  - changes in global symptoms and functioning measured by CGI-S (Clinical Global Impression-Severity) and in global improvement measured by CGI-I

(Clinical Global Impression-Improvement). Clinical response is defined as a score of 1-2 on CGI-S and CGI-I, respectively.

- All these variables are considered necessary to achieve the trial objectives

4.3. Secondary variable(s)

- Changes in:
  - OCD symptoms measured with the CY-BOCS scale
  - Level of functioning in everyday life assessed by the ABAS II scale (rated by parent or other caregiver and from the responsible teacher/preschool teacher)
  - Quality of life assessment (CHIP-CE scale - Parent report, rated by parent or other caregiver).
  - Neuropsychiatric and neurodevelopmental symptoms assessed by the parent-rated 5-15 scale.
  - Motor/neurologic functioning (neurologic assessment of choreiform movements, balance (Rombergs test with extended arms), diadochokinesis, finger-nose tapping, eye movements, muscle tone, reflexes, figure copying, drawing, handwriting).
  - Cognitive functioning (auditory working memory subtest from WISC-V. Visual working memory. VMI (visual perception test).
  - School-PANS (short version of PANS-scale rated by teacher or school assistant; Murphy, personal communication)
  - Parental situation: Sick leave, reduced working hours.
  - Days absent from school during the study period compared to the 3-month period before baseline.
  - AEs, suspected adverse drug reactions (suspected ADRs), serious AEs (SAEs), and discontinuations due to AEs and SAEs
  - Vital signs during clinic visits (temperature [T], respiratory rate [RR], heart rate [HR], systolic blood pressure [SBP] and diastolic blood pressure [DBP]).
  - Physical assessments: physical exams will be recorded as normal or abnormal, according to the physician's judgment criteria, and findings will be recorded.
  - Laboratory assessments including chemistry, hematology, and urinalysis.
  - Trough concentrations of total IgG, IgA, IgM at baseline, 3 months, 6 months and 12 months
  - In a subgroup of participants who can tolerate Cerebral Magnetic Resonance Tomography (MRI) without general anesthesia, MRI will be done according to a specific protocol (Hadjikani, personal communication, see Appendix)

5. Study design and procedures

5.1. Overall study design

Open-label prospective 6-month Phase II study of IVIG treatment to children with PANS

5.1.1 Screening visit

- Parents and children have received oral and written information describing the study, and will give informed consent or assent, as appropriate, before any study-related procedures are initiated.
- Medical and psychiatric history (record relevant medical history defined as any history impactful on the subject's condition in terms of current functioning, disability, treatment, or management)
- Family history: (Tics, Tourette's syndrome, chorea, Obsessive compulsive disorder, hoarding, Anxiety, panic disorder, social phobia, Eating disorder, alcoholism and other substance abuse or addiction problem, Mood disorders: Depression, manic/depressive episodes/bipolar disorder, rages, emotional lability, Schizophrenia/psychotic disorders, Autism/pervasive developmental disorder, attention-deficit/hyperactivity disorder (ADHD), learning disorders, intellectual disability, Autoimmune or autoinflammatory diseases, Kawasaki's disease, Henoch–Schönlein purpura, other vasculitis, Familial Mediterranean fever, other recurrent fever syndromes, Thyroiditis, Addison's disease, Type 1 diabetes, Idiopathic thrombocytopenia purpura, hemolytic anemia, Antiphospholipid antibody syndrome, Guillain–Barre´ syndrome, transverse myelitis. Multiple sclerosis or neuromyelitis optica, acute disseminate encephalomyelitis, autoimmune encephalitis, brain vasculitis, Celiac disease, inflammatory bowel disease, gluten, alopecia, vitiligo, psoriasis, recurrent infections and immunodeficiency syndromes, chronic fatigue syndrome, fibromyalgia, and other pain disorders
- Subject's own medical and psychiatric history:
- All screening patients should be recorded and any reason for exclusion given
- Assess inclusion and exclusion criteria to determine subject eligibility
- Full physical exam. Vital signs
- CGI-S
- PANS Symptom and Impairment Scale (parent interview)
- Blood sample:
    - Total IgG, IgA, IgM, CRP, ferritin, anti-DNase B, ANA, transglutaminase antibodies.
    - For assessing exclusion criteria: Complete blood count with differential, AST, ALT, Hepatitis B and C, Creatinine, HIV. Urine dipstick for proteinuria. For females of childbearing potential a urine pregnancy test (HCG-based assay).

5.1.2 Baseline Visit (2-3 weeks after screening).

The visit will be divided into three days during one week: Day 1: Assessments, Day 2: MRI, Day 3: IVIG treatment.

- Re-assess inclusion and exclusion criteria to determine subject eligibility
- Assign subject number
- Record specific diagnosis (PANS or PANDAS), date of diagnosis, and date and dose of current medications
- Concomitant medications assessment
- Vital signs
- Neuromotor assessment
- Record available results from relevant blood tests, bacterial cultures, MRI, lumbar puncture
- CGI-S
- PANS Symptom and Impairment Scale (parent interview)
- School PANS Scale
- CY-BOCS symptom scale
- ABAS-II
- CHIP-CE
- 5-15 scale
- Cognitive tests
- Days absent from school 3 months before baseline.
- Parental care load
- Adverse events report
- Blood sample:
    - TPO antibodies, complements (C3, C4, C3d), TAU, Glia Fibrillary Acid Protein and neurofilament (Zetterberg lab, Mölndal), cytokines (TNF-alfa, IL-18, IL-6, IL-8, IFN-gamma, Glaichenhaus lab Nice).
- MRI in a subgroup who tolerates MRI without general anaesthesia
- First IVIG treatment

5.1.3 Visit 1 (1 month after treatment 1):

- Concomitant medications assessment
- Vital signs
- CGI-S, CGI-I
- PANS Scale (parent interview)
- Days absent from school since last visit (1 month)
- Adverse events report
- Second IVIG treatment

5.1.4 Visit 2 (2 months after treatment 1):

- Concomitant medications assessment
- Vital signs
- Adverse events report
- Third IVIG treatment

5.1.5 Visit 3 (3 months after treatment 1):

The visit will be divided into two days: Day 1: Assessments. Day 2: IVIG treatment.

- Concomitant medications assessment
- Vital signs, physical exam and neuromotor assessment
- CGI-S, CGI-I
- PANS scale (parent interview)
- School PANS Scale
- CY-BOCS symptom scale
- ABAS-II
- CHIP-CE
- 5-15 scale
- Cognitive tests
- Days absent from school since baseline (last 3 months)
- Parental care load
- Adverse events report
- Blood sample:
    - Total IgG, IgA, IgM, CRP, ferritin, complete blood count with differential, AST, ALT, creatinine, anti-DNase B, complements (C3, C4, C3d). Urine dipstick for proteinuria.
    - TAU, Glia Fibrillary Acid Protein and neurofilament (Zetterberg lab, Mölndal).
    - Cytokines (TNF-alfa, IL-18, IL-6, IL-8, IFN-gamma, Glaichenhaus lab Nice).
- Fourth IVIG treatment

5.1.6 Visit 4 (4 months after treatment 1):

- Concomitant medications assessment
- Vital signs
- Adverse events report
- Fifth IVIG treatment

5.1.7 Visit 5 (5 months after treatment 1):

- Concomitant medications assessment
- Vital signs

- Adverse events report
- Blood sample:
    - Total IgG, IgA, IgM, CRP, ferritin, complete blood count with differential, AST, ALT, creatinine, anti-DNase B, ANA, TPO antibodies, complements (C3, C4, C3d). Urine dipstick for proteinuria.
    - TAU, Glia Fibrillary Acid Protein and neurofilament (Zetterberg lab, Mölndal).
    - Cytokines (TNF-alfa, IL-18, IL-6, IL-8, IFN-gamma, Glaichenhaus lab Nice).
- Sixth IVIG treatment

5.1.8 Visit 6 (6 months after treatment 1):

- The visit will be divided into two days if MRI is performed: Day 1: Assessments. Day 2: MRI.
- Concomitant medications assessment
- Vital signs, physical exam and neuromotor assessment
- CGI-S, CGI-I
- PANS scale (parent interview)
- School PANS Scale
- CY-BOCS symptom scale
- ABAS-II
- CHIP-CE
- 5-15 scale
- Cognitive tests
- Days absent from school since visit 3 (last 3 months)
- Parental care load
- Adverse events report
- Repeat MRI if the baseline MRI showed inflammatory signs

5.1.9 Visit 7 (12 months after treatment 1):

- Concomitant medications assessment
- Vital signs, physical exam and neuromotor assessment
- CGI-S, CGI-I
- PANS scale (parent interview)
- School PANS Scale
- CY-BOCS symptom scale
- ABAS-II
- CHIP-CE
- 5-15 scale
- Cognitive tests
- Days absent from school since last visit (6 months)
- Parental care load

- Adverse events report
- Blood sample:
    - Total IgG, IgA, IgM, CRP, ferritin, complete blood count with differential, AST, ALT, anti-DNase B, ANA, TPO antibodies, complements (C3, C4, C3d). Urine dipstick for proteinuria.
    - TAU, Glia Fibrillary Acid Protein and neurofilament (Zetterberg lab, Mölndal).
    - Cytokines (TNF-alfa, IL-18, IL-6, IL-8, IFN-gamma, Glaichenhaus lab Nice).

5.2.

5.3. Procedures and flow chart

Table 1 Flow chart

Procedure (W = week)	*Screening* *Week -2*	*Baseline* *W0 (±7 days)**	*Visit 1* *W4 (±7 days)*	*Visit 2* *W8 (±7 days)*	*Visit 3* *W12 (±7 days)**	*Visit 4* *W16 (±7 days)*	*Visit 5* *W20 (±7 days)*	*Visit 6* *W24 (±7 days)*	*Visit 7* *1 year after Baseline (± 2 w)*
Incl/exclusion criteria	√	√							
Informed consent	√								
Subject number assigned		√							
PANS diagnosis recorded		√							
Medical history/ concomitant medications	√	√	√	√	√	√	√	√	√
Vital signs	√	√	√	√	√	√	√	√	√
Physical exam	√				√			√	√
Neuromotor assessment		√			√			√	√
Record previous results from blood tests, bacterial cultures, MRI, lumbar puncture	√	√							
CGI-S	√	√	√		√			√	√
CGI-I			√		√			√	√

PANS scale	√	√	√		√			√	√
School PANS scale		√			√			√	√
CY-BOCS		√			√			√	√
ABAS-II		√			√			√	√
CHIP-CE		√			√			√	√
5-15 scale		√			√			√	√
Cognitive tests		√			√			√	√
Days absent from school 3 mo before baseline		√							
Days absent from school since last visit/last 3 mo			√		√			√	√
Parental care load		√			√			√	√
Blood sample	√				√		√		√
IVIG Treatment (T)		√	√	√	√	√	√		
MRI in a subgroup		√						√	
Adverse Events (AE & SAE)		√	√	√	√	√	√	√	√
Study end									√

*The baseline visit will be divided into three days and Visit 3 will be divided into two days to allow sufficient time for assessment and treatment. Visit 6 will be divided into two days if MRI is performed.

5.4. Biological sampling procedures

5.4.1. Handling, storage, and destruction of biological samples

Blood samples are drawn from venous puncture. At baseline and visits 3 and 6 blood will be drawn from the needle which is used to give the IVIG infusion, so no extra venous puncture will be necessary at these visits.

5.4.2. Total volume of blood per study subject

The total volume of blood taken from each subject during the study is maximum 6 ml. This amount entails no risk for the patients.

5.4.3. Biobank

All samples taken in this study are registered in a biobank and handled according to the current biobank laws and regulations. The samples are coded/pseudonymized to protect the study participants' identification. All samples and the identification/code list are stored securely and separately to prevent unauthorized persons from having access to them.

5.5. End of Study

The study ends when the last study participant has completed the last follow-up. The study may be prematurely terminated if it appears that the treatment involved a large number of undesirable serious events or if recruitment of study participants cannot be met within reasonable time limits. If the study is prematurely terminated or suspended, the investigator should immediately inform the study participants about this and ensure appropriate treatment and follow-up. The regulatory authority should be informed as soon as possible, but no later than within 15 days. Decisions on premature termination are taken by the sponsor.

Treatment of the study participants who completed the study will be provided according to current clinical practice. Treatment responders during the study will be offered IVIG after the study if it is considered essential for the subject.

6. Subject selection

6.1. Inclusion criteria

To be included in the study, subjects must meet the following criteria:

1. The subject and parents/caregivers have given written consent or assent to participate in the study.
2. Children and adolescents between the ages of 4 and 17 years at Baseline.
3. Documented and confirmed pre-existing diagnosis of post-infectious PANS/PANDAS
4. The subject has not been treated with IVIG previously or not been treated for the last 6 months
5. If the patient is on long-term antibiotic prophylaxis, this should be unchanged one month before baseline and during the trial. Throat culture for Group A Streptococcus (GAS) should be performed before study start and standard phenoximethyl penicillin treatment given if positive culture.

6. Infections occurring during the trial should be treated according to standard clinical practice.
7. Treatment with COX-inhibitors or corticosteroids should be discontinued at least one month before baseline and during the trial. Two-three days treatment with corticosteroids during and after IVIG treatment is allowed to reduce IVIG side effects such as headache and nausea.
8. Any psychopharmacological treatment (e.g. SSRI, antipsychotics), if considered essential for the subject, should be kept at a stable and unchanged dose from one month before baseline and during the trial. If not considered essential, it should be discontinued at least one month before baseline.
9. The medical records for all subjects should be available to document diagnosis, previous infections and treatment.
10. For female participants, adequate contraception should be used, see exclusion criteria. A negative pregnancy test can possibly be a requirement, specify requirement/type of pregnancy test. Contraceptive requirements may also apply to male participants.

6.2. Exclusion criteria

Subjects must not be included in the study if any of the following criteria are met:

1. Clinical evidence of any significant acute or chronic disease that, in the opinion of the Investigator, may interfere with successful completion of the trial or place the subject at undue medical risk. If encephalitis cannot be excluded by clinical history alone, spinal tap results are required before study start to rule out encephalitis (which would need to be treated according to encephalitis treatment guidelines). MRI should have been performed if clinically indicated.
2. The subject has had a known serious adverse reaction to immunoglobulin or any severe anaphylactic reaction to blood or any blood-derived product
3. Females of childbearing potential who are pregnant, have a positive pregnancy test at Baseline (human chorionic gonadotropin [HCG]-based assay), are breastfeeding, or unwilling to practice a highly effective method of contraception (oral, injectable or implanted hormonal methods of contraception, placement of an intrauterine device [IUD] or intrauterine system [IUS], condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilization, or true abstinence) throughout the study Note: True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.)
4. The subject has significant proteinuria (dipstick proteinuria ≥ 3+, known urinary protein loss > 1 g/24 hours, or nephrotic syndrome), has a history of acute renal failure, has severe renal impairment (blood urea nitrogen [BUN] or creatinine more than 2.5 times the upper limit of normal [ULN]), and/or is on dialysis
5. The subject has Screening Visit values of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding 2.5 times the ULN for the expected normal range for the testing laboratory.
6. The subject has hemoglobin < 90 g/L at Screening

7. The subject has a known previous infection with or clinical signs and symptoms consistent with current hepatitis B virus (HBV) or hepatitis C virus (HCV) infection
8. The subject has a history of or current diagnosis of deep venous thrombosis or thromboembolism (e.g., myocardial infarction, cerebrovascular accident, or transient ischemic attack); history refers to an incident in the year prior to Baseline or 2 episodes over lifetime.
9. The subject currently has a known hyperviscosity syndrome
10. The subject has an acquired medical condition that is known to cause secondary immune deficiency, such as chronic lymphocytic leukemia, lymphoma, multiple myeloma, chronic or recurrent neutropenia (absolute neutrophil count less than 1.0 x 10^9/L], or HIV infection/acquired immune deficiency syndrome (AIDS).
11. The subject is HIV positive by NAT based on a Screening blood sample.
12. The subject has non-controlled arterial hypertension at a level of greater than or equal to the 90th percentile blood pressure (either systolic or diastolic) for their age and height
13. The subject is receiving any of the following medications: (a) immunosuppressants including chemotherapeutic agents, (b) immunomodulators, (c) long-term systemic corticosteroids defined as daily dose > 1 mg of prednisone equivalent/kg/day for > 30 days. Note: Intermittent courses of corticosteroids of not more than 10 days would not exclude a subject. Inhaled or topical corticosteroids are allowed.
14. The subject has known substance or prescription drug abuse.
15. The subject has participated in another clinical trial within 30 days prior to Baseline (observational studies without investigative treatments [non-interventional] are permitted) or has received any investigational blood product within the previous 3 months
16. The subject/caregiver is unwilling to comply with any aspect of the protocol, including IV infusions, blood sampling
17. Mentally challenged subjects who cannot give independent informed consent
    In the opinion of the Investigator the subject may have compliance problems with the protocol and the procedures of the protocol.

6.3. Screening

Subject eligibility (that subjects fulfill all inclusion criteria and do not meet any exclusion criteria) is established before inclusion and treatment.

6.4. Withdrawal criteria

Subjects can discontinue their participation in the study at any time without any consequence to his/her continued treatment. This may happen for several reasons, including but not limited to the occurrence of what the participant perceives as an intolerable adverse event, inability to comply with trial procedures, and participant decision (participant may withdraw his/her consent). The Investigator may discontinue a participant from the trial treatment at any time if the Investigator considers it necessary for any reason including, but not limited to: Ineligibility arising during the trial, significant protocol deviation, significant non-compliance with the treatment regimen or trial requirements, an adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures, and disease progression which requires discontinuation of the trial medication or

results in inability to continue to comply with trial procedures. If the subject discontinues the study, follow-up of this subject will be performed according to the clinic's routine. A Competent Authority can terminate the study. Data for subjects who discontinue the study prematurely will be handled using the Last Observation Carried Forward (LOCF) approach, se section 9: Statistics.

6.5. Description of investigational product(s)

Intravenous immunoglobulin (IVIG).

Brand name: Privigen.

Manufacturer: CSL Behring. The product is prescribed in the same manner as in standard clinical practice. According to the label, Privigen is registered for use in immune deficiencies and autoimmune diseases, in children and adults.

Only Privigen will be used in the study. Any reconstitution and administration is performed in accordance with the SmPC (FASS).

6.6. Dose and administration

Dosage in the study: Intravenous immunoglobulin IVIG (Privigen), 2 g/kg BW every 4th week for 6 months (= 6 infusions). The dosage 2 g/kg is the same as that used in clinical practice for treatment of autoimmune diseases according to the product's label (see FASS) and has also been used in previous randomized controlled trials of PANDAS (Perlmutter et al. 1999, Williams et al. 2016).

6.7. Packaging, labelling, and handling of investigational products(s)

The IMP will be provided from a pharmacy to the trial site in its original Swedish commercial labelling (according to normal routine), and the IMP will be administered in the clinical trial site at the children's hospital, only to the patients in the study. The IMP will be stored in refrigerators or in room temperature, not above 25 degrees Celsius, according to recommendations in the SmPC. The temperature will be monitored continuously during the entire study, and a temperature log will be kept.

6.8. Drug accountability and treatment compliance

A drug accountability log will be used to follow the pathway of the study medication during the study. The IVIG infusions are only given at the children's hospital, and compliance will be observed and recorded by the study nurses at the hospital. If a dose is missed for any reason, additional opportunities will be given to receive this treatment dose. Acceptable compliance for being included in the full analysis set is defined as a maximum of 2 of the 6 doses missed during the entire study.

6.9. Randomization

Not applicable.

6.10. Blinding

Open-label trial, no randomization.

6.11. Code breaking

Not applicable.

6.12. Concomitant medications

Medications that are considered necessary for the safety and well-being of the subject can be given at the discretion of the investigator, unless otherwise specified as an exclusion criterion. This applies both before, during, and after the study. Concomitant medications should be reported in the Case Report Form (CRF). The medications allowed in Inclusion and exclusion criteria are considered to be safe and to entail minimal risk of confounding study results.

Concomitant medications which are allowed in certain circumstance are described in Inclusion criteria 5-8 (see below and also the list of Inclusion criteria above):

5. If the patient is on long-term antibiotic prophylaxis, this should be unchanged one month before baseline and during the trial.

6. Infections occurring during the trial should be treated according to standard clinical practice.

7. Treatment with COX-inhibitors or corticosteroids should be discontinued at least one month before baseline and during the trial. Two-three days treatment with corticosteroids during and after IVIG treatment is allowed to reduce IVIG side effects such as headache and nausea.

8. Any psychopharmacological treatment (e.g. SSRI, antipsychotics), if considered essential for the subject, should be kept at a stable and unchanged dose from one month before baseline and during the trial. If not considered essential, it should be discontinued at least one month before baseline.

Concomitant medications which are not allowed are described in Exclusion criterion 13 (see below and also the list of Exclusion criteria above):

13. The subject is receiving any of the following medications: (a) immunosuppressants including chemotherapeutic agents, (b) immunomodulators, (c) long-term systemic corticosteroids defined as daily dose > 1 mg of prednisone equivalent/kg/day for > 30 days. Note: Intermittent courses of corticosteroids of not more than 10 days would not exclude a subject. Inhaled or topical corticosteroids are allowed.

6.13 Destruction

The intravenous immunoglobulin product (Privigen) will only be given in the ward of the children's hospital, and any rest product will be handled and destroyed there by competent hospital staff.

7 Assessment of efficacy and safety

7.1 Assessment of clinical efficacy

7.1.1 Primary variable

- Primary efficacy variables:
  - changes in symptom severity and impairment on the investigator-rated Pediatric Acute Neuropsychiatric Symptom (PANS) scale (Swedo, Leckman et al.). Clinical response is defined as >30% reduction in symptoms and impairment, respectively.
  - changes in global symptoms and functioning measured by CGI-S (Clinical Global Impression-Severity) and in global improvement measured by CGI-I (Clinical Global Impression-Improvement). Clinical response is defined as a score of 1-2 on CGI-S and CGI-I, respectively.
  - The primary variables will be assessed at baseline and after 1, 3, 6 and 12 months

7.1.2 Secondary variable(s)

- Changes in:
  - OCD symptoms measured with the CY-BOCS scale
  - Level of functioning in everyday life assessed by the ABAS II scale (rated by parent or other caregiver and from the responsible teacher/preschool teacher)
  - Quality of life assessment (CHIP-CE scale - Parent report, rated by parent or other caregiver.
  - Neuropsychiatric and neurodevelopmental symptoms assessed by the parent-rated 5-15 scale.
  - Motor/neurologic functioning (neurologic assessment of choreiform movements, balance (Rombergs test with extended arms), diadochokinesis, finger-nose tapping, eye movements, muscle tone, reflexes, figure copying, drawing, handwriting).
  - Cognitive functioning (auditory working memory subtest from WISC-V. Visual working memory. VMI (visual perception test).
  - School-PANS (short version of PANS-scale rated by teacher or school assistant; Murphy, personal communication)
  - Days absent from school during the study period compared to previous 3 months
  - Parental situation, e.g. sick leave, reduced working hours
  - Trough concentrations of total IgG, IgA, IgM
  - AEs, suspected adverse drug reactions (suspected ADRs), serious AEs (SAEs), and discontinuations due to AEs and SAEs
  - Vital signs during clinic visits (temperature [T], respiratory rate [RR], heart rate [HR], systolic blood pressure [SBP] and diastolic blood pressure [DBP]).

- Physical assessments: physical exams will be recorded as normal or abnormal, according to the physician's judgment criteria, and findings will be recorded.
- Laboratory assessments including chemistry, hematology, and urinalysis.
- In a subgroup of participants who can tolerate Cerebral Magnetic Resonance Tomography (MRI) without general anesthesia, MRI will be done according to a specific protocol (Hadjikani, personal communication)

The secondary variables will be assessed at baseline and after 3, 6 and 12 months

7.2 Assessment of clinical safety

- Privigen is registered and used for treatment in children in clinical practice for other indications (immune deficiency and autoimmune diseases), see SmPC (FASS).
- In the study, the safety and tolerability of the IVIG therapy will be assessed by:
    - Physical exams with vital signs at all visits. Clinical signs and symptoms (nausea, headache, local reactions)
    - Blood samples: liver and renal function test, Hemoglobin and complete blood count including leucocyte differential analyzed at the Children's Hospital laboratory.

8 Handling of Adverse Events

8.1 Definitions

8.1.1 Adverse Event (AE)

Adverse event (AE): Any untoward medical occurrence in a clinical investigation subject administered a medicinal product and, which does not necessarily have a causal relationship with the treatment, can be an unfavorable and unintended sign (including an abnormal laboratory discovery), symptom or disease temporally associated with the use of the medicinal (investigational) product, whether or not related to the medicinal (investigational) product. The clinical significance of an abnormal laboratory result will be determined on a case by case basis by the medically qualified investigator.

8.1.2 Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or new use of a medicinal product, and particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to the medicinal product related to any dose should be considered adverse drug reaction (ADR). The phrase "response" to a medicinal product means that the causal relationship between the medical product and an adverse event is at least a reasonable possibility, that is the relationship cannot be ruled out.

8.1.3 Serious Adverse Event (SAE)

Serious adverse event (SAE): Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization

- results in persistent or significant disability or incapacity
- results in a congenital anomaly/malformation

Medical and scientific assessment will be made to determine if an event is “serious” and whether it would prompt reporting in other situations, for example important medical events that may not be directly life-threatening or result in death or hospitalization but may compromise the study subject or may require intervention to prevent one of the other results set forth in the definitions above. These should also normally be considered as SAEs.

8.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

SUSAR: A reaction/event that is unexpected, serious, and suspected to be caused by the treatment, i.e. adverse events that are not included in the Investigator’s Brochure (IB) or SPC.

8.2 Assessment of adverse events

8.2.1 Assessment of causal relationship

The investigator is responsible for determining whether there is a causal relationship between the AE/SAE and use of the investigational product.

Those AEs which are suspected of having a relationship to the investigational product will be followed up until the study subject has recovered or is well taken care of and on their way to good recovery (see also section 8.4, Follow-up of Adverse Events).

All AE will be categorized either as likely related, possibly related, or not related, in accordance with the definitions below:

Likely related: Clinical event, including abnormal results from laboratory analyses, occurring within a reasonable time after administration of the intervention/investigational product. It is unlikely that the event can be attributed to underlying disease or other medications, but is most likely caused by the investigational product and its emergence is reasonable in relationship with use of the investigational product.

Possibly related: Clinical event, including abnormal results from laboratory analyses, occurring within a reasonable time after administration of the intervention/investigational product. The event could be explained by the investigational product and its emergence is reasonable in relationship with use of the investigational product, but there is insufficient information to determine the relationship. The event could be explained by an underlying disease or other medications.

Not related: Clinical event, including abnormal results from laboratory analyses, that is not reasonably related to the use of the intervention/investigational product. The event is unlikely related to the intervention/investigational product and can be explained by other medications or underlying disease.

8.2.2 Assessment of severity

Each adverse event shall be classified by an investigator as mild, moderate or severe.

Mild: The adverse event is relatively tolerable and transient in nature but does not affect the study subject's normal life.

Moderate: The adverse event causes deterioration of function but does not affect health. The event can be sufficiently unpleasant and interferes with normal activities but does not completely obstruct them.

Severe: The adverse event causes deterioration of function or work ability or poses a health risk to the study subject.

8.3 Reporting and registration of adverse events

At each study visit, the study subjects will be asked by the investigator/study nurse about how they have been feeling since the previous visit. Adverse events (AE) are registered, starting at baseline up to and including 6 months after the study subject has ended their treatment with the investigational product. All AE that occur during the study and which are observed by the investigator/study nurse or reported by the subject will be registered in the CRF regardless of whether they are related to the investigational product or not. Assessment of causal relationship, severity, and whether the AE is considered to be an SAE or not will be done by the investigator (a licensed physician) directly in CRF. At minimum, for each AE/SAE, a description of the event is recorded (diagnosis/symptom if diagnosis is missing), start and stop dates, causal relationship, severity, if the AE is considered to be an SAE or not, measures and outcome.

Expected adverse events are based on knowledge of the disease in question and expected clinical course.

8.3.1 Reporting of adverse events (AE)

All AE shall be registered in the CRF within 5 days of being observed or reported.

8.3.2 Reporting of serious adverse events (SAE)

Serious adverse events (SAE) are reported to the sponsor on a special SAE form within 24 hours of the investigator being informed of the SAE.

Follow-up information describing the outcome and handling of the SAE is reported as soon as this information is available. The original should be kept in the Investigator Site File.

Based on knowledge of the disease in question and expected clinical course, some events that are otherwise serious are not considered as SAEs in this study. The following is a list of SAEs that shall not be reported as SAEs:

Headache and nausea may be severe enough to require slightly extended observation at the hospital, but if not complicated, this is expected and shall not be reported as an SAE.

8.3.3 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSAR)

Those SAE which are assessed by sponsor to be SUSAR are reported via a CIOMS form to the European Medicines Agency (EudraVigilance database) according to the specified time frames.

SUSAR that are fatal or life-threatening are reported as soon as possible and no later than 7 days after the incident has become known to the sponsor. Relevant follow-up information is sent thereafter within an additional 8 days. Other SUSAR are reported as soon as possible and no later than 15 days after they have come to the sponsor's knowledge.

Information about SUSAR occurring during the study is compiled by the sponsor and sent out to the principal investigator at all participating centers by clinical site email without identifying any subject.

8.4 Follow-up of Adverse Events

All study subjects with an AE will be followed up and appropriately treated according to the Investigator's clinical judgment until all safety concerns are resolved. This applies both during and after study completion.

8.5 Annual Safety Report (Development Safety Update Report, DSUR)

As long as the study is ongoing, the sponsor will submit an annual safety report to the Swedish Medical Products Agency. The report will define for which time period the report applies and it will include a list of all SAE that have occurred as well as possibly SUSAR, and a summary assessment of the safety situation for the study subjects, and a risk/benefit evaluation for the study.

8.6 Procedures in case of emergencies, overdose or pregnancy

If a study subject who participates in a clinical trial for investigational products becomes pregnant, this person must be followed up until the birth has taken place. If the fetus/child has any congenital malformation, this must be reported as a serious adverse event (SAE). In case of emergencies or overdose, appropriate treatment and follow-up will be given at the children's hospital.

8.7 Reference Safety Information

FASS is used as Reference Safety Information for assessing whether an adverse event is expected or not.

According to Fass.se 2019-12-04, some adverse events may appear more often:

- At high infusion speed
- In patients with hypogammaglobulinemia or agammaglobulinemia, and patients who receive IVIG for the first time, or after a long interval.

Complications can often be avoided by making sure that the patients:

- Are not sensitive to human normal immunglobulin by initially infusing the product slowly (0,3 ml/kg BW/hour), and by closely observe symptoms during the entire infusion period. Patients who have switched from another IVIG-product, or when long time has passed since the last infusion, should be observed during the first infusion and for an hour thereafter, to discover signs of adverse effects. All other patients should be observed for at least 20 minutes after the infusion.

If adverse effects appear, the infusion speed must be reduced or the infusion be stopped. Any necessary treatment depends on the type and severity of the adverse effects. In chock standard treatment for this should be given.

For all patients receiving IVIG, the following applies:

Ensure adequate hydration before starting IVIG-infusion, monitor urine production, serum creatinine, and avoid giving loop diuretic drugs.

Adverse effects such as shivering, headache, vertigo, fever, vomiting, allergic reactions, nauseas, arthralgia, low blood pressure, moderate pain in lower back can sometimes appear in connection with IVIG infusion.

In rare cases can IVIG cause a sudden fall of blood pressure, and very rarely anaphylactic chock, even if the patient has not shown hypersensitivity from previous IVIG-infusions.

Cases of reversible aseptic meningitis and rare cases temporary skin reactions have been observed.

9 Statistics

9.1 Analysis population

A statistical analysis plan (SAP) is planned in collaboration with a statistician. The primary and secondary efficacy analyses will be performed on all included subjects (Intention-to-Treat (ITT) population) and on the Full Analysis Set (FAS) defined as all subjects with any baseline and any post-treatment measurements, with the Last Observation Caried Forward (LOCF) to endpoint for dropouts. A sensitivity analysis may be performed comparing the Per Protocol (PP) population (subjects who completely followed the protocol). Safety analyses will be performed on the safety population, defined as all subjects who have received at least one dose of IVIG treatment.

9.1.1 Statistical methods

Since this is an open-label exploratory uncontrolled trial, the sample size is not based on a statistical power calculation. Changes from baseline to post-baseline visits will be assessed using a two-sided, one-sample t test at a 0.05 significance level. Analyses of covariance, covarying for baseline values, will be used to compare posttreatment assessment scores. A responder analysis will be performed. Clinical response is defined as >30% reduction in

symptoms and impairment, respectively, as measured on the PANS scale. Gender subgroup analyses will be performed. The distribution of continuous and interval scaled variables will be given as mean, SD, median, minimum and maximum, and distribution of categorical variables will be numbers and percentages. Subjects who completed the study and subjects who withdrew from study prematurely will also be presented with a breakdown of the reasons for withdrawal by treatment group for the FAS and safety populations.

9.1.2 Drop-outs

See statistical methods above. Data for subjects who discontinue before study end will be analyzed using a Last Observation Carried Forward (LOCF) approach. Occurrence of, and reasons for, missing data will be described.

9.2 Adjustment of significance and confidence interval

Adjustments for multiple comparisons will be made.

9.3 Sample size calculations

Not calculated given the open design of the study

10 Quality Control and Quality Assurance

The sponsor will be responsible for Quality Control (monitoring) and Quality Assurance (auditing), for appointing a monitor and for the quality of the trial throughout the study; design, conduct, data collection, evaluation, reporting, and archiving. Methods used will be proportionate to the study's risks.

10.1 Quality Assurance and Sponsor oversight

Before the study start, study personnel will receive appropriate training in study procedures and ICH-GCP. The investigators will allow study-related monitoring, auditing, and regulatory inspections by providing direct access to the CRF, medical records, as well as other source data and other study-specific documentation.

The sponsor is responsible for the study's monitoring plan, which will be based on the identified risks, as well as follow-up of risks during the study and timeliness of the monitoring plan.

10.2 Monitoring

The study will be monitored by an independent monitor before the study begins, during the study conduct, and after the study has been completed, so as to ensure that the study is carried out according to the protocol and that data is collected, documented, and reported according to ICH-GCP and applicable ethical and regulatory requirements. Monitoring is performed as per the study's monitoring plan and is intended to ensure that the subject's rights, safety, and well-being are met as well as data in the CRF are complete, correct, and consistent with the source data.

10.3 Source data

The investigator must keep source documents for each subject in the study. A document describing what has been classified as source data in the study should be included in the Investigator Site File (ISF). The investigator must ensure that all source documents are accessible for monitoring and other quality control activities. Source data is defined before study start at each individual site.

10.4 Deviations or serious breaches

Serious breaches and deviations from the study protocol, GCP and other regulations that significantly and directly affects, or with high likelihood could affect, the subjects in Sweden or the scientific value of the study, shall be immediately reported within 7 days (from knowledge) to the Swedish Medical Products Agency (MPA). It is the sponsor's responsibility to judge the consequences of deviations that have occurred, and thus also to decide whether the MPA should be informed.

Minor deviations that do not affect subjects' integrity or safety, nor significantly affect the study's scientific value, are documented in the study documentation of the principal investigator and the sponsor.

10.5 Audits and inspections

Authorized representatives for the sponsor and Competent Authorities (CA) may carry out audits or inspections at the study site, including source data verification. The investigator must ensure that all source documents are available for audits and inspections. The purpose of an audit or inspection is to systematically and independently review all study-related activities and documents, so as to determine whether these activities were performed, registered, analyzed and reported correctly according to protocol, Good Clinical Practice (GCP) and applicable regulations.

11 Ethics

11.1 Compliance to the protocol, GCP and regulations

The study will be performed in accordance with the study protocol, ICH-GCP E6 (R2), the latest version of the Declaration of Helsinki and applicable regulatory requirements. This is to ensure the safety and integrity of the study subjects as well as the quality of the data collected.

11.2 Ethical review of the study

The final study protocol, including the final versions of the informed consent form and other information provided to subjects, must first be approved or given a written positive opinion by the Swedish Ethical Review Authority (Etikprövningsmyndigheten, EPM). The EPM must be informed of any changes in the study protocol in accordance with applicable requirements.

11.3 Procedure for obtaining informed consent

The principal investigator at each site shall ensure that the subject is given full and adequate oral and written information about the study, its purpose, any risks and benefits as well as inclusion and exclusion criteria. Subjects must also be informed that they are free to discontinue their participation in the study at any time without having to provide a reason. Subjects should be given the opportunity to ask questions and be allowed time to consider the provided information. If the subject chooses to participate, the parents and the child and the investigator shall sign the informed consent form, or give assent, as appropriate. A copy of the subject information as well as the informed consent form shall be provided to the subject. According to the Swedish law (The Medical Product Act; Läkemedelslagen 2015: 315 7 kap 3§) “both parents” need to sign the informed consent before the child can participate in the clinical trial. The parents and subject’s signed and dated informed consent or assent must be obtained before performing any study-specific activity in the study. Each subject who participated in the study will be identified by a subject number on a subject identification list. The parents and subject agree that monitors and inspectors may have access to their medical records. If new information is added to the study, the subject has the right to reconsider whether he/she will continue their participation.

11.4 Data protection

If any part of the data is handled by any other organization, inside or outside the EU, appropriate agreements and/or other documentation will be established, to ensure that the data processing is performed in accordance with the provisions of the General Data Protection Regulation (GDPR) and other relevant legislation, before any data transfer takes place.

The content of the informed consent form complies with relevant integrity and data protection legislation. In the subject information and the informed consent form, the subject will be given complete information about how collection, use and publication of their study data will take place. The subject information and the informed consent form will explain how study data are stored to maintain confidentiality in accordance with national data legislation. All data will be stored in locked archives cabinets at the Gillberg Neuropsychiatry Centre. All information processed by the sponsor will be pseudonymized and identified with <<Study code/Study ID/Initials>>.

The informed consent form will also explain that for verification of the data, authorized representatives of the sponsor, as well as relevant authority, may require access to parts of medical records or study records that are relevant to the study, including the subject’s medical history.

11.5 Insurances

All subjects are insured through Swedish patient insurance (Patientskadeförsäkring): The Swedish healthcare regions have signed a patient insurance with Landstingens Ömsesidiga Försäkringsbolag, Löf. Privigen (CSL Behring) is covered by the Swedish Pharmaceutical Insurance.

12 Substantial changes to the study

Substantial changes to the signed study protocol are only possible through approved protocol amendments and by agreement from all responsible persons. Information on non-substantial changes should be clearly noted in the amended protocol.

In the event that substantial changes to the protocol (e.g., changing of the main objective, primary or secondary variables, method to measure the primary variable, changing of the investigational product or dosage) will be made during the course of the study, approval from the Swedish Ethical Review Authority (Etikprövningsmyndigheten, EPM) as well as the Swedish Medical Products Agency (Läkemedelsverket) shall be obtained before any changes are implemented. A change that concerns a new site, new investigator or a new study patient information sheet shall only be approved by EPM. The investigator may however implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior ethics committee/competent authorities' approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) will be submitted: a) to the ethics committee/competent authorities for review and approval/favorable opinion, b) to the sponsor for agreement and, if required, c) to the regulatory authority. The revised version of the protocol will contain the aforementioned information about substantial protocol amendments.

Non-substantial changes will be recorded and later entered in documentation that is submitted, for example in any subsequent notifications of a substantial change or in connection with End of Trial reporting.

13 Collection, handling, and archiving data

Subjects who participate in the study are coded with a specific study identification number. All subjects are registered in a subject identification list (subject enrolment and identification list) that connects the subject's name and personal number with a study identification number.

All data will be registered, managed, and stored in a manner that enables correct reporting, interpretation, and verification. The sponsor shall have a Trial Master File with documentation for the whole study. The principal investigator shall have an Investigator Site File with all study documentation for the study site. The files should have relevant content according to the study and follow ICH-GCP chapter 8 "Essential documents". The complete Trial Master File, as well as source documents, will be archived for at least 10 years after the study is completed. Source data in the medical records system is stored and archived in accordance with the respective hospital regulations.

13.1 Case Report Form (Forskningspersonsformulär)

A paper Case Report Form (CRF) is used for data collection. The investigator must ensure that data is registered and any corrections in the CRF are made as stated in the study

protocol and in accordance with the instructions. The investigator must ensure that the registered data is correct, complete, and that reporting takes place according to the timelines that have been predefined and agreed. The investigator signs the completed CRF. A copy of the completed CRF will be archived at the study site.

If an examination/test is not performed and data does not exist, ND (Not done) or NK (Not known) is marked. If the question is irrelevant NA (Not applicable) is written. Corrections in the paper CRF are done by striking out the incorrect information and adding the correct information next to the incorrect information, signing, and dating the correction.

14 Notification of study completion, reporting, and publication

The Swedish Medical Products Agency shall be informed of the study's completion at latest 90 days after study end, through submission of a "Declaration of End of Trial Notification" form.

Within 6 months after the study is completed, the results shall be analyzed, a clinical study report with individual data shall be prepared, and the study results shall also be reported in the EudraCT database. A complete report with individual data shall be available from the sponsor on request or for any inspections by the Swedish Medical Products Agency throughout the entire retention period. A published article is not to be equated with a summary of a report. The report must contain sufficient information so that the Swedish Medical Products Agency can make an evaluation. If the results are summarized in a manuscript with the purpose to publish in a scientific journal, it is recommended that the study's EudraCT number is stated in the abstract.

If the study is prematurely terminated, the form "Declaration of End of Trial Notification" should only be used if the reason concerns the study's safety. In other cases, it is sufficient that the authorities are informed. If the sponsor terminates an ongoing study, the concerned authorities shall be informed as soon as possible, but no later than within 15 days.

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