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Clinical Study Protocol

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NCT Number: NCT04508530

Title: A Superiority Phase 3 Study to Compare the Effect of Panzyga Versus Placebo in Patients with Paediatric Acute-Onset Neuropsychiatric Syndrome (PANS/PANDAS)

Study Number: NGAM-13

This document may include redaction of names, addresses, and other personally identifiable information, as well as redaction of trade secrets and/or confidential commercial information.

A SUPERIORITY PHASE III STUDY TO COMPARE THE EFFECT OF PANZYGA VERSUS PLACEBO IN PATIENTS WITH PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME

Investigational Product:	Immune Globulin Intravenous, Human 10% (Panzyga)
Indication:	Pediatric acute-onset neuropsychiatric syndrome
Study Design:	Prospective, multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase III superiority study with an additional double-blind, crossover safety and efficacy follow-up phase
Sponsor:	Octapharma Pharmazeutika Produktionsges.m.b.H. Oberlaaer Str. 235, 1100 Vienna, Austria
Study Number:	NGAM-13
IND Number: **EudraCT Number;**	19740 2020-000867-21
Development Phase:	Phase III
Planned Clinical Start:	Q3 2021
Planned Clinical End:	Q4 2024
Date of Protocol:	21 July 2023
Version:	6.0
Co-ordinating Investigator:	[redacted] University of Arizona, [redacted] 888 N. Euclid Ave., #510, Tucson, Arizona 85719 USA

STUDY OUTLINE

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H.	
Name of Investigational Product: Panzyga	**Protocol Identification Code:** NGAM-13
Name of Active Ingredient: Immune Globulin Intravenous, Human 10%	**Date of Final Protocol:** 21 July 2023

Title of Study:

A Superiority Phase III Study To Compare The Effect of Panzyga Versus Placebo in Patients with Pediatric Acute-onset Neuropsychiatric Syndrome

Indication:

Pediatric acute-onset neuropsychiatric syndrome (PANS)

Number of Study Center(s):

Up to 30 centers (USA and rest of the world)

Objectives:

Primary Objective:

The primary objective of this study is to confirm that Panzyga is superior to placebo (0.9% w/v sodium chloride) for reducing the severity of symptoms associated with PANS in pediatric patients.

Secondary Objectives:

The secondary objectives of this study are to:

- verify the sustainability of the reduction of the severity of symptoms in pediatric patients treated with Panzyga
- assess the efficacy of Panzyga treatment in reducing functional impairment associated with PANS.

Exploratory Objectives:

The exploratory objectives of this study are to:

- assess the safety parameters of Panzyga administration
- characterize the pharmacokinetic (PK) exposure and the fluctuation thereof throughout the treatment course

Additional exploratory objectives of this study are to:

- assess the correlation between CGI-I and CY-BOCS
- assess the PANS improvement in pediatric patients

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Study Design:

Prospective, multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase III superiority study with three infusion cycles of Panzyga or placebo administered over 2 days every three weeks for a total of nine weeks, with an additional double-blind, crossover safety and efficacy follow-up phase of three infusion cycles of Panzyga or placebo administered over 2 days every three weeks for a total of nine weeks.

The study will be conducted in a two-stage adaptive design with one interim analysis. An interim analysis will be performed by an independent statistician after ■ patients have completed the first nine week treatment period, to adjust sample size, if required (the entire study team will remain blinded until the end of the study).

After ■ patients have completed blinded treatment (Visit Week 9), an interim review of the preliminary safety and efficacy data will be conducted by Independent Data Monitoring Committee (IDMC). At this timepoint, the IDMC will independently evaluate all data accrued in this pivotal study to provide a statement on whether emerging data confirm the prospect of direct benefit and positive risk-benefit ratio for PANS patients treated with Panzyga. IDMC confirmation will justify the submission to concerned Health Authorities of additional study protocol(s) evaluating other dose regimens of Panzyga treatment in patients with PANS. The actual numeric results will not be shared with the Sponsor or Investigators to ensure that bias will not affect subsequent study decisions since the data of the first ■ patients will be included in the final statistical analysis. Details will be provided in the IDMC Charter.

Number of Patients:

It is estimated that a minimum of ■ pediatric patients will need to be enrolled to ensure that ■ patients are evaluable for the primary endpoint (considering a 10% dropout rate). The total number of patients enrolled for the final analysis may increase, depending on the outcome of the interim analysis.

Enrollment was staggered in the sense that it was paused after the first ■ patients had been randomized and enrolled in the study, in order to enable a planned IDMC review of unblinded safety and PK data, including IgG trough levels. Enrollment resumed only after IDMC data review of the first ■ patients had been completed, and the IDMC had recommended to continue enrollment in the study.

Patient Selection Criteria:

Inclusion Criteria:

1. Patients ≥6 to ≤17 years of age.
2. Confirmed diagnosis of moderate to severe PANS with prominent and stable obsessive-compulsive disorder (OCD) symptoms (i.e. Clinical Global Impression

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(CGI)—Severity-OCD rating of ≥ 4 or higher on 2 ratings without a change of more than 1 unit between measurements) based on the following criteria [1]:

a. Abrupt dramatic onset of OCD meeting DSM-5 diagnostic criteria for OCD as confirmed by the MINI-KID-7
b. Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of the following seven categories, that are not better explained by a known neurologic or medical disorder, such as Sydenham chorea (SC), systemic lupus erythematosus, Tourette disorder, or other:
    - Anxiety (particularly, separation anxiety)
    - Emotional lability (extreme mood swings) and/or depression
    - Irritability, aggression and/or severely oppositional behaviors
    - Behavioral (developmental) regression (examples, talking baby talk, throwing temper tantrums, etc.)
    - Deterioration in school performance
    - Sensory or motor abnormalities
    - Somatic signs and symptoms, including sleep disturbances, bed wetting or urinary frequency

3. Signed informed consent of patient's legal representative(s)/guardians(s). If patients are old enough to understand the risks and benefits of the study (as determined by each institution), they should provide written assent/consent.
4. Legal representative(s)/guardians(s) must be capable of understanding and complying with the relevant aspects of the study protocol.

Patients who will additionally meet the following optional inclusion criteria will be identified as patients with Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS):

1. An episodic (relapsing-remitting) course of symptom severity
2. Temporal association between symptoms onset or exacerbation and infections with group A streptococcal infection (GAS, positive throat culture and/or anti-GAS antibody titers)

Exclusion Criteria:

1. Onset of current PANS episode more than 12 months prior to first investigational medicinal product (IMP) treatment.
2. a. In patients with relapsing episodes: Onset of initial PANS episode more than 24 months prior to first IMP treatment.

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b. In patients with relapsing episodes: Absence of significant improvement and stabilization between the episodes according to investigator's judgment.

3. Contraindications to receiving intravenous immunoglobulin (IVIG), including:
    a. History of severe hypersensitivity, e.g., anaphylaxis or severe systemic response, to immunoglobulin, blood or plasma-derived products, or any component of Panzyga.
    b. Immunoglobulin (Ig) A deficiency with antibodies to IgA (<7 mg/dL).
    c. Hyperviscosity syndromes or known or suspected hypercoagulable conditions, as inferred from clinical history, which can increase risks of thrombosis associated with IVIG administration.
    d. History of arterial or venous thrombotic or thromboembolic events (TEEs) within the last year prior to Baseline. History of acquired or inherited thrombophilia any time prior to Baseline.
    e. Need for live virus vaccine within three months after receiving study drug.
    f. Renal dysfunction (creatinine >120 µmol/L or 1.36 mg/dL), history of renal dysfunction, or known risk factor for renal dysfunction (chronic renal insufficiency, diabetes mellitus, taking known nephrotoxic medication). For Italy, estimated glomerular filtration rate (eGFR) needs to be calculated with the 2009 Schwartz equation (eGFR = k * height/Serum creatinine (SCr), where k is 0.413) [2]. eGFR must not be below 30.
4. Severely restricted food intake likely to require parenteral nutrition, and <5th percentile BMI-for-age (BMI Percentile Calculator for Child and Teen based on Centers for Disease Control and Prevention growth charts for children and teens ages 2 through 19 years)
5. Body mass index ≥ 40 kg/m^2
6. Presence of symptoms consistent with autism or schizophrenia, bipolar disorder, or other psychotic disorder (unless psychotic symptoms have onset coincident with PANS).
7. Presence of serious or unstable medical illness, psychiatric (e.g. high suicide risk) or behavioral symptoms that would make participation unsafe or study procedures too difficult to tolerate.
8. Treatment with systemic corticosteroids within eight weeks before randomization.
9. Treatment with NSAIDs within five days before randomization.
10. Treatment with melatonin within one week before randomization.
11. History of rheumatic fever, including SC (neurological manifestation).
12. Past treatment of neuropsychiatric symptoms with immunomodulatory therapy (such as IVIG, rituximab or mycophenolate mofetil) or plasmapheresis.
13. Initiation of cognitive behavioral therapy (CBT) within eight weeks before randomization.

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14. Start of treatment or change in dosing with selective serotonin reuptake inhibitors [SSRIs] within eight weeks before randomization.
15. Treatment with alpha-2 agonists or antipsychotics within eight weeks before randomization.
16. Start of treatment or change in dosing with stimulants (Methylphenidate, Amphetamine and similar products) for Attention-Deficit Hyperactivity Disorder (ADHD) within four weeks prior to randomization.
17. Active use of tetrahydrocannabinol (THC) containing agents within four weeks prior to enrollment or during the trial. Use of cannabidiol- (CBD) / cannabimovone- (CBM) containing agents without THC is allowed if started more than eight weeks before enrollment in a stable dose/frequency.
18. Use of antibiotics or antiviral drugs at therapeutic dose within one week before randomization. Use of antibiotics at a prophylactic dose is allowed if started at least four weeks before randomization (Section 4.2).
19. Severe liver disease (alanine aminotransferase [ALT] three times above normal value).
20. Known hepatitis B, hepatitis C or HIV infection as per patient medical history.
21. Cardiac insufficiency (New York Heart Association [NYHA] classification III-IV), cardiomyopathy, significant cardiac dysrhythmia requiring treatment.
22. Medical conditions with symptoms and effects that could alter protein catabolism and/or IgG utilization (e.g. protein-losing enteropathies, nephrotic syndrome).
23. Pregnant and/or lactating women.
24. Female patients of childbearing potential unwilling to use a protocol-required method of contraception (as per protocol Section 7.3.9 b) from Screening throughout the study treatment period and for four weeks following the last dose of study drug. A woman of childbearing potential is defined as a fertile woman or adolescent, from the beginning of menstruation, unless permanently sterile.
25. Participation in another interventional clinical trial that is either blinded or involves an investigational (not approved) product within three months before Baseline or during the course of the clinical study. Participation in observational clinical trials or open-label trials involving an approved product may be permitted after consultation with the medical monitor.

Test Product, Dose, and Mode of Administration:

Panzyga is a 10% solution of IVIG ready for intravenous (IV) administration. The product is delivered as ready-to-use solution in glass bottles. Panzyga should be stored and transported light-protected at +2°C to +8°C (36°F to 46°F) and must not be frozen.

Patients are randomly assigned (1:1) to Panzyga or placebo as initial treatment arm. In the Panzyga arm, Panzyga will be administered in a dose of 1 g/kg body weight (BW) daily for two consecutive days, and if tolerated, administered in three-week intervals up to nine weeks

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(total Panzyga exposure 6 g/kg BW). After completion of the first phase of the study, blinded crossover assignment will be done: patients previously in the Panzyga arm will be assigned placebo and patients previously in the placebo arm will be assigned Panzyga, administered at the same regimen.

Duration of Treatment:

The duration of the first double-blind treatment phase (Panzyga vs. placebo) will be nine weeks. The duration of the second double-blind crossover phase will also be nine weeks. Thus, the overall study duration will be 18 weeks, plus up to 28 days from Screening to randomization.

Placebo Therapy, Dose and Mode of Administration:

0.9% w/v sodium chloride.

Patients treated with placebo will receive the same volume and infusion rate as would have been given for the Panzyga treatment arm. Therefore, patients will receive a placebo dose of 20 mL/kg given over two days and will receive three infusion cycles at three-week intervals in the first or second phase of the crossover study.

Study Outcome Parameters (Primary and Secondary Endpoints):

Primary Efficacy Endpoint:

Improvement of neuropsychiatric symptomatology and behavior in PANS patients determined by clinician-rated CY-BOCS score. The mean changes in the total CY-BOCS score from Baseline to Week 9 will be compared between Panzyga and placebo treatment to demonstrate superiority.

Secondary Efficacy Endpoints:

To assess behavioral changes by means of the following standardized assessments:

- CY-BOCS score at the end of the follow-up period at Week 18 will be compared to the Week 9 scores within the (Panzyga – Placebo) treatment sequence group to assess the durability of the clinical benefit associated with Panzyga treatment
- Clinical Global Impression (CGI)
- Parent & Child OC Impact Scale – Revised (COIS-RP and COIS-RC)
- The Swanson, Nolan, and Pelham Rating Scale (SNAP-IV, 26 item)
- Parent Tic Questionnaire (PTQ)

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Exploratory Endpoints:

- All adverse events (AEs) throughout the study period, with particular emphasis on TEEs and hemolytic transfusion reactions (HTRs).
- Vital signs (blood pressure, heart rate, body temperature and respiratory rate).
- Physical examinations.
- Laboratory parameters (hematology, clinical chemistry).
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Pharmacokinetic parameters:
  - Prior to start of the first infusion of each of the three infusion cycles, i.e. three trough levels per patient in all patients
  - 10 to 60 minutes after the end of the last infusion cycle in all patients
  - In the PK-subset (first [redacted] enrolled patients), in addition to the samples above, the following will be collected:
    (i) a trough sample prior to the second infusion of the first cycle;
    (ii) a sample within 10 to 60 minutes after the end of the first infusion of the first cycle;
    (iii) a sample within 10 to 60 minutes after the end of the second infusion of the first cycle
- Correlations between change in CY-BOCS from baseline to Week 9 (from Week 9 to Week 18) and CGI-I assessments at Week 9 (Week 18)
- Percentage of pediatric patients with PANS improvement at Week 9 and Week 18

Study Procedures:

Patients who experienced a bacterial infection thought to have triggered PANS are required to complete a course of antibiotics prior to randomization. Rescreening is allowed in patients who are eligible based on the onset of symptoms who have e.g. recently initiated CBT, psychotropic medication, systemic corticosteroids, anti-virals or antibiotics, provided these treatments are completed within the timelines stated in the exclusion criteria. Details of antibiotic treatment will be recorded in the patients' medical history.

Patients who meet all inclusion criteria will be randomized 1:1 to two possible treatment sequences:

- (Panzyga – Placebo): three administration cycles with Panzyga, followed by three administration cycles with placebo
- (Placebo – Panzyga): three administration cycles with placebo, followed by three administration cycles with Panzyga

Each infusion cycle with Panzyga will consist of 1 g/kg BW daily for two consecutive days, infusion cycles with placebo (0.9% w/v sodium chloride) will also consist of two infusions on

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two consecutive days and feature infusion volumes identical to the Panzyga dosing. Behavioral and laboratory parameter assessments will be performed in both treatment sequence groups at Baseline.

After having completed the Baseline assessments, the infusion cycles will be performed at the study site and the patients' conditions will be monitored throughout the infusion session.

During the first phase of the study (i.e. three infusion cycles), patients will repeat the behavioral and laboratory parameter assessments performed at Baseline and the primary endpoint will be evaluated at Week 9 Visit. Data for evaluation of secondary endpoints will also be collected. Thereafter, crossover treatment assignment will occur in a blinded fashion for the second phase of the study. In the second phase of the study (Week 9, 12, 15, and 18 visits), patients who received Panzyga in the first phase will be assigned placebo and vice versa. During this second phase, three infusion cycles of either Panzyga (1 g/kg BW daily for two consecutive days) or placebo (0.9% w/v sodium chloride infusion equivalent in volume to 1 g/kg BW Panzyga daily for two consecutive days) will be given at three-week intervals at the study site. The patients' conditions will be monitored throughout the infusion session. Upon completion of the second phase of the study, at the Week 18 Visit, data for evaluation of secondary endpoints, including durability of the clinical benefit and safety data, will be collected.

If a patient shows worsening of their symptoms based on CGI-Improvement ratings they will be presented to the site PI for review and treatment planning. Patients for whom worsening continues at a minimal level ("5" or "mildly worse") for an extended period of six weeks (2 visits) or moderately or greater level ("6" or "7"; much worse or very much worse) since last visit (up to three weeks) will be considered for premature withdrawal from the study drug and administration of appropriate standard of care treatment unless clinical interventions using approved study procedures and/or mediations have a reasonable likelihood to improve symptoms. Patients who experience an emergency worsening of symptoms may at the discretion of the site clinician be withdrawn from the study drug at any time to obtain necessary standard of care treatment. In addition, patients who develop exclusionary criteria (e.g. bipolar disorder, suicide attempt) will be withdrawn from the study drug and will receive appropriate standard of care treatment. All patients withdrawn from the study drug prematurely will be asked to continue the study as planned with modification of the study schedule (e.g. IMP administration and related to it safety lab tests will be omitted). Details of concomitant mediations and procedures administrated per standard of care will be captured in patient case reports.

Patients who need to be discontinued from the study will undergo a termination visit and will be treated according to standard of care at the site according to the treating physician.

The study assessments and scheduled time points for the first and second phases of the crossover study are summarized in the flow charts following this Study Outline and in Section 15.2 for sites in Europe.

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Statistical Analysis Plan:

[redacted]

[redacted]

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7. [redacted]
8. [redacted]
9. [redacted]
10. [redacted]
11. [redacted]
12. [redacted]
13. [redacted]
14. [redacted]

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1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]

[redacted]

[redacted]

1. [redacted]
2. [redacted]

PROTOCOL SIGNATURES

Signature of the Sponsor's Representatives

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

[redacted]

24. JULY 2023

Signature Date

[redacted]

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Signature Date

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Signature of the Co-ordinating Investigator

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

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Co-ordinating Investigator Signature Date

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Description
ADHD	Attention-Deficit Hyperactivity Disorder
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
BUN	Blood Urea Nitrogen
BW	Body Weight
CBD	Cannabidiol
CBM	Cannabimovone
CBT	Cognitive Behavioral Therapy
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression-Improvement Scale
CGI-S	Clinical Global Impression-Severity Scale
COIS-RP and COIS-RC	Parent & Child Obsessive Compulsive Impact Scale – Revised
CRO	Contract Research Organization
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Association
FAS	Full Analysis Set
FDA	Food And Drug Administration
GAS	Group A Streptococci
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HTR	Hemolytic Transfusion Reactions
IB	Investigator's Brochure
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-To-Treat
IV	Intravenous

Abbreviation	Description
IVIG	Intravenous Immunoglobulin
LDH	Lactate Dehydrogenase
MINI-KID	Mini-International Neuropsychiatric Interview for Children and Adolescents
NSAIDs	Non-steroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
OCD	Obsessive-Compulsive Disorder
PANDAS	Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections
PANS	Pediatric Acute-Onset Neuropsychiatric Syndrome
PP	Per Protocol
PTQ	Parent Tic Questionnaire
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Sydenham Chorea
SCr	Serum Creatinine
SD	Standard Deviation
SNAP-IV	The Swanson, Nolan, and Pelham Rating Scale
SOPs	Standard Operating Procedures
SSRIs	Selective Serotonin Reuptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBV	Total Blood Volume
TEE	Thromboembolic Events
THC	Tetrahydrocannabinol
WOCBP	Women Of Childbearing Potential
YGTSS	Yale Global Tic Severity Scale

1 INTRODUCTION

Obsessive compulsive disorder (OCD) affects 1–2% of children and adolescents, and is characterized by the presence of recurrent, unwanted thoughts (obsessions) and repetitive behaviors (compulsions) that create psychological distress and impair daily activities at home, at school, and with peers [4]. An unknown proportion of pediatric OCD cases have features related to two putative OCD subtypes: pediatric acute-onset neuropsychiatric syndrome (PANS) and/or pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS).

The first description of PANDAS, published in 1998, defined it as the sudden onset of obsessive-compulsive or tic disorder symptoms following a GAS infection [5]. In a clinical setting, PANDAS is observed as a cluster of abrupt onset symptoms following a GAS infection, including a pathogenic flare with severe obsessive compulsions (e.g. shoe licking) and/or tics (e.g. whooping), and concomitant symptoms, including developmental (behavioral) regression marked in separation anxiety and aggression [1, 6]. Due, in part, to the challenge of determining temporal association between GAS infection and the onset of OCD and/or tic symptoms, relatively few PANDAS cases have been confirmed through these strict criteria [7]. Thus, the validity of PANDAS as a unique clinical entity has been brought into question, becoming a topic of significant debate and controversy among psychiatrists and neurologists [8]. In an effort to resolve this debate, a new diagnostic syndrome was proposed in 2012. Termed PANS, this new definition addressed the primary criticism of the PANDAS definition by eliminating the requirement of a preceding GAS infection [9]. Hereafter, in the context of this clinical study protocol, any mention of PANS also includes a minority of patients with PANDAS.

Cognitive behavior therapy (CBT) including exposure and response prevention, and selective serotonin re-uptake inhibitors (SSRIs) are the primary evidence-based therapies for OCD [10, 11]. Approximately 50%–80% of patients with OCD respond to these treatments, but a substantial proportion of patients subsequently experience lifelong treatment resistance [12]. Behavioral interventions, such as habit reversal training, and psychopharmacological treatment strategies are the recommended treatments for tic disorders [13]. In contrast to the recommended treatments, when an infectious or autoimmune etiology is suspected, these treatments for OCD and tics may be insufficient.

Supplemental or alternative treatment options when suspecting PANDAS include antibiotics or tonsillectomy to treat and/or prevent GAS infection [14]. To suppress the immune system in patients with putative autoimmune-based OCD, corticosteroids [15], therapeutic plasma exchange [16, 17], IVIG [17], or anti-CD20 monoclonal antibodies (rituximab) [15] have been given. Administration of non-steroidal anti-inflammatory drugs (NSAIDs) to ameliorate psychiatric symptoms of PANS also has been suggested and is in line with the autoimmune etiology theory [18]. A consortium of clinicians and researchers have authored three consensus papers regarding treatment of PANS using psychiatric and behavioral interventions [19], immunomodulatory therapies [20], and antibiotics [21]. These guidelines of the clinical management of PANS are based on clinical experience and on research, and support use of immunomodulatory treatment and antibiotics, beside standard psychiatric treatment. A

systematic review on the management of PANS and related disorders identified 12 studies involving the following treatments: penicillin, azithromycin, IVIG, plasma exchange, tonsillectomy, CBT, NSAIDs, and corticosteroids [12]. A further 65 case reports in which patients received immunomodulatory treatments, antibiotics, and/or psychotropics were identified [12]. Research on PANS treatment (and related disorders) is scarce, and further investigation is needed in which treatment strategies are rigorously investigated.

As mentioned above, immunoglobulins have been used in the treatment of PANS. Panzyga is a 10% human normal immunoglobulin solution ready for intravenous administration (IVIG) developed by Octapharma. It is supplied as a ready-to-use liquid formulation. The Panzyga manufacturing process achieves significant viral reduction through a combination of [redacted] dedicated virus inactivation/removal steps. Adverse drug reactions (ADRs) reported for Panzyga were similar in type and intensity to those reported with other IVIG preparations. Panzyga is currently registered in [redacted] countries, with the first marketing authorization granted in Germany in February 2016 [22].

1.1 Rationale for Conducting the Study

Accumulating evidence supports conceptualizing PANS as an immune-mediated brain disease, akin to Sydenham chorea (SC) and PANDAS, involving the caudate, putamen, and other basal ganglia structures [20]. Evidence that the onset of PANS is driven by inflammation is based on animal models from a number of different research groups [23], clinical data showing overlap between PANS and other inflammatory diseases [4, 24], imaging studies [25, 26], and other research suggesting a link between inflammation and obsessive-compulsive symptoms [27-32]. Increased rates of arthritis and autoimmune/inflammatory disorders have been reported among patients with PANS and their first-degree relatives, with more than 70% of families having at least one affected family member [23, 33]. There is also emerging clinical literature reporting response of PANS symptoms to therapies, including NSAIDs, oral and intravenous corticosteroids, IVIG, and plasmapheresis [20, 34, 35]. In a retrospective review of patients in the Stanford PANS-PANDAS clinic, symptomatic improvement in neuropsychiatric symptoms became evident in roughly one-third of NSAIDS treatment trials [35]. Similarly, children with more severe symptoms treated with oral corticosteroids were found to have shorter exacerbations and longer periods of remission than children not receiving steroid treatment [34]. Provisional data demonstrate a positive impact of IVIG treatment in PANS patients on psychometric parameters [36].

Although the use of IVIG in the treatment of PANS/PANDAS has received considerable attention in the past decade, no additional placebo-controlled trials were published until 2016. A placebo-controlled trial of IVIG was undertaken at the National Institute of Mental Health and the Yale Child Study Center. Thirty-five children meeting criteria for PANDAS and moderate-to-severe OCD were randomized in double-blind, placebo-controlled 6-week trial of IVIG (1 g/kg body weight [BW] on two consecutive days; total dose 2 g/kg BW) [37]. Non-responders were offered open-label treatment with IVIG at six weeks, and follow-up evaluations for all participants occurred at 12 and 24 weeks. The primary outcome measures were the CY-BOCS and the CGI improvement (CGI-I) rating. “Responders” were defined, a priori, by a >30% decrease in CY-BOCS total score, and “much” or “very much” improved on CGI-I. IVIG was

safe and generally well-tolerated. The mean decrease in CY-BOCS score during the double-blind phase was 24±31% in the IVIG group (n=17) and 12±27% in the placebo group (n=18). This difference was not statistically significant (effect size = 0.28, 95% confidence interval -0.39–0.95), with six responders in the IVIG group (35%) and four responders in the placebo group (22%). Notably, the blinded phase included only one treatment cycle, which might not be enough to show a full effect of treatment and detect a difference between IVIG and placebo. Twenty-four children met criteria for non-response and received open-label treatment (n=10 IVIG, n=14 placebo). Across all participants, a mean CY-BOCS improvement from baseline at week 12 of 55±33% was observed [37]. A number of unanticipated events (multiple patients acquired new GAS infections during the trial), as well as study design issues, may have decreased the effect size of the trial. Further to the above-mentioned reason, in particular, participants may also have over-reported symptom severity in the double-blind portion of the study to increase the possibility of getting open-label IVIG at six weeks.

Since there are scarce data from rigorously designed double-blind controlled trials with IVIG, Octapharma plans to assess the efficacy and safety of Panzyga treatment compared with placebo in PANS patients.

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and to the Regulatory Authority. The study will be conducted in compliance with the protocol, good clinical practice (GCP) guidelines, and applicable regulatory requirements.

1.2 Dose Rationale

According to published literature, patients with PANS respond to IVIG doses of 2 g/kg BW (divided over two consecutive days) [17, 37]. Initial high dose induction IVIG treatment (one to six monthly courses) for moderate-to-severe PANS is recommended by the guidelines adopted by PANS Research Consortium [20]. This induction dose is equivalent to that used for other pediatric inflammatory disorders, including, but not limited to autoimmune encephalitis, Kawasaki disease, juvenile dermatomyositis, idiopathic thrombocytopenic purpura, and Guillain-Barre syndrome [38, 39]. Additionally the dose of 2 g/kg BW was used in another randomized controlled study that can be regarded as a reference study in terms of IVIG dose regimen [37].

Efficacy and safety of high-dose IVIG induction treatment was shown in a multicenter, phase I/II blinded-withdrawal study with stratified entry in 25 polyarticular juvenile rheumatoid arthritis (poly-JRA) patients. Similar to PANS, autoimmune inflammation is the underlying pathophysiologic disease mechanism in poly-JRA. In this pediatric study, IVIG was given in a dose of 1.5–2.0 g/kg BW bimonthly for two months (up to a total dose of 8 g/kg over eight weeks) followed by monthly infusions [40].

Patients in the Panzyga arm will, therefore, receive 1 g/kg BW daily for two consecutive days, if tolerated, administered in three-week intervals up to nine weeks (total Panzyga exposure: 6 g/kg BW).

1.3 Benefit-Risk Statement

Risks associated with assignment to the placebo arm include adverse events (AEs) or worsening of symptoms. At this time, no data from pediatric PANS/PANDAS or OCD clinical trials suggest a risk of permanent worsening of symptoms or long-term outcome in children assigned to a placebo arm up to nine weeks' duration. The delay in access to active treatment is similar to what might be experienced by patients waiting for a clinician appointment and insurance authorization for treatment with IVIG in the community.

The risks of IVIG administration are well documented. In general, the incidence of AEs associated with IVIG tends to increase with the rate of infusions, and thus the recommended dosage, infusion rates, and monitoring procedures should be adhered to. Patients who are naïve to IVIG are more at risk than those who are well maintained and on regular therapy. In clinical studies with Panzyga, most ADRs observed in children were graded as mild, and many of them responded to simple measures, such as reduction of the infusion rate or temporary discontinuation of the infusion. With respect to the type of ADR, all were recognized for IVIG preparations. The most frequent ADR observed in the pediatric population was headache [22, 41].

The safety profile of IVIG is well characterized and, in general, the same type of adverse reactions may be expected for Panzyga. No new or unknown safety problems are expected to emerge, which are not already described in the Investigator's Brochure (IB) [22]. In general, adverse reactions such as headache, dizziness, vomiting, allergic reactions, chills, back pain, arthralgia, fever, low blood pressure and nausea may occasionally occur.

The safety profile of Panzyga is satisfactory and the number of ADRs are below the levels recommended by the US Food and Drug Administration (FDA) for products of this class. Efficacy and safety data with Panzyga are available from three clinical studies in 51 patients (including pediatric patients) with primary immunodeficiency and in 40 patients with immune thrombocytopenia [22].

The expected clinical benefit of using Panzyga in this study is improvement of neuropsychiatric symptomatology and behavior in PANS patients. IVIGs are recommended by the PANS Research Consortium for the treatment of moderate to severe PANS . A recent open label study showed statistically significant improvements in psychometric assessments from baseline after six infusions every three weeks in pediatric patients with PANS

The main known risks of IVIG administration are listed below

- Thrombosis and thromboembolic events (TEEs) such as myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis may occur with IVIG products, including Panzyga. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.
- Renal dysfunction, acute renal failure, osmotic nephropathy, and death may occur with the administration of IVIG products in predisposed patients (e.g. pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medicinal products or age over 65 years). Renal dysfunction and acute renal failure occur

more commonly in patients receiving IVIG products containing sucrose. Panzyga does not contain sucrose.

- Standard measures are taken to prevent infections resulting from the use of medicinal products prepared from human blood or plasma. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. During the manufacturing process of Panzyga, significant viral reduction is obtained.
- Reversible hemolytic reactions have been observed in patients, especially those with blood groups A, B, and AB. Rarely, hemolytic anemia requiring transfusion may develop after high dose IVIG treatment.
- Aseptic meningitis syndrome is a rare but known adverse reaction that has been reported to occur infrequently in association with IVIG treatment.

Inclusion and exclusion criteria, recommendations on the rate of infusion, dosage, and monitoring procedures provided in this protocol sufficiently mitigate above-mentioned risks and must be adhered to. No new or unknown safety problems are expected to emerge in pediatric PANS population, which are not listed above or described in the IB.

Based on available data, we postulate that PANS treatment with Panzyga outweighs potential disadvantages.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to confirm that Panzyga is superior to placebo (0.9% w/v sodium chloride) for reducing the severity of symptoms associated with PANS in pediatric patients who meet PANS clinical criteria.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- verify the sustainability of the reduction of the severity of symptoms in pediatric patients treated with Panzyga.
- assess the efficacy of Panzyga treatment in reducing functional impairment associated with PANS.

2.3 Exploratory Objectives

The exploratory objectives of this study are to:

- assess the safety parameters of Panzyga administration.
- characterize the pharmacokinetic (PK) exposure throughout the treatment course.

Additional exploratory objectives of this study are to:

- assess the correlation between CGI-I and CY-BOCS
- assess the PANS improvement in pediatric patients

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

Improvement of neuropsychiatric symptomatology and behavior in PANS patients determined by clinician-rated CY-BOCS score. The mean changes in the total CY-BOCS score from Baseline to Week 9 will be compared between Panzyga and placebo treatment to demonstrate superiority.

3.1.2 Secondary Endpoint

- To assess behavioral changes by means of the following standardized assessments:
  - CY-BOCS score at the end of the follow-up period at Week 18 will be compared to the Week 9 scores within the (Panzyga – Placebo) treatment sequence group to assess the durability of the clinical benefit associated with Panzyga treatment
  - Clinical Global Impression (CGI)
  - Parent & Child OC Impact Scale – Revised (COIS-RP and COIS-RC)
  - SNAP-IV 26 item Scale
  - Parent Tic Questionnaire (PTQ)

3.1.3 Exploratory Endpoints

- All AEs throughout the study period, with particular emphasis on TEEs and HTRs.
- Vital signs (blood pressure, heart rate, body temperature and respiratory rate).
- Physical examination at Baseline, and targeted physical examinations at Week 3, Week 6, Week 9/Early Termination Visits.
- Laboratory parameters (hematology, clinical chemistry) at Baseline and Week 9/Early Termination Visits.
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Pharmacokinetic parameters related to IgG sampling (Table 3):
  - Prior to start of the first infusion of each of the three infusion cycles, i.e. three trough levels per patient in all patients
  - 10 to 60 minutes after the end of the last infusion cycle in all patients
  - In the PK-subset (first six enrolled patients), in addition to the samples above, the following three samples were collected:
    - (i) a trough sample prior to the second infusion of the first cycle;
    - (ii) a sample within 10 to 60 minutes after the end of the first infusion of the first cycle;

  - (iii) a sample within 10 to 60 minutes after the end of the second infusion of the first cycle

- Correlations between change in CY-BOCS from baseline to Week 9 (from Week 9 to Week 18) and CGI-I assessments at Week 9 (Week 18)
- Percentage of pediatric patients with PANS improvement at Week 9 and Week 18. For this analysis, PANS improvement is defined as a CGI-I rating of 1 (Very much Improved), 2 (Much improved), or 3 (Minimally Improved).

3.2 Overall Study Design and Plan

The study is planned to start in Q3 2021 and to be clinically completed by Q4 2024. The study will be a prospective, multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase III superiority study in a minimum of [redacted] pediatric patients with confirmed diagnosis of moderate to severe PANS with prominent and stable OCD symptoms (i.e. CGI—Severity-OCD rating of ≥ 4 or higher on 2 ratings without a change of more than 1 unit between measurements). The study includes an additional double-blind, crossover safety and efficacy follow-up phase of three infusions of Panzyga or placebo administered over 2 days every three weeks for a total of nine weeks.

After the first [redacted] patients had been enrolled, the study enrollment was put on hold to further enhance the safety monitoring of Panzyga administration. The study resumed only after the Independent Data Monitoring Committee (IDMC) had reviewed unblinded safety and PK data of these [redacted] patients and given the green light to pursue the study.

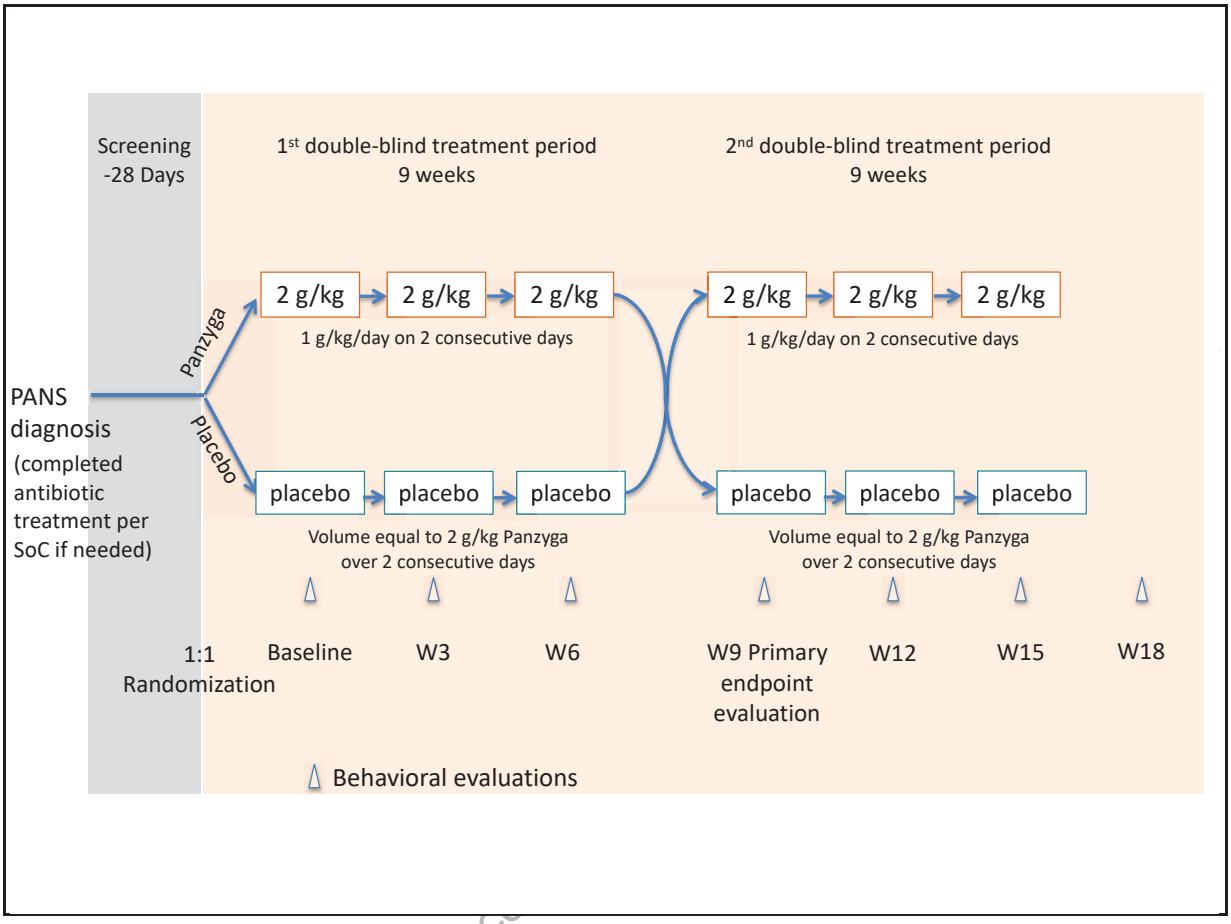
Up to 30 sites are projected to participate in this clinical study.

Eligible patients will be randomized 1:1 to two possible treatment sequences:

- (Panzyga – Placebo): three administration cycles with Panzyga, followed by three administration cycles with placebo
- (Placebo – Panzyga): three administration cycles with placebo, followed by three administration cycles with Panzyga

Patients will undergo repeated efficacy and safety assessments relating to each cycle. After completion of the first double-blind treatment period, blinded crossover assignment will be done; patients previously in the Panzyga arm will be assigned placebo and patients previously in the placebo arm will be assigned Panzyga, administered at the same regimen. Figure 1 depicts the study design. Rescreening is allowed for patients who were eligible based on the onset of symptoms, but have recently initiated CBT, psychotropic medication, corticosteroids, anti-virals, or antibiotics, provided these treatments are completed within the timelines stated in the exclusion criteria (Section 4.1.2).

Figure 1: Scheme of Study Design



3.3 Discussion of Study Design and Choice of Control Group(s)

3.3.1 Study Design

Octapharma designed this prospective, multicenter, randomized double-blind superiority study comparing Panzyga with placebo (0.9% w/v sodium chloride) to confirm efficacy and safety of Panzyga in PANS patients. The study includes an additional double-blind, crossover safety and efficacy follow-up phase. In case of clinically important deterioration during the study, patients will be discontinued from the study, have termination visit procedures performed, and may optionally receive standard of care treatment at the site according to the treating physician.

Due to the previously described uncertainty on the expected effect size, the study will be set up in an adaptive, two-stage design using enrichment. This involves an interim analysis by an independent statistician after [redacted] patients have completed the nine week treatment period (the entire study team will remain blinded until the end of the study).

In the context of this interim analysis, effect sizes for different subpopulations will be studied and statistically compared between treatments. After the interim analysis, the study may be adapted with respect to the study cohort and sample size. This may involve the exclusion of defined subgroups of patients for which no substantial treatment effect could be established.

Based on the observed effect sizes in the interim analysis, a re-estimation of the sample size for the post-interim analysis study part will be performed and the protocol may be amended accordingly. More details are provided in Section 9 of this protocol.

The study population will be prospectively balanced according to the choice of antibiotic prophylactic treatment, disease type (PANS/PANDAS) and treatment with stable dose of SSRIs.

3.3.2 Control Group(s)

The study compares Panzyga with placebo and includes a double-blind, crossover phase. There is no appropriate alternative treatment available known to be effective over a nine week period that would allow for a comparative efficacy trial (and negate the need for placebo). In this study, all eligible patients diagnosed with moderate/severe PANS will receive both Panzyga and placebo, owing to the crossover design.

3.3.3 Study Parameters

The selected study parameters are appropriate to verify the clinical efficacy of Panzyga in PANS. With the exception of MINI-KID, all scales will be completed electronically, and sites are requested to use electronic questionnaires to reduce variability across patients and to ensure critical consistency of measurements. All assessments except CY-BOCS can be carried out by the treating physician, to prevent unblinding. A strategic central reader system has been established that serves as an independent expert panel to standardize reliability on the study's primary outcome measure (CY-BOCS). Standardization will also include a training program to ensure that all raters from different sites are reliable and remain so throughout the trial. To overcome rater variability as far as possible, the CY-BOCS rater should remain the same person. For the clinical interview scales CY-BOCS, CGI-S/I, and MINI-KID, the rater should meet the following credentials: MD/DO with Board Certification or Board Eligible in Child/Adolescent Psychiatry or related discipline; MD/DO with Board Certification or Board Eligible in Neurology/ Immunology/ Neuroimmunology; or PhD/PsyD with a degree in clinical psychology or related discipline. The clinical raters should also have significant clinical experience with psychiatric interviews and working with children with PANS. Whenever possible, raters should remain the same throughout the study for individual subjects.

The **CY-BOCS** scale score is a clinician-rated, semi-structured interview for rating the presence or absence, as well as the severity of obsessive-compulsive symptoms. Considerable data support the reliability and validity of both the adult [42, 43] and child versions of this scale [44]. The CY-BOCS yields a total obsession score, a total compulsion score and combined total score (maximum total CY-BOCS score=40). If in-person administration is not possible, the interview may be carried out via video conference (Zoom, WebEx etc.), but telephone administration without video is not permitted.

The **CGI** rating scales are commonly used measures of symptom severity, treatment response and the efficacy of treatments in clinical trials of patients with mental disorders. The Clinical Global Impression - Severity scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience,

a patient is assessed on severity of mental illness at the time of rating 1 = normal; not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill. The Clinical Global Impression - Improvement scale (CGI-I) is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention and is rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse [45]. Telemedicine platforms such as video/phone can be utilized.

A specific and commonly used measure of OCD-related impairment is the COIS-R [46], which is a revision of the original **COIS** and is available in parallel parent- and child-report versions, assessing impairment due to OCD across multiple functional domains [47]. The Child Obsessive-Compulsive Impact Scale-Revised consists of parallel 33-item parent and child-report versions assessing impairment due to OCD across multiple functional domains (parent-report: Daily Living Skills, Family, Social, School; child-report: School, Social, Activities). Items are rated on a 4-point scale from 0 (not at all) to 3 (very much) [46]. The parent and child versions of the COIS-R exhibit good to excellent internal consistency and acceptable to good test–retest reliability across subscales [48]. The parent-report version has demonstrated sensitivity as a predictor of treatment response, while the child-report version is sensitive to treatment response for both cognitive behavioral therapy (CBT) and medication [48]. Telemedicine platforms such as video/phone can be utilized.

The Parent Tic Questionnaire (**PTQ**) is a commonly used tool suggested by Tourette syndrome international guidelines [49]. The PTQ assesses tic severity in the past week, allowing for individual parent ratings of tic presence or absence for 14 vocal tics and 14 motor tics. Additionally, the measure allows for separate ratings of tic frequency and intensity, completed for each tic. Frequency ratings range from 1 to 4 with the following anchors: weekly, daily, constantly, hourly. Intensity ratings range from 1 to 4, with higher scores indicative of greater tic intensity. The frequency and intensity ratings can be summed to yield a severity score ranging from 0 (i.e., tic is absent, thus no frequency or intensity ratings are given) to 8 for each tic. The PTQ includes subtotals for motor and vocal tic severity, which are summed to produce a total tic score. A 55% reduction and 10-point decrease in PTQ Total score were reported as optimal for defining positive treatment response. The PTQ demonstrates good internal consistency, excellent test-retest reliability, and good convergent validity with the Yale Global Tic Severity Scale (YGTSS) [50]. Completion via video conference is allowed.

The Swanson, Nolan, And Pelham Scale – Version IV (**SNAP-IV**) is a 26-item, parent- or teacher-reported scale which elicits reporting on each of the DSM cardinal symptoms of Attention-Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD) in children and adolescents. The 26-item scale also includes items on aggression, mood, and school performance and behavior. It is used extensively in ADHD and disruptive behavior disorder intervention trials and is sensitive to change [51]. Telemedicine platforms such as video/phone can be utilized.

The Mini International Neuropsychiatric Interview for Children and Adolescents (**MINI-KID** version 7.0.2) is a short standardized diagnostic interview for DSM-5 and the International

Statistical Classification of Diseases and Related Health Problems - Tenth Revision (ICD-10) psychiatric disorders in children and adolescents. The instrument uses two to four screening questions for each disorder. If the screening questions are positively answered, additional symptom questions are given for the particular disorder. The instrument can be administered by interviewing parent(s) and adolescents together or separately. MINI-KID has an administration time of 15 to 50 minutes [52]. MINI-KID disorder classifications have shown test-retest reliability and validity comparable to other standardized diagnostic interviews. Thus, MINI-KID is a useful tool for diagnostic screening in child and adolescent psychiatry [53, 54]. Completion via video conference is allowed.

Suicidality was evaluated using the Columbia Suicide Severity Rating Scale (**C-SSRS**), a semi-structured interview validated in pediatric patients for systematic assessment of the presence and severity of suicidal ideation and suicidal behavior in clinical trials [55]. The severity scale is a 6-point ordinal scale, ranging from 1 (wish to be dead) to 5 (suicidal intent with plan). Participants who deny suicidal ideation score zero. The C-SSRS intensity scale is comprised of five items (i.e., frequency, duration, controllability, deterrents, reasons for ideation), each rated on an ordinal scale (total scores ranging from 2 to 25). These five items are completed only with participants who endorse at least one of the severity items. Those without any suicidal ideation score 0 on intensity. The behavior scale is a 5-point nominal scale that investigates interrupted, aborted, and actual suicide attempts, preparatory behavior for a suicide attempt, and non-suicidal self-injurious behavior. Telemedicine platforms such as video/phone can be utilized.

Whenever remote administrations are carried out the users should determine whether they are subject to HIPAA (US) or other health data privacy laws and use appropriate telemedicine/telecommunications tools, such as Zoom or Doximity.

4 STUDY POPULATION

4.1 Population Base

Patients will be aged 6–17 years, with moderate to severe symptoms PANS with prominent and stable OCD symptoms (i.e. CGI—Severity-OCD rating of ≥ 4 or higher on 2 ratings without a change of more than 1 unit between measurements). All patients will meet criteria for PANS, including the sudden onset of obsessive-compulsive symptoms and at least two of seven additional associated neuropsychiatric symptoms. It is estimated that a minimum of [redacted] patients will need to be enrolled, to ensure that at least [redacted] patients are evaluable for the primary endpoint. The total number of patients enrolled for the final analysis may change, depending on the outcome of the interim analysis. Patients who drop out or are withdrawn from the study will not be replaced, but enrollment will continue until the total evaluable number of required patients for primary endpoint assessment has been reached.

Enrollment was staggered in the sense that it was paused after the first [redacted] patients had been randomized and enrolled in the study, in order to enable a planned IDMC review of unblinded safety and PK data, including IgG trough levels. Enrollment resumed only after IDMC data review of the first [redacted] patients had been completed, and the IDMC had recommended to continue enrollment in the study.

4.1.1 Inclusion Criteria

Patients who meet all of the following criteria are eligible for the study:

1. Patients ≥6 to ≤17 years of age.
2. Confirmed diagnosis of moderate to severe PANS with prominent and stable OCD symptoms (i.e. CGI—Severity-OCD rating of ≥ 4 or higher on 2 ratings without a change of more than 1 unit between measurements) based on the following criteria [1]:
    a. Abrupt/dramatic onset of OCD meeting DSM-5 diagnostic criteria for OCD as confirmed by the MINI-KID-7
    b. Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of the following seven categories, that are not better explained by a known neurologic or medical disorder, such as SC, systemic lupus erythematosus, Tourette disorder, or other:
        i. Anxiety (particularly, separation anxiety)
        ii. Emotional lability (extreme mood swings) and/or depression
        iii. Irritability, aggression and/or severely oppositional behaviors
        iv. Behavioral (developmental) regression (examples, talking baby talk, throwing temper tantrums, etc.)
        v. Deterioration in school performance
        vi. Sensory or motor abnormalities

vii. Somatic signs and symptoms, including sleep disturbances, bedwetting or urinary frequency

3. Signed informed consent of patient's legal representative(s)/guardians(s). If patients are old enough to understand the risks and benefits of the study (as determined by each institution), they should provide written assent/consent.
4. Legal representative(s)/guardians(s) must be capable of understanding and complying with the relevant aspects of the study protocol.

Patients who will additionally meet the following optional inclusion criteria will be identified as PANDAS patients:

1. An episodic (relapsing-remitting) course of symptom severity.
2. Temporal association between symptoms onset or exacerbation and GAS infections (positive throat culture and/or anti-GAS antibody titers).

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria are not eligible for the study:

1. Onset of current PANS episode more than 12 months prior to first IMP treatment.
2. a. In patients with relapsing episodes: Onset of initial PANS episode more than 24 months prior to first IMP treatment

   b. In patients with relapsing episodes: Absence of significant improvement and stabilization between the episodes according to investigator's judgment.
3. Contraindications to receiving IVIG, including:
   a. History of severe hypersensitivity, e.g. anaphylaxis or severe systemic response, to immunoglobulin, blood or plasma-derived products, or any component of Panzyga.
   b. IgA deficiency with antibodies to IgA (<7 mg/dL).
   c. Hyperviscosity syndromes or known or suspected hypercoagulable conditions as inferred from clinical history, which can increase risks of thrombosis associated with IVIG administration.
   d. History of arterial or venous thrombotic or TEEs within the last year prior to Baseline. History of acquired or inherited thrombophilia any time prior to Baseline.
   e. Need for live virus vaccine within three months after receiving study drug.
   f. Renal dysfunction (creatinine > 120 µmol/L or 1.36 mg/dL), history of renal dysfunction, or known risk factor for renal dysfunction (chronic renal insufficiency, diabetes mellitus, taking known nephrotoxic medication). For Italy, estimated glomerular filtration rate (eGFR) needs to be calculated with the 2009 Schwartz equation (eGFR = k * height/Serum creatinine (SCr), where k is 0.413) [2]. eGFR must not be below 30.

4. Severely restricted food intake likely to require parenteral nutrition, and <5th percentile BMI-for-age (BMI Percentile Calculator for Child and Teen based on Centers for Disease Control and Prevention growth charts for children and teens ages 2 through 19 years).
5. Body mass index ≥ 40 kg/m^2.
6. Presence of symptoms consistent with autism or schizophrenia, bipolar disorder, or other psychotic disorder (unless psychotic symptoms have onset coincident with PANS).
7. Presence of serious or unstable medical illness, psychiatric (e.g. high suicide risk) or behavioral symptoms that would make participation unsafe or study procedures too difficult to tolerate.
8. Treatment with systemic corticosteroids within eight weeks before randomization.
9. Treatment with NSAIDs within five days before randomization.
10. Treatment with melatonin within one week before randomization.
11. History of rheumatic fever, including SC (neurological manifestation).
12. Past treatment of neuropsychiatric symptoms with immunomodulatory therapy (such as IVIG, rituximab or mycophenolate mofetil) or plasmapheresis).
13. Initiation of CBT within eight weeks before randomization.
14. Start of treatment or change in dosing with SSRIs within eight weeks before randomization.
15. Treatment with alpha-2 agonists or antipsychotics within eight weeks before randomization.
16. Start of treatment or change in dosing with stimulants (Methylphenidate, Amphetamine and similar products) for ADHD within four weeks prior to randomization.
17. Active use of THC-containing agents within four weeks prior to enrollment or during the trial. Use of CBD/CBM-containing agents without THC is allowed if started more than eight weeks before enrollment in a stable dose/frequency.
18. Use of antibiotics or antiviral drugs at therapeutic dose within one week before randomization. Use of antibiotics at a prophylactic dose is allowed if started at least four weeks before randomization (Section 4.2).
19. Severe liver disease (ALT three times above normal value).
20. Known hepatitis B, hepatitis C or HIV infection as per patient medical history.
21. Cardiac insufficiency (NYHA classification III-IV), cardiomyopathy, significant cardiac dysrhythmia requiring treatment.
22. Medical conditions with symptoms and effects that could alter protein catabolism and/or IgG utilization (e.g. protein-losing enteropathies, nephrotic syndrome).

23. Pregnant and/or lactating women
24. Female patients of childbearing potential unwilling to use a protocol-required method of contraception (as per protocol Section 7.3.9 b) from Screening throughout the study treatment period and for four weeks following the last dose of study drug. A woman of childbearing potential (WOCBP) is defined as a fertile woman or adolescent, from the beginning of menstruation, unless permanently sterile.
25. Participation in another interventional clinical trial that is either blinded or involves an investigational (not approved) product within three months before Baseline or during the course of the clinical study. Participation in observational clinical trials or open-label trials involving an approved product may be permitted after consultation with the medical monitor.

4.2 Prior and Concomitant Therapy

Details on medications taken prior to randomization and any concomitant medications taken during the study must be recorded in the electronic case report form (eCRF). The data that will be collected are summarized in Table 4.

Table 4: Categories of Concomitant Therapy

Category	Details to be collected	Timelines
Antibiotics	Names, dose, date of administration	Allowed for prophylaxis if started >4 weeks before randomization
SSRIs	Names, dose, date of administration	Allowed if started or dose changed >8 weeks before randomization
CBT	Date of administration	Allowed if started >8 weeks before randomization and unchanged
NSAIDs	Names, dose, date of administration	Required as premedication only for infusions but not for treatment of PANS/PANDAS
Vaccines	Name, date of administration	Live virus vaccine allowed if administered >2 weeks before IMP and >3 months after last IMP infusion
Other concomitant medication	Name, date of administration	Within 28 days before randomization and during the study

4.2.1 Permitted Concomitant Therapy

Review of all concomitant medications and doses, and other interventions will be obtained at each study visit. Parents and patients will be advised to avoid the addition of new psychosocial or medical treatments such as e.g. probiotics, herbal remedies, over the counter medicine, supplements or antioxidants (e.g. N-acetyl cysteine – shown to decrease compulsions) during the double-blind phase, unless deemed medically necessary.

Application of a topical numbing agent is allowed prior to any intervention with a needle (blood draw or IMP administration).

Prescribed medication(s) and over the counter medications not listed as prohibited in Section 4.2.2 are allowed. In addition, permitted concomitant treatments include:

- Antibiotics for prophylaxis if started more than four weeks before randomization and the dose and frequency remain unchanged over the course of the study;
- CBT if started more than eight weeks before randomization and the frequency and intensity of treatment remains unchanged over the course of the study;
- Stimulants for ADHD if started more than four weeks before randomization and the dose and frequency remain unchanged over the course of the study;
- CBD/CBM-containing agents without THC if started more than eight weeks before randomization and the dose and frequency remain unchanged over the course of the study;
- NSAIDs as premedication to alleviate possible side effects of Panzyga infusions or as a short-term treatment (single doses over a few days) for the management of AEs, excluding the disease under study (PANS/PANDAS);
- SSRIs if started more than eight weeks before randomization and the dose remains unchanged over the course of the study;
- Prophylaxis for TEEs, if deemed necessary by the investigator, is allowed as a precautionary measure and should follow standard of care. Its use must be documented.

4.2.2 Forbidden Concomitant Therapy

Administration of forbidden concomitant therapy as listed below does not automatically trigger patient withdrawal; the patient will be moved from the per protocol analysis set to the intent-to-treat set (see Section 9.2.1). The following medications or therapies are not permitted during participation in this study:

- Immunosuppressive agents
- Antibiotics (unless given per protocol Section 4.2.1);
- CBT (unless applied per protocol Section 4.2.1);
- SSRIs (unless given as allowed per protocol Section 4.2.1);
- Mood stabilizers (e.g. Depakote, Lamotrigine, Lithium)
- Psychotropic medication for OCD, anxiety or tic disorder (e.g. alpha-2 agonists or antipsychotics), unless given in single doses prior to blood draws or infusions and after completion of psychiatric evaluations when dealing with agitated patients (e.g. one-time doses of Lorazepam);
- Stimulants for ADHD (unless given per protocol Section 4.2.1);
- THC-containing agents;
- CBD/CBM-containing agents without THC (unless applied given per protocol Section 4.2.1);
- NSAIDs (unless given per protocol Section 4.2.1);

- Immunoglobulin treatment other than Panzyga. Patients will be withdrawn from study treatment if IgG preparations other than Panzyga are administered;
- Other blood or plasma-derived products;
- Plasma exchange procedures, plasmapheresis;
- Known nephrotoxic medication;
- Live attenuated vaccines such as measles, rubella, mumps and varicella;
- Any experimental drug;
- Melatonin.

4.3 Withdrawal and Replacement of Patients

4.3.1 Premature Patient Withdrawal from the Study

Patients have the right to withdraw from the study at any time for any reason, without the need to justify their decision. The investigator also has the right to withdraw patients in case of AEs, poor compliance, or other reasons. Since an excessive rate of withdrawals can render the study non-interpretable, any unnecessary withdrawal of patients should be avoided.

For any withdrawals after study entry, the investigator will obtain all the required details and document the reason(s) for discontinuation in the eCRF. If the reason for withdrawal of a patient is an AE, the main specific event or laboratory test will be recorded in the eCRF, and the investigator will make thorough efforts to clearly document the outcome.

Patients who terminate the study prematurely are considered drop-outs. The investigator will schedule an Early Termination Visit, which is identical to the Week 18 Visit procedures.

Other reasons for premature termination of patients may be:

- Withdrawal of patient's consent.
- Pregnant and lactating patients will be immediately excluded from the study.
- Investigator's opinion that the patient may be severely harmed if he/she continues study participation, namely by the treatment and procedures requested by the study protocol.
- Patients do not comply with the study protocol.

4.3.2 Premature Patient Withdrawal from Study Treatment

Patients may be withdrawn from study treatment for the following reasons:

- Occurrence of a condition or disease that interferes with the study treatment or represents an exclusion criterion.
- Administration of IVIG other than Panzyga. All patients who received at least one dose of the study treatment should be followed up per protocol until the study end without administration of the study product.

- Occurrence of an AE or SAE, which in the opinion of the investigator, precludes further treatment with study medication (Section 7.3.2).

If a patient shows worsening of their symptoms based on CGI-Improvement ratings, they will be presented to the site PI for review and treatment planning. Patients for whom worsening continues at a minimal level ("5" or "mildly worse") for an extended period of six weeks (2 visits) or moderately or greater level ("6" or "7"; much worse or very much worse) since last visit (up to three weeks) will be considered for premature withdrawal from the study drug and administration of appropriate standard of care treatment unless clinical interventions using approved study procedures and/or mediations have a reasonable likelihood to improve symptoms. Patients who experience an emergency worsening of symptoms may at the discretion of the site clinician be withdrawn from the study drug at any time to obtain necessary standard of care treatment. In addition, patients who develop exclusionary criteria (e.g. bipolar disorder, suicide attempt) will be withdrawn from the study drug and will receive appropriate standard of care treatment. All patients withdrawn from the study drug prematurely will be asked to continue the study as planned with modification of the study schedule (e.g. IMP administration and related to it safety lab tests will be omitted). Details of concomitant mediations and procedures administrated per standard of care will be captured in patient case reports.

The eCRF will contain an End of Treatment and an End of Study page. The End of Treatment page will record whether the patient will be followed up per protocol, to allow for correct patient status tracking and to provide the reason for the drug withdrawal.

4.3.3 Patient Replacement Policy

There will be no patient replacement in this study, but enrollment will continue until it is foreseeable that the number of patients required (according to the possible adaptations and the revised sample size determined at the interim analysis) for the evaluation of the primary endpoint will be achieved with the currently enrolled patients. 'Foreseeable' in this context means that the required number of evaluable patients will be achieved if the drop-out rate at the time remains unchanged for the remainder of the study.

4.4 Assignment of Patients to Treatment Sequences

Patients will be identified by unique codes, including the site identification number and a sequence number assigned by an electronic system in strict order of enrollment. Randomization will be managed centrally by means of an interactive response technology (IRT) system and ensure balanced allocation of the patients to the two randomization arms within the defined strata. The fact that a patient has been randomized will be reported immediately and automatically to the investigator, the contract research organization (CRO) and the Sponsor.

Randomized patients are not permitted to re-enroll under any circumstance.

4.5 Protocol Deviations

Deviations from the protocol should be avoided. If deviations occur, the investigator should promptly inform the monitor and the implication of the deviation must be assessed and discussed. Any deviation must be documented, stating the reason and date and the action taken. The documentation must be kept in the investigator's study file and the Sponsor's study master file. A complete list of all critical, major and minor deviations will be compiled and regularly updated by the Project Manager and provided for preparation of the Clinical Study Report (CSR).

In case of any critical/major protocol deviation, the investigator and Octapharma will decide on the further participation of the patient in this study after having discussed all relevant aspects.

Examples of critical/major protocol deviations are:

- Patients who entered the study even though they did not satisfy the entry criteria.
- Patients who received the wrong treatment or incorrect dose (also see Section 5.4).
- Patients who received forbidden concomitant medication.

4.6 Subsequent Therapy

All patients who leave the study – be it prematurely or per-protocol (PP) – will continue PANS treatment as per the discretion of the investigator.

5 INVESTIGATIONAL MEDICINAL PRODUCT(S)

5.1 Characterization of Investigational Product(s)

Panzyga and placebo (0.9% w/v sodium chloride) will be referred to as Investigational Medicinal Products (IMP).

Panzyga is a 10% IVIG ready for IV administration. Panzyga is produced from a pool of at least 1000 donations of human fresh frozen plasma per batch. The large donor pool ensures that the product contains a broad range of antibodies directed against pathogens and foreign antigens, which is far more diverse than that of plasma from an individual donor. Donor plasma sampling, the manufacturing of the product and the measures to ensure the product's viral safety are subject to strict regulations laid down by regulatory authorities. Octapharma exclusively uses plasma that has been tested by nucleic acid testing techniques.

During the manufacturing process of Panzyga, significant viral reduction is obtained via a combination of [redacted] dedicated virus inactivation/removal steps. The composition with the most important ingredients and the biochemical characteristics are summarized in the IB [22].

For placebo, 0.9% w/v sodium chloride solution for intravenous infusion will be used. The placebo will be handled and monitored with the same diligence as Panzyga. Placebo and Panzyga should be stored and transported according to their respective product information. Conditions will be stated in the IMP Handling Manual.

5.2 Packaging and Labeling

The IMP will be labeled per each kit (container) with unique kit identifiers. Panzyga is delivered as ready-to-use solution in glass bottles. Placebo for intravenous infusion will be purchased and provided by Octapharma.

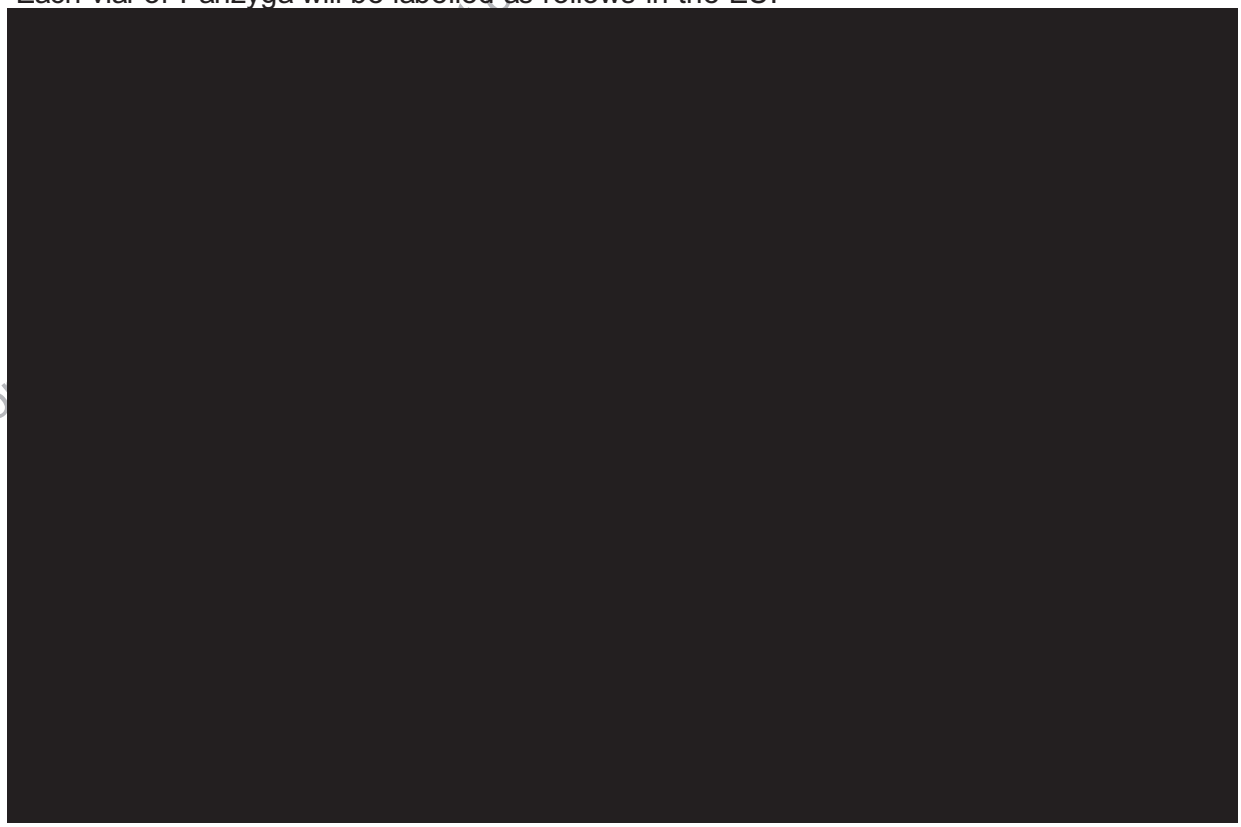
In order to prepare the infusion, IMP (Panzyga or placebo) is pooled into sterile and labeled infusion-bags (Polyvinyl Chloride (PVC)-free, Diethylhexylphthalate (DEHP)-free and latex–free). The IMP will be blinded with a labeled over-pouch (both the infusion bag and the over-pouch will be labeled). The blinded labels for infusion bags and over-pouches are provided below. Final labeling will be in compliance with the national requirements of each country where the study is to be conducted.

Each vial of Panzyga will be labelled as follows in the US:

Each bag of placebo will be labelled as follows in the US:

Blinding labels for infusion bags and over-pouches will be labelled as follows in the US:

Each vial of Panzyga will be labelled as follows in the EU:



Each bottle of placebo will be labelled as follows in the EU:

Blinding labels for infusion bags and over-pouches will be labelled as follows in the EU:

5.3 Conditions for Storage and Use

Panzyga should be stored and transported light-protected at +2 °C to +8 °C (36 °F to 46 °F) and must not be frozen. Panzyga must not be used after its expiration date.

Placebo solution should be stored and transported according to its product information between 2 °C (36 °F) and 25 °C (77 °F) and must not be frozen.

The authorized personnel will ensure that the IMP is stored in appropriate conditions with restricted access and in compliance with national regulations.

5.4 Dose and Dosing Schedule

Panzyga is available in glass bottles with different volumes of human immunoglobulin. Glass bottles of different volume should be combined in order to reach the required amount of IgG, based on the IRT assignment.

Body weight will be measured at each visit once before each cycle prior to IMP administration and entered into the IRT, which will calculate the required IMP dose for both day 1 and day 2 infusions.

All patients should be clinically assessed for being adequately hydrated prior, during, and after IMP administration. Prophylaxis for TEEs should be considered for patients with risk factors for TEE or patients in the early phase of diagnosis as a precautionary measure. Please refer to Section 4.2.1.

The initial infusion rate will be [redacted] mL/kg BW/min ([redacted]) and it may be progressively increased as tolerated by the patient also considering the tolerance level(s) of previous administrations [56]:

For infusion cycles 1 and 4 (when IMP is first given or switched at crossover [Figure 1]):

- [redacted]
- [redacted]
- [redacted]
- [redacted]

For infusion cycles 2, 3, 5, and 6 (when the same IMP is repeatedly administered during the same phase of the crossover design [Figure 1]):

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Importantly, the progressive increase in infusion rates is only intended in patients who can tolerate it. There is no obligation to increase the infusion rate to [redacted] mL/kg BW/min in all patients. Assuming a maximum infusion rate of [redacted] mL/kg BW/min, the duration of one infusion applied according to the rates described above is [redacted] (hr:min). Patients must be observed for any symptoms at least once throughout the infusion period and at least one hour thereafter (Section 5.5). In patients at risk of thromboembolic adverse reactions and acute renal failure (such as hypertension, history of thrombotic episodes, patients with prolonged periods of immobilization, concomitant nephrotoxic medication, diabetes mellitus, overweight, hypovolemia), IMP should be administered at the minimum rate of infusion practicable.

The total dose for a single infusion cycle will be 2 g/kg BW (1 g/kg BW daily for two consecutive days). Patients will receive three infusion cycles at three-week intervals in the first phase of the study, followed by three additional infusion cycles at three-week intervals in the second blinded crossover phase of the study (patients previously in the Panzyga arm will be assigned placebo and patients previously in the placebo arm will be assigned Panzyga, administered at the same regimen).

If a patient is assigned placebo, the same volume and infusion rate as would have been applied in case of 2 g/kg BW Panzyga administration should be used. Therefore, placebo (0.9% w/v sodium chloride) will be administered at a dose of 20 mL/kg BW given over two consecutive days.

If AEs occur during the infusion, the infusion rate will be reduced to half the rate at which the event occurred, or the infusion will be interrupted until symptoms subside. The infusion may then be resumed at a rate tolerated by the patient. The administration of Panzyga 10% or sodium chloride 0.9% w/v must be completed within 8 hours after preparation. In case additional IMP is needed (e.g. lost or damaged), a separate IMP assignment via IRT transaction needs to be accomplished.

5.5 Preparation and Method of Administration

Each bottle of Panzyga and each bag of placebo must be examined visually by the site staff for particulate matter and discoloration prior to administration. Non-homogenous solutions or those that have a deposit must not be used.

IMP must be allowed to warm to room or body temperature prior to administration.

Patients must be monitored before IMP infusion, observed for any symptoms at least once throughout the infusion period and at least one hour thereafter.

Panzyga solution for IV infusion must not be mixed with other medicinal products or saline. For other IV products, a separate IV line must be used.

The special warnings and precautions for Panzyga use (see IB) must be followed

5.6 Blinding and Breaking the Study Blind

Study personnel blinded to treatment assignment will not have access to unblinded information until the study is formally unblinded.

The investigators will be provided with an unblinding procedure to disclose the actual treatment of a particular patient in case of medical emergency; this will be done through the IRT system.

To maintain blinding, infusions will be given in blinded infusion bags (corresponding to a volume of 2 g/kg BW Panzyga per cycle or placebo at each infusion day as tolerated by the patient, or by investigator's discretion).

The infusion bag is then blinded with a non-transparent over-pouch. The non-transparent over-pouch will be put over the infusion bag to maintain blinding. Both containers (infusion bag and over-pouch) will be re-labeled with a blinding label. The blinding label will be stuck on by the unblinded hospital pharmacist or designee.

The blinding labels will be identical for both Panzyga and placebo, so that the content of the bags is only known to the unblinded hospital pharmacist or designee. The unblinded hospital pharmacist or designee will send the infusion bag(s) per patient (potentially already fixed to the non-transparent infusion line) to the ward.

Infusion bags, over-pouches, labels, and non-transparent infusion lines/transparent lines with sleeves will be provided to the site.

To further ensure the blinded character of the study, the investigator or designee who applies the medication to the patient will not be involved in any other study procedures other than drawing blood samples or checking for vital signs, i.e. will not be involved in any patient ratings

or AE assessments. In an effort to protect the blinding of key efficacy ratings, the independent evaluator who completes clinician efficacy ratings (CY-BOCS) will not have knowledge of or access to adverse event reports.

The patient will be blinded with respect to study treatment throughout the study.

Emergency patient unblinding will be managed in the IRT system. In the event an investigator needs to unblind a study patient due to a medical emergency or for necessary medical reasons, authorized study personnel at the site will log into the IRT to request access to the unblinded randomization code for the patient in question. In order to do so, the investigator will have to acknowledge the serious circumstances that require unblinding. Upon taking these steps, the dedicated web-based system will then provide the investigator with the specific treatment arm for that patient. Upon finalization of the unblinding request, an email notification of this action will automatically be sent to appropriate management and safety officials acknowledging the patient unblinding without providing the specific treatment arm.

5.7 Treatment Compliance

5.7.1 Drug Dispensing and Accountability

Any IMP provided to the site will be accounted for. Unblinded Drug Accountability Logs will be kept current by the unblinded site staff, detailing the dates and quantities of IMP received and assigned to each patient, and the remaining quantity.

The logs will be available to the unblinded study monitor to verify drug accountability during the study.

Investigational medicinal product can be destroyed at the study site or returned to the Sponsor depot for destruction. If possible, the original vial/bottle and the unblinded label will be discarded only after study drug reconciliation by the unblinded study monitor. The unblinded study monitor confirms the verification of the usage as described in the IMP Handling Manual.

Unused and expired IMP will be verified by the unblinded study monitor and destruction or return has to be confirmed in writing by the Sponsor prior to the transfer of the product.

5.7.2 Assessment of Treatment Compliance

All patients will be infused at the study site under the surveillance of authorized study personnel. Infusion details will be documented together with the unique kit numbers and batch number(s) in the IRT system, which will be checked regularly by the unblinded study monitor.

6 STUDY CONDUCT

Patients and legal representative(s)/guardians(s) have to be informed about the study details and have to give their written informed consent/assent. If patients are old enough to understand the risks and benefits of the study (as determined by each institution), they should provide written assent/consent. A written informed consent must be obtained by the investigator or trained healthcare professional and signed by the investigator before the start of any screening activities.

[redacted] Investigators must have received and reviewed the latest available laboratory results from the previous visit before initiating the next infusion cycle. Additionally, if a peripheral line is used for drawing blood, it must be flushed thoroughly.

Prior to randomization, patients will be screened for eligibility (inclusion and exclusion criteria) and to determine the baseline characteristics used for stratification (prophylactic use of antibiotics, treatment with stable dose of SSRIs during enrollment, and PANS/PANDAS disease subtype).

Screening procedures should be completed within 28 days before randomization. Based on the screening results, the patients' eligibility for the study is determined. To ensure the blinded character of the study, the investigator or designee who applies the medication to the patient will not be involved in any other study procedures other than drawing blood samples or checking for vital signs, i.e. will not be involved in any patient ratings or AE assessments.

The total time for the first study visit during an infusion cycle will be approximately 6-7 hours whereas the second infusion day will last for approximately 5 hours. Overnight stay at the study site between the two infusions will be at the discretion of the investigator.

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6.1.1 [redacted]

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6.1.2 [redacted]

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6.1.3 [redacted]

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6.1.4 [redacted]

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6.1.5 [redacted]

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6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The duration of the first double-blind treatment phase (Panzyga vs. placebo) will be nine weeks. The duration of the second double-blind crossover phase will also be nine weeks. Thus, the overall study duration will be 18 weeks, plus up to 28 days from Screening to randomization

The study will be considered completed when all patients have completed the end of follow-up or Early Termination Visits.

6.2.2 Premature Termination of the Study

Both the investigator and the Sponsor reserve the right to terminate the study at any time. In this event, any necessary procedures for orderly study termination will be arranged after review and consultation by both parties. In terminating the study, the Sponsor and the investigator will ensure that adequate consideration is given to the protection of the patients' interests.

In addition to the ongoing safety monitoring and periodic IDMC data review, the following rule will be implemented to apply temporary suspension of study drug administration, pending a safety investigation, for an unacceptable increased venous TEE or acute renal failure risk in the Panzyga group compared to the placebo group:

- For both venous TEEs or acute renal failures, the event risk will be calculated separately as (number of events reported)/(number of infusions) in both randomization arms, and the 90% confidence interval for the resulting risk ratio ($R_{Panzyga}/R_{Placebo}$) will be determined by means of the /relrisk option of the SAS procedure FREQ. In case no Events are observed in the placebo group, 1 will be added to each cell in the 2X2 table to enable this risk ratio evaluation. The stopping rule will be triggered if the lower confidence limit is greater than 1.0.
- This stopping rule will be applied whenever an unblinded evaluation is done, and a total of 30 or more infusion cycles have been administered.
- For the first 30 infusion cycles a fixed rule was applied by the IDMC to temporary suspend study drug administration in case the number of related serious TEEs or acute renal failures as assessed by IDMC in the Panzyga group was twice the number in the placebo group. If no TEE or acute renal failure was observed in the placebo group during this initial study phase, temporary suspension of study drug administration and safety investigation was initiated if two related serious TEEs as assessed by IDMC or acute renal failures had been reported in the Panzyga group.

Regulatory authorities and IECs/IRBs should be informed in accordance with national regulations.

6.2.2.1 Early Termination of the Entire Clinical Study

At any time, the study as a whole may be terminated prematurely if:

- New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk-assessment.
- Requested by the competent authorities.

6.2.2.2 Early Termination at an Individual Study Center

At any time, the study may be terminated at an individual center if:

- The center cannot comply with the requirements of the protocol.
- The center cannot comply with GCP standards.
- The center's first patient is not recruited within 24 weeks after initiation of the center.
- The expected recruitment rate is not met.

Should the study be prematurely terminated, all study materials (completed and partially completed eCRFs, IMP, etc.) must be returned to the Sponsor. IMP could be also destroyed at the site according to the local procedures.

7 ASSESSMENTS AND METHODS

7.1 Demographic and Baseline Information

The following information will be recorded during Screening:

7.1.1 Demographic and baseline characteristics

[redacted]

7.1.2 Medical history and prior/concomitant medications

[redacted]

7.1.3 Physical examination

A physical examination should include [redacted]

Any abnormality identified at Baseline should be recorded in the General Medical History and Baseline Conditions eCRF.

Targeted physical examinations should be limited to systems of primary relevance and will only be carried out to follow-up any significant medical condition identified at Screening.

Changes from baseline abnormalities at subsequent visits should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as AEs in the Adverse Event eCRF.

7.1.4 Laboratory parameters

[redacted]

7.2 Efficacy Assessments

7.2.1 Assessments for Primary Efficacy Endpoint(s)

To study improvement of neuropsychiatric symptomatology and behavior in PANS/PANDAS patients, mean changes in the total CY-BOCS score from Baseline to Week 9 will be compared between Panzyga and placebo treatment to demonstrate superiority. The following measurement scores on obsessive-compulsive symptoms will be recorded in investigator-led interviews:[redacted]

As described in Section 3.3.3, the CY-BOCS yields a total obsession score, a total compulsion score and combined total score (maximum total CY-BOCS score = 40).

7.2.2 Assessments for Secondary Efficacy Endpoint(s)

To assess behavioral changes, durability of improvement of neuropsychiatric symptomatology and behavior in PANS patients will determined with the clinician-rated CY-BOCS score. The mean change in total CY-BOCS score from Week 9 to Week 18 within the (Panzyga – Placebo)

treatment sequence group will be assessed to demonstrate that no statistically significant increase occurred in this period.

[redacted]

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- [redacted]
- [redacted]
- [redacted]

7.3 Safety Assessments

7.3.1 Assessments for Exploratory Safety Endpoints

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[redacted]

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7.3.2 Adverse Events (AEs)

7.3.2.1 Definitions

- **Adverse event (AE):** An AE is any untoward medical occurrence in a study patient which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.
- **Adverse drug reaction (ADR):** An ADR is any noxious and unintended response to an IMP related to any dose. The phrase 'response to an IMP' means that a causal relationship between the IMP and an AE carries at least a reasonable possibility, i.e., the relationship cannot be ruled out.
- **Other significant AEs:** Any marked laboratory abnormalities deemed clinically significant or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction, or significant additional concomitant therapy.

- **Withdrawal due to AE/ADR:** AE/ADR leading to discontinuation of treatment regardless of treatment arm. Any such events will be followed up by the investigator until the event is resolved or until the medical condition of the patient is stable. All follow-up information collected will be made available to the Sponsor.

7.3.2.2 Collection of AEs

Adverse events will be collected throughout the study from the date of informed consent until the last study visit (end of study) and SAEs will be collected a further four weeks after last IMP dose if the site becomes aware of the event (no proactive monitoring).

The condition of the patient will be monitored throughout the study from the moment that informed consent has been given. During each visit, whether scheduled or unscheduled, AEs will be elicited using a standard non-leading question such as "How have you been since the last visit/during the previous study period?" Adverse events should be collected from the moment that informed consent has been given and at each subsequent visit.

Any AE or ADR which occurs during the study will be noted in detail in the appropriate pages of the eCRF. If the patient reports several signs or symptoms representing a single syndrome or diagnosis, the diagnosis should be recorded in the eCRF. The investigator will grade the severity of all AEs or ADRs (mild, moderate, or severe), the seriousness (non-serious or serious), and the causality as defined in Sections 7.3.2.3, 7.3.3, and 7.3.2.4. The Sponsor is responsible for assessing the expectedness of each ADR (expected or unexpected) as defined in Section 7.3.2.5.

In the event of clinically significant abnormal laboratory findings, the tests will be repeated as deemed necessary by the treating physician and the patient followed up until the laboratory values have returned to normal and/or an adequate explanation for the abnormality has become available.

Diseases, signs and symptoms, and/or laboratory abnormalities already present before informed consent will not be considered AEs unless an exacerbation in intensity or frequency (worsening) occurs.

Fluctuations of PANS/PANDAS symptoms will not be considered untoward medical occurrences and will not be reported as AEs if the investigator deems them to be within the expected range of normal symptom fluctuation or if they do not require concomitant medications or procedures.

The investigator will provide detailed information about any abnormalities and about the nature of and reasons for any action taken as well as any other observations or comments that may be useful for the interpretation and understanding of an AE or ADR.

7.3.2.3 Severity of AEs

The intensity/severity of AEs will be graded as follows:

- **Mild:** an AE, usually transient, which causes discomfort but does not interfere with the patient's routine activities

- **Moderate:** an AE which is sufficiently discomforting to interfere with the patient's routine activities
- **Severe:** an AE which is incapacitating and prevents the pursuit of the patient's routine activities

The grading of an AE is up to the medical judgment of the investigator and will be decided on a case-by-case basis.

7.3.2.4 Causality of AEs

The relationship of AEs to the administered IMP will be assessed by the investigator:

- **Probable:** reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the patient's clinical state.
- **Possible:** reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.
- **Unlikely:** reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the patient's clinical state or by environmental factors or other therapies administered.
- **Not related (unrelated):** events for which sufficient information exists to conclude that the etiology is unrelated to the IMP.

7.3.2.5 Classification of ADRs by Expectedness

ADRs will be classified by the Sponsor as either expected or unexpected:

- **Expected:** an ADR that is listed in the current edition of the IB.
- **Unexpected:** an ADR that is not listed in the current edition of the IB, or that differs because of greater severity or greater specificity.

7.3.2.6 Outcome of AEs

The outcome of all reported AEs has to be documented as follows:

1. Recovered, resolved
2. Recovering, resolving
3. Not recovered, not resolved
4. Recovered, resolved with sequelae

5. Fatal
6. Unknown

NOTE: A patient's **death** per se is not an event, but an outcome. The event which resulted in the patient's death must be fully documented and reported, even in case the death occurs within four weeks after IMP treatment end and regardless of whether or not it is considered treatment-related.

7.3.2.7 Action(s) taken

AEs requiring action or therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment in an emergency situation.

The action taken by the investigator must be documented:

General actions taken in the event of an AE

- None
- Medication (other than IMP) or other (e.g., physical) therapy started
- Test performed
- Other (to be specified)

IMP-related actions taken in the event of an AE

- Dose Not Changed
- Dose Reduced
- Drug Interrupted
- Drug Withdrawn
- Not Applicable
- Unknown

The investigator will follow up on each AE until it has resolved or until the medical condition of the patient has stabilized. Any relevant follow-up information will be reported to the Sponsor.

7.3.3 Serious Adverse Events (SAEs)

A **serious AE (SAE)** is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (see below),
- requires hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is another important medical event.

NOTE: The term 'life-threatening' refers to an event in which the patient was, in the view of the reporting investigator, at immediate risk of death at the time of the event; it does not refer to an event which may hypothetically have caused death had it been more severe.

In deciding whether an AE/ADR is serious, medical judgment should be exercised. Thus, important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definitions above should also be considered serious.

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent should be reported as SAE. A suspected virus transmission means that virus antigen has been detected in the patient. A passive transmission of antibodies alone does not constitute a suspected virus transmission.

7.3.4 SAE Reporting Timelines

All SAEs, whether or not they are suspected to be related to study treatment, are to be reported within 24 hours after recognition of the event.

To report the SAE, the SAE form needs to be completed electronically in the electronic data capture (EDC) system for the study without delay and within 24 hours of awareness. When the form is completed, the Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the EDC system cannot be accessed, either an email needs to be sent to Medpace Safety at [redacted] or the Medpace SAE hotline (phone number listed below) has to be called, and the completed paper SAE form has to be faxed/emailed to Medpace (fax number listed below) without delay and within 24 hours of awareness. A confirmation of the submission of the SAE form has to be filed in the investigator study file. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information:

Medpace Clinical Safety

E-mail: mailto:[redacted]

Medpace SAE hotline – USA:

Telephone: [redacted]

Facsimile: [redacted]

Medpace SAE hotline – Europe:

Telephone: [redacted]

Fax: [redacted]

Follow-Up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g. subject discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail to ensure continuous safety monitoring. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

All SAEs, whether or not they are suspected to be related to study treatment, will be submitted by Medpace Clinical Safety to:

Octapharma's Corporate Drug Safety Unit

OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.

Oberlaaer Strasse 235, 1100 Vienna, Austria

Fax: [redacted]

E-mail: [redacted]

24 hours emergency telephone number: [redacted]

In parallel, the Clinical Project Manager or designee will be notified by Medpace Clinical Safety.

Waivers from SAE Reporting Requirement

The following exceptions are not considered SAEs for this study:

- hospitalizations due to infusions on consecutive days (e.g. for patients with long travel hours);
- surgeries that are elective or were planned before study entry;
- prolongation of existing hospitalizations for non-medical reasons.

The sponsor/designee will report all relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening as soon as possible to the FDA and all applicable European competent authorities in all participating countries concerned as well as to the IRB/IEC and in any case no later than seven days after knowledge by the sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within additional eight days.

All other SUSARs will be reported to the FDA and all applicable European competent authorities in all participating countries concerned as well as to the IRB/IEC as soon as possible but within a maximum of 15 days of first knowledge by the sponsor/designee.

The sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation. The sponsor/designee will also inform all investigators as required per local regulation.

7.3.5 Adverse Events of Special Interest (AESI)

The following AEs are defined as AESI:

- thromboembolic events (TEEs);
- hemolytic transfusion reactions (HTRs).

For these AESI, the general definitions and procedures that are described in Section 7.3 also apply. These AESI must be reported as SAEs as described in Section 7.3.4.

7.3.5.1 Thromboembolic Events (TEEs)

There is clinical evidence of an association between IVIG administration and TEEs [22], such as ischemic stroke, transient ischemic attack, cerebral infarction, cerebrovascular accident, cerebral thrombosis, embolic infarctions, [acute] myocardial infarction, deep vein thrombosis, pulmonary embolism, venous thrombosis.

As a component of the assessment of AE, the investigator will be questioned regarding the occurrence of TEEs. These are defined according to the Standardized Medical Dictionary for Regulatory Activities query (SMQ) "Embolic and thrombotic events". Thromboembolic events will be reported as SAEs. All TEEs must also be recorded in the AE page of the eCRF. If TEEs are suspected at any time during the study, appropriate examinations according to local standards should be performed (e.g. Doppler scan using color duplex, X-ray) and the results documented. Therapeutic measures managing suspected TEEs shall be initiated according to local clinical practice (e.g. anticoagulation).

7.3.5.2 Hemolytic Transfusion Reactions (HTRs)

Hemolytic transfusion reactions can develop subsequent to IVIG therapy; IVIG-related hemolysis is associated with passive transfer of anti-A and anti-B hemagglutinins. Hemolytic transfusion reactions will be reported as SAEs.

Hemolytic transfusion reactions will be monitored at each visit (see Flow Chart of Assessments):

- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

The results of these additional tests and any clinical signs or symptoms potentially related to hemolysis will be documented in the patient's medical record.

Therapeutic measures managing suspected HTRs shall be initiated according to local clinical practice.

7.3.6 Laboratory Tests

The following laboratory parameters will be investigated during the study at the time points specified in Section 6.

[redacted]

[redacted]

7.3.7 Viral Safety Tests

[redacted]

7.3.8 Vital Signs and Physical Examination

[redacted]

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g. high blood pressure), only the diagnosis (i.e. hypertension) should be recorded in the Adverse Event eCRF.

Physical examinations will be performed at the visits specified in Section 6.1. [redacted]

Targeted physical examinations should be limited to significant medical conditions identified at Screening. Changes from baseline abnormalities at subsequent visits should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as AEs in the Adverse Event eCRF.

7.3.9 Other Relevant Safety Information

a. Post-study related safety reports

Any SAE which occurs up to four weeks after the last IMP administration should be reported by the investigator to the Sponsor in case the investigator becomes aware of it (see Section 7.3.4). Proactive monitoring for post-study SAEs is not required.

In case a post-study SAE is identified, the investigator should complete an SAE form and also state the relation to the clinical study in the report.

Deaths occurring within four weeks after the last IMP administration should also be reported, regardless of whether or not they are considered treatment-related.

b. Pregnancies

Clinical experience with immunoglobulins suggests that no harmful effects are to be expected on the course of pregnancy, or on the fetus and the neonate, or on fertility. As such, no contraception measures are needed for male subjects with a pregnant or non-pregnant WOCBP partner.

Every effort will be made to avoid a pregnancy during the use of an IMP. For WOCBP, if the patient is unwilling to use a protocol-recommended method of contraception from Screening throughout the study treatment period and for four weeks following the last dose of study drug, this constitutes an exclusion criterion. Pregnancies occurring during the study (fetal exposure to the IMP) need to be reported. Women of childbearing potential using an acceptable effective contraceptive method during the study will be enrolled. Pregnancy tests will be completed at Screening. A WOCBP is defined as a fertile woman, from the beginning of menstruation, unless permanently sterile. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Acceptable effective contraceptive measures include the following:

- combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion

- vasectomized partner
- sexual abstinence
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide

In case of pregnancy during the study, the investigator should complete the Pregnancy Notification Form and send or fax it to Medpace within 24 hours of becoming aware of the pregnancy (see Section 7.3.4).

Follow-up information on the outcome of both mother and fetus will be requested by a Sponsor representative.

c. Overdose, interaction, and medication error

The following safety relevant information should be reported as an AE or, if the reaction fulfills one of the criteria for seriousness, as a SAE.

d. Drug overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than the known therapeutic dose that is of clinical relevance. The reaction must be clearly identified as an overdose.

e. Drug interaction

A drug interaction is a situation in which a substance or medicinal product affects the activity of an IMP, i.e., increases or decreases its effects, or produces an effect that none of the products would exhibit on its own. The reaction must be clearly identified as a drug interaction.

f. Medication error

A medication error involves the inadvertent administration or unintended use of a medicinal product, which may be caused by the naming, presentation of pharmaceutical form/packaging, or instructions for use/labeling. The reaction must be clearly identified as a medication error.

7.4 Other Assessments

7.4.1 Drug Concentration Measurements

[redacted]

[redacted]

The concentration data will be used to characterize the extent of exposure and the fluctuation thereof over the course of treatment in all patients, by measuring the following parameters (details are provided in the statistical analysis plan [SAP]):

- C_0: trough concentration prior to the first infusion
- C_{max}: maximum observed concentration
- C_{min}: minimum observed concentration
- T_{max}: time of C_{max} (anticipated within one hour after completion of the third infusion cycle)
- T_{min}: time of C_{min} (anticipated at baseline before the first infusion of the first cycle)
- C_{max} recovery: concentration gain over the total treatment, i.e. level within 60 minutes after completion of the third infusion cycle *minus* C_0
- Trough fluctuation between/across cycles: increase in the levels before each infusion cycle over the course of the three cycles

Of note, infusion lines need to be flushed thoroughly before withdrawing blood for PK analyses.

In summary, the PK data will primarily be used to describe the fluctuating exposure to Ig throughout treatment and within the three infusion cycles (each including two IVIg infusions) in relation to the endogenous baseline levels at the start of treatment. In addition, for the PK-subset of [redacted] patients with three extra blood samples, the objective is to build individual mechanistic constructs and to derive PK measures that might correlate with these fluctuations.

7.4.2 Blood Sample for Biomarkers

Blood samples will be collected from patients who have consented for biomarker sampling. Please refer to Section 6.1 and flow charts (Table 1 and Section 15.2 for Europe) for timepoint details.

7.5 Appropriateness of Measurements

The measurements selected in this study are appropriate to verify the superior clinical efficacy of Panzyga vs placebo and the efficacy of Panzyga to improve psychiatric symptoms. The selected endpoints for this study rely on validated tools and study parameters that have been used in this study population (see Section 3.3.3).

- Considerable data support the reliability and validity of the pediatric version of the CY-BOCS scale
- The CGI rating scales are commonly used measures of symptom severity, treatment response and the efficacy of treatments in clinical trials of patients with mental disorders

- The COIS-R is a specific and commonly used measure of OCD-related impairment [46, 47].
- The PTQ is widely used, correlates highly with the YGTSS, and is supported by use in intervention trials [49].
- The SNAP-IV Parent scale has been used in children and has served as a primary outcome measure in a number of medication trials
- The C-SSRS interview has been validated in pediatric patients [55, 60] and has been used as a primary outcome in several pediatric clinical trials [61, 62].

All assessments except CY-BOCS can be carried out by the treating investigator, to prevent unblinding. A strategic central reader system has been established that serves as an independent expert panel to standardize reliability on the study's primary outcome measure (CY-BOCS). Standardization will also include a training program to ensure that all raters from different sites are reliable and remain so throughout the trial. To overcome rater variability as far as possible, the CY-BOCS rater should remain the same person. For the clinical interview scales CY-BOCS and MINI-KID, the rater should meet the following credentials: MD/DO with Board Certification or Board Eligible in Child/Adolescent Psychiatry or related discipline or PhD/PsyD with a degree in clinical psychology or related discipline. The clinical raters should also have significant clinical experience with psychiatric interviews and working with children with PANS and should remain the same throughout the study.

As discussed, for added safety monitoring, enrollment was be paused after the first [redacted] patients have been randomized and enrolled in the study, for a planned IDMC review of unblinded safety and PK data, including IgG trough levels. Enrollment resumed only after IDMC data review of the first [redacted] patients had been completed, and the IDMC had recommended to continue enrollment in the study. In addition, after [redacted] patients have completed blinded treatment (Visit Week 9), an interim review of the preliminary safety and efficacy data will be conducted by IDMC. At this timepoint, the IDMC will independently evaluate all data accrued in this pivotal study to provide a statement on whether emerging data confirm the prospect of direct benefit and positive risk-benefit ratio for PANS patients treated with Panzyga. IDMC confirmation will justify the submission to concerned Health Authorities of the additional study protocol(s) evaluating other dose regimens of Panzyga treatment in patients with PANS. The actual numeric results will not be shared with the Sponsor or Investigators to ensure that bias will not affect subsequent study decisions since the data of the first [redacted] patients will be included in the final statistical analysis. Details will be provided in the IDMC Charter.

In addition to the ongoing safety monitoring and periodic IDMC data review, study drug administration will be temporarily suspended, pending a safety investigation, in the event of an unacceptable increase in any AE the Panzyga group compared to the placebo group, with particular emphasis on TEEs and HTRs.

As specified by the EMA and the FDA, safety evaluation will include monitoring of short-term tolerance (blood pressure, heart rate, temperature, and monitoring of other AEs) at repeated intervals following IVIG infusion. All AEs that begin during or within 72 hours after an infusion will be classified and analyzed as infusional AEs. Adverse events will be evaluated with regard

to the infusion rates [57, 63]. The safety evaluation will also include a measure of suicidal ideation (C-SSRS), as recommended by the FDA for drug trials in patients with psychiatric symptoms [64].

A pre-treatment serum sample and one at the end of the study from each patient included in the clinical study will be stored at -70 ˚C for possible future testing [63].

The effect of passive transmission of blood group antibodies will be evaluated by searching for hemolysis and performing a direct antiglobulin test (direct Coombs' test). In addition, routine hematology and serum chemistry tests will be obtained at Baseline and at the Week 9/Early Termination Visit.

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records, allowing reconstruction and evaluation of the clinical study.

The investigator will maintain adequate source records (e.g., case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations. Any copies of the source documents should be certified according to the current legislation.

For each patient enrolled, the investigator will indicate in the source record(s) that the patient participates in this study.

All data entered in the eCRF must be supported by source data in the patient records.

The investigator will permit study-related monitoring, audit(s), IEC/IRB review(s), and regulatory inspection(s), by providing direct access to the source data/records.

The investigator may authorize site staff (e.g., sub-investigators, nurses) to enter study data into the eCRF. This must be documented in the Delegation of Authority Log signed by the investigator.

8.1.2 Electronic Case Report Forms

For each patient enrolled, an eCRF will be completed within the Electronic Data Capture (EDC) system and approved by the investigator.

Study site staff (e.g., research nurse) will be responsible for entering patient data into the validated EDC system. All site personnel will be trained on the EDC system and study specific eCRFs prior to receiving access to the live database for data entry.

The site is also provided with the approved eCRF Completion Guidelines, which will assist in data entry and data issues/questions. The site will be notified once the database is active to begin data entry. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or change eCRF data must be listed in the Delegation of Authority Log.

8.1.3 Changes to Electronic Case Report Form (eCRF) Data

Monitors will perform source data verification as defined for the study.

If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated programmatically within the EDC system, and 'manual' queries will be generated by either the study monitor or Data Management.

Discrepancies and queries can only be corrected by the investigator(s) or other authorized site personnel. An audit trail documents all changes to the data over the entire study period. If the reason for a change is not obvious, a comment must be supplied in the query's response, stating the reason for the change, prior to closing. The study monitor should provide guidance to investigator(s) and the investigator(s)' designated representatives on making such corrections.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks are performed and programs are run throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, source data verification will be confirmed as complete by the study monitor, and all eCRFs will be approved by the investigator prior to database lock.

8.2 Information to Investigators

An IB will be provided to the investigator before the start of the study. The IB contains all information in the Sponsor's possession necessary for the investigator to be fully and accurately informed about the safety of the IMP under evaluation and the respective benefit-risk ratio.

The IB will be updated by the Sponsor at regular intervals and whenever relevant new information concerning the IMP becomes available.

The investigator will be informed about the methods for rating relevant study outcomes and for completing eCRFs to reduce discrepancies between participating investigator and study sites.

The investigator will be kept informed of important data that relate to the safe use of the IMP as the study proceeds.

8.3 Responsibilities

The principal investigator is accountable for the conduct of the clinical study. Responsibilities may be delegated to appropriately qualified persons.

A Delegation of Authority Log will be filled in and signed by the principal investigator. In accordance with this authority log, study site staff (e.g., sub-investigators, nurses) is authorized to perform tasks relating to the study.

All parties involved in the study are responsible to comply with local and international obligations, regulatory requirements and duties in accordance with local laws, GCP and Good Laboratory Practice guidelines, standard operating procedures (SOPs) and other applicable regulations.

8.4 Investigator's Site File

At each study site, the investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (e.g., copies of the protocol, study approval letters, all original informed consent forms, site copies of all eCRF pages, drug dispensing and accountability logs, correspondence pertaining to the study, etc.) should be filed accurately and kept by the investigator for the maximum period of time required by local regulations.

The investigator is responsible for maintaining a confidential patient identification code list, which provides the unique link between named source records and eCRF data for the Sponsor. The investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the investigator and the Sponsor. Should the investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.5 Provision of Additional Information

On request, the investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records, ensuring that the patient's confidentiality is maintained. This is particularly important when eCRFs are illegible or when errors in data transcription are encountered. In case of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the patient's confidentiality is protected in accordance with applicable regulations.

8.6 Independent Data Monitoring

8.6.1 Strategic Central Reader System

A team of expert advisors, who are clinical psychologists or neuropsychologists with extensive experience (e.g. clinical experience with individuals with neuropsychiatric disorders) and expertise in the administration and scoring of the test will be deployed by the Sponsor. This deployment will allow ongoing feedback on errant administration and scoring practices. The feedback may include recommendations on how to address scoring errors, reminders of best practices, and —in the worst cases— recommendation that the rater receive remedial training. The following central monitoring modalities will be applied:

- Source document review
- Review of audio recordings that are obtained during the CY-BOCS interviews

This central reader process serves to minimize errors over time and increase assessment accuracy and data quality.

The members of the central reader system must not actively recruit patients.

The central reader process will be developed before study start to serve as the central reference document for this procedure.

In addition to the central reader system described above, a central rating panel will be introduced for sites that are unable to provide qualified experts for rating the CY-BOCS and MINI-KID scales.

8.6.2 Independent Data Monitoring Committee

An IDMC will be established by the Sponsor. The IDMC will be composed of recognized experts in the fields of pediatric immunology, neurology, psychiatry and statistics, respectively, who are not actively recruiting patients. Enrollment was discontinued after the first six patients had been enrolled in order to enable a planned IDMC review of unblinded safety and PK data. Enrollment resumed only after the IDMC data review of these first six patients had been completed at Week 6 (Cycle 3), and the IDMC had recommended to continue enrollment into the study. Thereafter, IDMC meetings will be scheduled on a quarterly basis.

The IDMC will review relevant data periodically during the study and will give advice on the continuation, modification, or termination of the study. A written study-specific procedure will define in detail the composition, responsibilities, and procedures of the IDMC.

The IDMC will have the following responsibilities:

- to review relevant safety data periodically;
- to review TEEs and HTRs in a timely fashion;
- to give advice on the continuation, modification, or termination of the study.

A Charter will be prepared before study start and will define in detail the composition, responsibilities, and procedures of the IDMC.

8.6.3 Steering Committee

A Steering Committee will be appointed by the Sponsor. This committee will be composed of investigators, other experts in immunology, neurology, and psychiatry, and representatives of the Sponsor.

The Steering Committee will be responsible, among others, for the scientific integrity of the study, maintaining the quality of study conduct, scientific quality of any protocol amendments and the final study report, and providing input to or co-authoring publications.

9 STATISTICAL METHODS AND SAMPLE SIZE

The statistical analysis will be delegated under an agreement of transfer of responsibilities to an external CRO. All Octapharma procedures and policies have to be met by this CRO. Discrepancies or exceptions are to be approved by the Sponsor's Manager of Biometrics.

9.1 Determination of Sample Size

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

9.2 Statistical Analysis

[redacted]

[redacted]

9.2.1 Populations for Analysis

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.2.2 Efficacy Analysis Plan

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

9.2.3 Safety Analysis Plan

[redacted]

- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

9.2.4 Handling of Missing Data

[redacted]

9.3 Randomization, Stratification, and Code Release

[redacted]

[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

9.4 Interim Analysis

[redacted]

[redacted]

10 ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical/Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an IEC/IRB and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP guidelines, and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (e.g., CRO) as required by national law.

10.2 Approval of Study Documents

The study protocol, a sample of the patient information and informed consent form, any other materials provided to the patients, and further requested information will be submitted by the Sponsor or the investigator to the appropriate IEC/IRB and the Regulatory Authority. The study must be approved by the IEC/IRB and the Regulatory Authority before any IMP may be shipped to the study sites and any patient is exposed to a study-related procedure.

The Sponsor, the investigator, and any third party (e.g. CRO) involved in obtaining approval must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

10.3 Patient Information and Informed Consent

The investigator or trained healthcare professional experienced in working with pediatric populations will obtain freely given assent from each patient and written consent from patients or legal representative(s)/guardians(s) where applicable after justifying why this pediatric population needs to be investigated in the trial by presenting an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study which is relevant to the patient's decision to participate, in a way adapted to their age and maturity. If the patient is considered old enough according to local requirements, the informed consent form must be signed, with name and date and time noted by the patient, before the patient is exposed to any study-related procedure, including screening tests for eligibility. Of note, the optional blood collection for central storage will be the subject of a separate informed consent for secondary use of personal data.

For patients not qualified to give legal informed consent, written consent must be obtained from the legal representative(s)/guardians(s). Patients and legal representative(s)/guardians(s) must be given the opportunity to ask questions.

The investigator or trained healthcare professional will explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify. The investigator or trained healthcare professional will complete the informed consent section of the eCRF for each patient enrolled.

Each patient will be informed that his/her medical (source) records may be reviewed by the study monitor, a quality assurance auditor, or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

All patient-related procedures will be described in informed consent forms and assent forms (where applicable). The information given to the subject and to his or her legally designated representative will be collected in the Investigator study file.

If site or IRB/EC requires both legal representative(s)/guardians(s) to consent, the second legal representative/guardian informed consent can be obtained remotely (e.g. by telephone) as per country regulatory requirements. The remote consent process needs to be documented in the source documents. Remote informed consent will be acceptable under the condition that an adequate exchange of information has taken place, to ensure that the signee of the consent form is the legally authorized representative of the subject. Remote informed consent will allow the investigator and potential participant to engage in the informed consent process in a way that is similar to what would be conducted in-person under usual circumstances. The remote consent process will be prospectively reviewed and approved by the IRB/EC.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Co-ordinating investigator and the Sponsor prior to its implementation. Any such amendments will be submitted to the any competent IEC/IRB and/or competent authority responsible as required by applicable regulations.

IEC/IRB approval will, at a minimum, be requested for any change to this protocol which could affect the safety of the patients, the objective/design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Patient Data

The investigator will ensure that the patient's confidentiality is preserved. On eCRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient identifier. Documents not intended for submission to the Sponsor, i.e., the confidential patient identification code list, original consent forms, and source records, will be maintained by the investigator in strict confidence.

10.6 Protection of Patient Data

The investigator, the Sponsor and its representatives will ensure that a potential or actual personal data breach will be immediately (and at the latest within 24 hours of awareness of the incident) notified to the corporate data protection team of the Sponsor ([redacted]), including a detailed description of the incident. The notification shall be made in accordance with the Sponsor's incident reporting guidance and by using the latest reporting template, indicating the circumstances of the data incident type and amount of personal data involved in the incident. The notification will also report the action

taken to contain or control the incident, estimate the potential harm for the affected individual, and describe the changes that will be implemented to prevent or reduce the risk of a reoccurrence. The Sponsor will investigate all reported incidents to confirm whether a personal data breach has occurred. If a personal data breach is confirmed, the Sponsor will follow the relevant authorized procedure based on the criticality and quantity of the personal data involved.

Potential or actual information security breaches will also be brought immediately (and at the latest within 24 hours of the awareness of the incident) to the attention of the corporate information security team of the Sponsor by using the following e-mail address: [redacted].

10.7 Risk Mitigation Plan in Response to the COVID-19 Pandemic

The Sponsor will continuously monitor and evaluate the development of the COVID-19 pandemic in the areas of study sites to determine if any measures need to be implemented to mitigate undue risks to the subjects or in response to local governmental recommendations. Because patients are required to be on site for administration of the IMP, there is no risk mitigation plan in place. Measures may include temporarily halting further recruitment. Any measure would be communicated to the relevant competent authority and IRB/EC.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The study monitor will contact and visit the investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries compared to source data. The investigator will co-operate with the study monitor to ensure that any discrepancies identified are resolved.

The study monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the eCRFs, including all laboratory results.

11.2 Audit and Inspection

The investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IEC/IRB/regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and efficacy of the IMP have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A CSR (in accordance with relevant guidelines and the Sponsor's SOPs) will be prepared by the Sponsor after completion of the study. The Co-ordinating investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study may be published or presented at scientific meetings.

If this is envisaged by an investigator, the investigator agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor prior to submission to an editorial board or scientific review committee. This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multi-center studies only in their entirety and not as individual center data. Authorship will be determined by mutual agreement.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a patient in association with the IMP or participation in the study, the Sponsor will contract insurance in accordance with local regulations.

The investigator is responsible for dispensing the IMP according to this protocol and for its secure storage and safe handling throughout the study.

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15 APPENDICES

15.1 Blood Draw Guidelines

The latest EMA guideline (Ethical considerations for clinical trials on medicinal products conducted with minors, dated 18 September 2017) states that the blood sampling volume related to the clinical studies has to be minimized and justified. In general, blood loss should not exceed 3% of total blood volume (TBV) over 4 weeks and it should not exceed 1% of TBV at any single time [59].

The following table shows the acceptable blood volumes for different age ranges:

Body weight (kg)	Circulating total blood volume (mL)	Maximum allowable sample volume over 4 weeks (mL) - 3% of total blood volume	Maximum allowable sample volume at single time (mL) - 1% of total blood volume
12–20	960–1600	28.8–48.0	9.6–16.0
20–30	1600–2400	48.0–72.0	16.0–24.0
30–70	2400–5600	72.0—168.0	24.0–56.0

Maximum allowable research-related blood sample volumes. Total blood volume is approximately 80-90 ml/kg body weight. Of note: when routine health care requires significant blood sampling, these maximums may even be excessive

Expected blood volume collections for patients ≥20 kg will be maximum 16 mL at single time and 48 mL over four weeks. Expected blood volume collection <20 kg will be maximum 12.8 mL at single time and 38.4 mL over four weeks. Following Exclusion Criterion 4 (Section 4.1.2) and the associated Centers for Disease Control and Prevention growth chart, no patients with body weight <16 kg are expected to be enrolled in the study.

15.2 Flow Chart of Assessments for Europe

1. [redacted]
2. [redacted]

3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7. [redacted]
8. [redacted]
9. [redacted]
10. [redacted]
11. [redacted]
12. [redacted]
13. [redacted]
14. [redacted]