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Clinical Study Protocol

Version: 7.0

Date: 14-Nov-2022

NCT Number: NCT04502030

Title: Double-blind, Randomized, Placebo-controlled, Prospective Phase III Study Evaluating Efficacy and Safety of Panzyga in Primary Infection Prophylaxis in Patients with Chronic Lymphocytic Leukemia ("PRO-SID" Study)

Study Number: NGAM-12

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CLINICAL STUDY PROTOCOL

DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PROSPECTIVE PHASE III STUDY EVALUATING EFFICACY AND SAFETY OF PANZYGA IN PRIMARY INFECTION PROPHYLAXIS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA ("PRO-SID" study)

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Investigational Product:	Immune Globulin Intravenous, Human 10% (Panzyga)
Indication:	Primary infection prophylaxis in patients with chronic lymphocytic leukemia (CLL) and secondary hypogammaglobulinemia
Study Design:	Double-blind, randomized, placebo-controlled prospective, multicenter, interventional phase III clinical study
Sponsor:	Octapharma Pharmazeutika Produktionsges.m.b.H. Oberlaaer Str. 235, 1100 Vienna, Austria
Study Number:	NGAM-12
EudraCT Number:	2019-004375-40
IND Number	19414
Development Phase:	Phase 3
Planned Clinical Start:	Quarter 3 2020
Planned Clinical End:	Quarter 4 2024
Date of Protocol:	14 November 2022
Version:	7.0
Co-ordinating Investigator:	Prof. Oliver A. Cornely MD, FACP, FIDSA Director Translational Research Institute CECAD Cluster of Excellence University of Cologne Kerpener Str. 62 50937 Cologne, Germany

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STUDY OUTLINE

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H.	
Name of Investigational Product: Panzyga	**Protocol Identification Code:** NGAM-12 (PRO-SID)
Name of Active Ingredient: Immune Globulin Intravenous, Human 10%	**Date of Final Protocol:** 14-Nov-2022

Title of Study:

Double-blind, Randomized, Placebo-controlled, Prospective Phase III Study Evaluating Efficacy and Safety of Panzyga in Primary Infection Prophylaxis in Patients with Chronic Lymphocytic Leukemia ("PRO-SID" study)

Indication:

Primary infection prophylaxis in patients with chronic lymphocytic leukemia (CLL) and secondary hypogammaglobulinemia

Number of Study Center(s):

Approximately 70 centers (North America, Europe, Turkey, and Russia)

Objectives:

Primary Objective:

The primary objective of this study is to demonstrate the benefit of Panzyga administration compared with placebo as primary infection prophylaxis in CLL patients with secondary immunodeficiency (SID) undergoing CLL antineoplastic therapy.

Secondary Objectives:

The secondary objectives of this study are to compare the following aspects in CLL patients with SID treated with and without primary Panzyga prophylaxis:

- Overall infection rate
- Frequency of prophylaxis with anti-infectives (antibacterials and antivirals)
- Duration of prophylaxis with anti-infectives (antibacterials and antivirals)

Exploratory Objectives:

The exploratory objectives of this study are to compare the following aspects in CLL patients with SID treated with and without primary Panzyga prophylaxis:

- Time to first major infection
- Overall mortality and mortality attributed to infection

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- Duration of anti-infective treatment
- EQ-5D quality of life (QoL) assessments
- Relationship between efficacy outcome (major infections, overall infection rate) and infection risk factors
- Infections by the categories used in the primary endpoint definition
- Proportion of subjects with one or more microbiologically-documented infection, overall as well as by infection type (Viral/Bacterial)
- Occurrence of COVID-19
- Deaths attributable to COVID-19

To determine the PK profile of Panzyga in CLL patients with SID.

To evaluate the minimum target IgG trough level for infection prophylaxis in CLL patients with SID.

Safety Objective:

To evaluate the product safety of Panzyga administration

Pharmacoeconomic Objectives:

To compare health economic effects in CLL patients with SID treated with and without primary Panzyga prophylaxis for the study duration. Secondary data usage is planned for pharmacoeconomic modeling.

Study Design:

Double-blind, randomized, placebo-controlled, prospective, multicenter, interventional phase III clinical study.

Number of Patients:

A minimum of 240 adult patients of any gender are to be enrolled and allocated 1:1 to one of the treatment arms.

For a subgroup of approximately 40 patients (at least 18 patients from the Panzyga arm) PK samples will be collected.

Patient Selection Criteria:

Inclusion Criteria:

1. Treatment-naïve or relapsed/refractory CLL patients undergoing CLL antineoplastic treatment. Diagnosis of B-cell CLL established according to International Workshop

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on Chronic Lymphocytic Leukemia (iwCLL) criteria and documented within medical records.
2. Hypogammaglobulinemia (IgG levels <5 g/L) as confirmed by the Central Laboratory.
3. ≥18 years of age.
4. Voluntarily given, fully informed written and signed consent obtained before any study-related procedures are conducted.

Exclusion Criteria:

1. IgG treatment within 3 months prior to Screening.
2. Antibiotic prophylaxis and/or treatment within 7 days prior to Baseline (with the exception of trimethoprim-sulfamethoxazole [TMP/SMX], diaminodiphenyl sulfone [dapsone] and pentamidine inhalation).
3. Current major infection or >1 major infection in the previous 6 months before Baseline.
4. History of anaphylaxis or severe systemic response to immunoglobulin, blood or plasma-derived products or any Panzyga component.
5. History of a non-CLL malignancy or other medical condition with life-expectancy of less than two years.
6. Severe liver disease, with signs of ascites and/or hepatic encephalopathy.
7. Severe kidney disease (as defined by estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2).
8. Body weight >140 kg.
9. Eastern Cooperative Oncology Group (ECOG) performance score of >2 (Appendix 1).
10. Female patients of childbearing potential unwilling to use a protocol-required method of contraception (as per protocol section 7.3.9 b) from the Screening Visit throughout the study treatment period and for 30 days following the last dose of study drug.
11. Human immunodeficiency virus (HIV) infection at Screening (defined for the study as positive HIV antibody test).
12. Patients found to be chronic carriers of hepatitis B virus (HBV), defined by positive surface antigen (HBsAg), positive Hepatitis B core antibodies (HBcAb) and/or low HBV titers, who will not receive targeted antiviral therapy while undergoing CLL therapy, and patients with active HBV, defined as high HBV titers.
13. Uncontrolled hepatitis C infection at Screening (defined for the study as positive hepatitis virus C [HCV] polymerase chain reaction [PCR]).
14. Pregnant and lactating women.
15. Subjects with a history of thromboembolic events (TEE) such as deep vein thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease (Fontaine IV) within 6 months before Baseline.

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16. Planned or ongoing immunosuppressive treatment (other than for CLL or corticosteroids) or other forbidden medication during the entire study duration after study enrollment.
17. Participation in another interventional clinical trial that is either blinded or involves an investigational (not approved) product within 3 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.
18. Known IgA deficiency with antibodies to IgA (as part of the patient´s medical history).
19. Known blood hyperviscosity, or other hypercoagulable states.
20. Patients unable or unwilling to understand or comply with the study protocol.

Test Product, Dose, and Mode of Administration:

Panzyga is an intravenous (IV) 10% immunoglobulin (IVIG) formulation ready for 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 in the Panzyga treatment arm will receive 0.4 g/kg (4 mL/kg) per single infusion every 4 weeks in addition to the standard of care (SoC) infection prophylaxis. SoC infection prophylaxis may depend on the practice of the participating center, including, but not limited to SARS-CoV-2 vaccine, influenza vaccine, pneumococcal vaccine, hematopoietic growth factors, antimicrobials, and antivirals.

Patients are randomly assigned to either one of the following treatment arms (1:1):

- SoC plus Panzyga
- SoC plus placebo

In order to obtain valid results and because of differences in treatment approaches in different countries, the study population will be prospectively balanced by geographic region.

Similarly, because of the potential effect on the endpoint of the CLL therapy and CLL disease stage, patients will be prospectively balanced according to treatment-naïve (in case patient is randomized at the start of or during the first line CLL antineoplastic therapy) or relapsed/refractory status, and into the following CLL treatment groups:

- Chemoimmunotherapy and anti-CD20 containing regimens
- Small molecule inhibitors
- Other treatment

Duration of Treatment:

The duration of the entire study for each patient will be up to 60 weeks and consists of the following segments: up to 8 weeks for screening, 48 weeks of treatment, then 4 weeks of follow-up.

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Reference Therapy, Dose, Mode of Administration,

Patients in the placebo arm will receive 4 mL/kg 0.9% w/v sodium chloride solution per single infusion every 4 weeks in addition to SoC infection prophylaxis.

Study Outcome Parameters (Primary and Secondary Endpoints):

Efficacy Parameters:

Primary: Occurrence of major infections in CLL patients with or without primary infection prophylaxis with Panzyga. Each potential infection will be assessed by an independent endpoint adjudication board (IEAB) consisting of clinical experts. All adjudications will be conducted in a blinded manner and the IEAB will be provided with all relevant details. The IEAB will have the right to downgrade/upgrade any infections based on the agreed process. A detailed description of the information to be provided to the IEAB will be developed with the clinical experts and will be included in an IEAB charter.

Major infection for this trial is defined as:

- Bacterial and/or viral infections resulting in death. Confirmed cases of COVID-19 are excluded.
- Bacterial and/or viral infections, which are microbiologically documented (MDI) or clinically documented (CDI) requiring treatment with anti-infectives; upper respiratory tract infections, bronchitis, lower urinary tract infections, localized skin infections and stomatitis (MDI or CDI) are considered major only if they require treatment with anti-infectives AND hospitalization or hospitalization prolongation. Confirmed cases of COVID-19 are excluded.
- Fever of unknown origin (FUO) requiring hospitalization or hospitalization prolongation

Secondary:

- Overall infection rate: infection rate for all infections.
- Frequency of prophylaxis with anti-infectives (antibacterials and antivirals)
- Duration of prophylaxis with anti-infectives (antibacterials and antivirals)

Exploratory Parameters:

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

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[redacted]

Safety Parameters:

[redacted]

Pharmacoeconomic Parameters:

[redacted]

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[redacted]

Study Procedures:

Patients are enrolled during the CLL antineoplastic treatment (during the period starting from 1 week before the 1st cycle till 2 weeks after start of the last cycle of a treatment line). For the study purposes cycle is defined as 28 calendar days in case continuous treatment.

Patients eligible after screening will be randomized 1:1 to receive either up to 13 infusions of Panzyga or Placebo every 4 weeks in addition to the SoC prophylaxis throughout the planned study duration. The study assessments and scheduled time points are summarized in the Flow Chart following this Study Outline. In the event that patients experience ≥2 major infections, IMP treatment will be stopped and they will receive secondary infection prophylaxis according to local standard of care. Such patients will stay in the study till Week 52 regardless at what visit they stopped treatment with IMP and will undergo all study procedures with the exception of IMP administration and related safety evaluations.

Statistical Analysis Plan:

A formal statistical analysis plan describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor.

The reported incidence of infections in patients with hematologic malignancies ranges between 20 and 50%. Of note, infection rates in patients with hypogammaglobulinemia are much higher and reported to be between 25 and 85% in CLL patients.

Most studies suggest a 4-fold reduction of infectious complications by IVIG. From this, our initial expectations for the proportions of patients with a primary infection would be around 20% for patients without prophylactic IVIG, and between 5% and 10% for patients with prophylactic IVIG. Our goal is to demonstrate superiority of Panzyga prophylaxis in preventing serious infections with an overall α of 0.025 (1-sided test) and a power of 80%.

Assuming the proportion of patients with a major infection is 7.5% in the Panzyga treatment arm and an adaptive study design with an interim look when 100 patients have provided evaluable data, then a sample size of approximately 240 patients would control overall type I error across interim and final analysis and ensure the desired power. Due to uncertainty in the assumed proportion of infections, sample size will be re-estimated at the interim stage up to a maximum of 450 patients. The interim analysis is intended for sample size recalculation. Patient recruitment will not be stopped after 100 patients have been randomized but will continue until at least 240 patients have been randomized. At the final analysis, the primary and secondary endpoints will be tested in the following fixed sequence:

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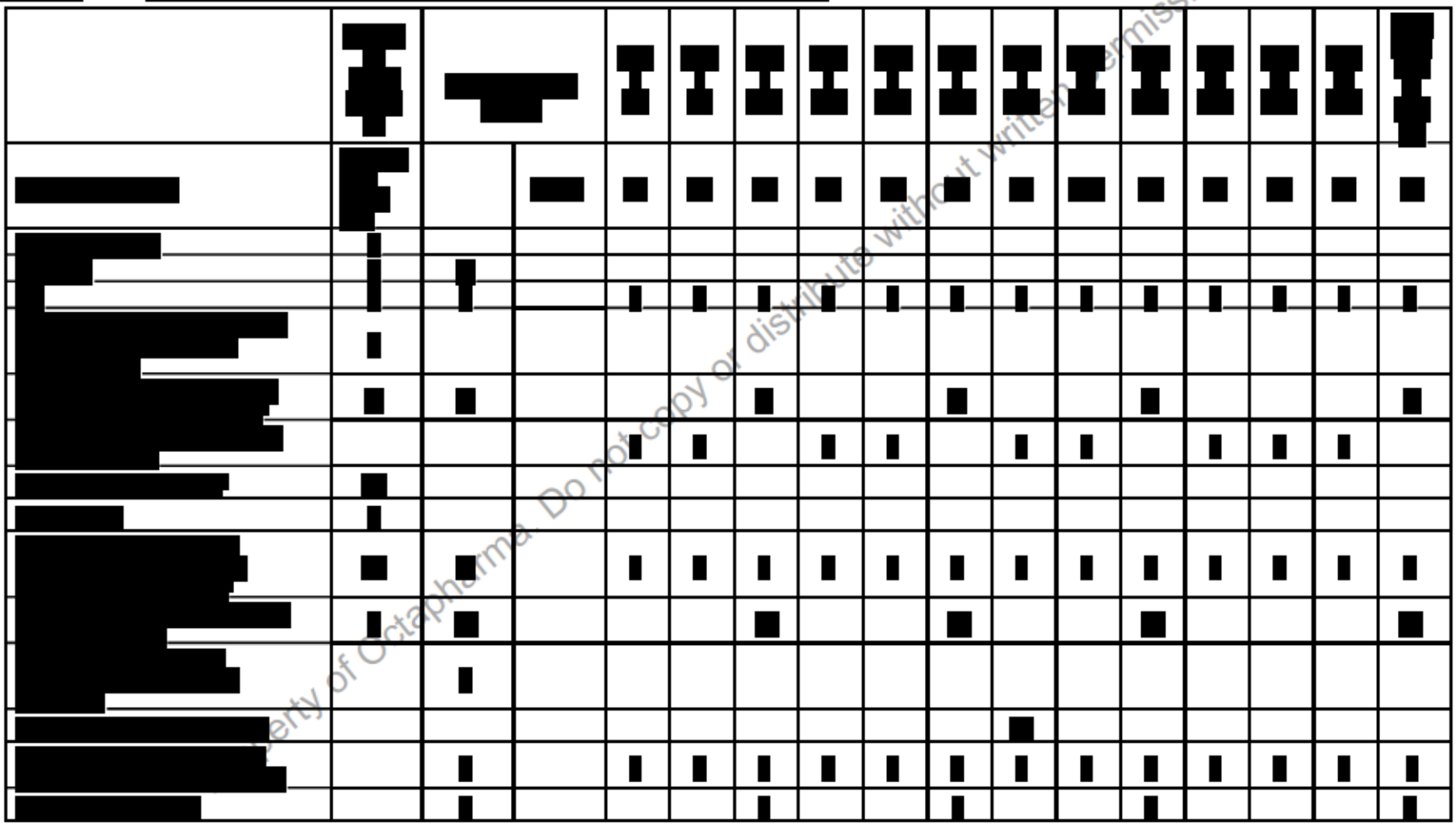
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1. Primary endpoint: Superiority of Panzyga with respect to the occurrence of major infections
2. 1st secondary endpoint: Superiority of Panzyga with respect to the overall infection rate
3. 2nd secondary endpoint: Superiority of Panzyga with respect to the frequency of prophylaxis with anti-infectives
4. 3rd secondary endpoint: Superiority of Panzyga with respect to the duration of anti-infective prophylaxis

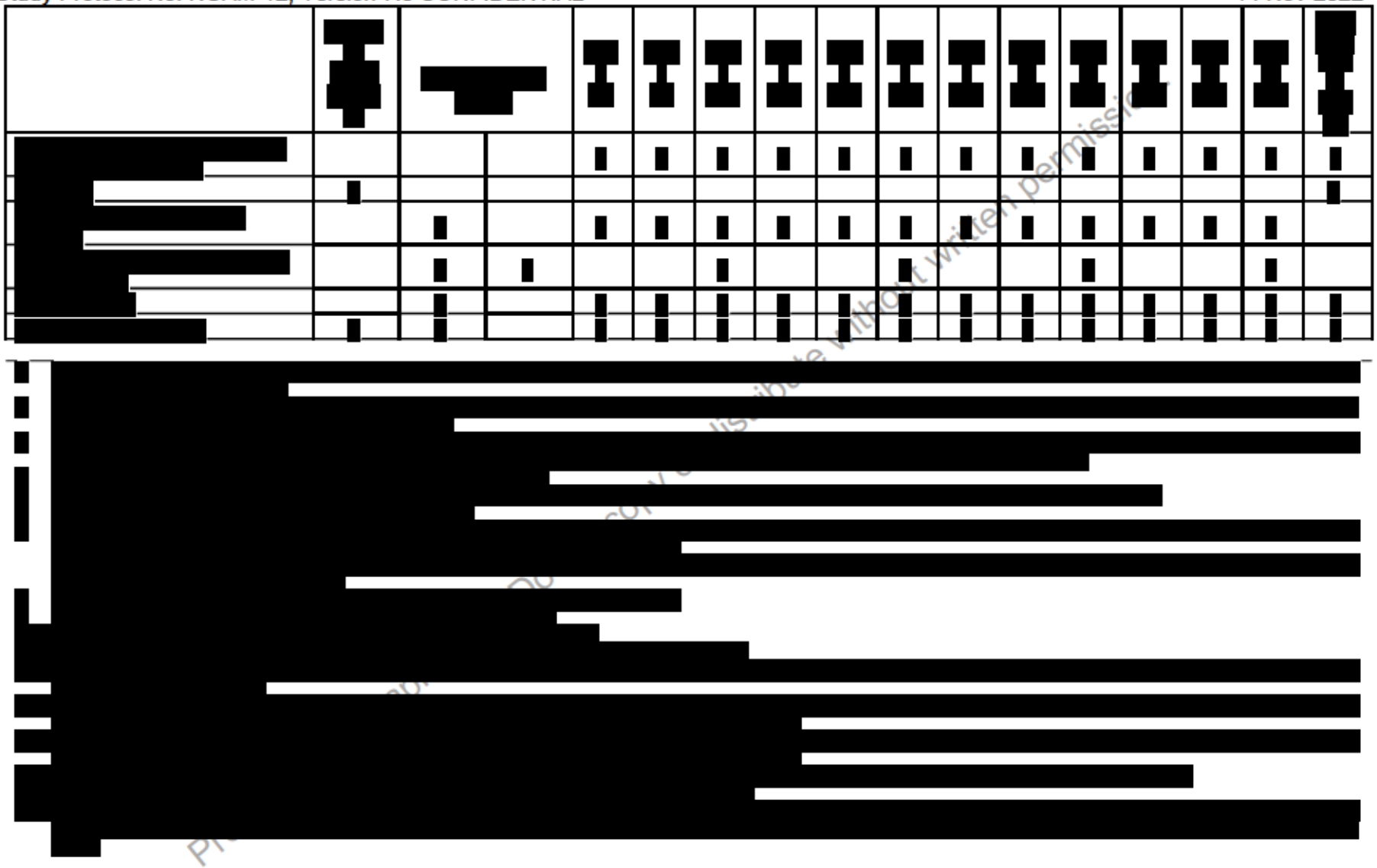
This will allow to test each pair of hypotheses at the alpha=0.025 level (1-sided) in this order, given that no preceding test failed, while preserving the overall type I error rate.

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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] [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.

[redacted] [redacted]

Co-ordinating Investigator Signature Date

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Description
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Events Of Special Interest
AUC_{0-t}	Area under the curve (time 0 to end of the dosing interval)
$AUC_{0-infinity}$	Area under the curve from time 0 extrapolated to infinity
CDI	Clinically Documented Infection
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CMV	Cytomegalovirus
CRO	Contract Research Organization
CSR	Clinical Study Report
C_{max}	Maximum observed plasma concentration
DNA	Deoxyribonucleic Acid
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
EBV	Epstein-Barr-Virus
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Association
EQ-5D	EuroQoL Five Dimension
ET	Early Termination
FAS	Full Analysis Set
FCR	Fludarabine, Cyclophosphamide, Rituximab
FDA	Food And Drug Administration
FUO	Fever of Unknown Origin
G-CSF	Granulocyte-Colony Stimulating Factor
GCP	Good Clinical Practice
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis Virus B
HCV	Hepatitis Virus C
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HTR	Hemolytic Transfusion Reactions
IB	Investigator's Brochure
IDMC	Independent Data Monitoring Committee
IEAB	Independent Endpoint Adjudication Board

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Abbreviation	Description
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous
IVIG	Intravenous Immunoglobulin
iwCLL	International Workshop On Chronic Lymphocytic Leukemia
LDH	Lactate Dehydrogenase
MDI	Microbiologically Documented Infection
OS	Overall Survival
PCP	Pneumocystis Pneumonia
PCR	Polymerase Chain Reaction
PE	Pulmonary Embolism
PK	Pharmacokinetic
PP	Per Protocol
QoL	Quality Of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SID	Secondary Immunodeficiency
SMX	Sulfamethoxazole
SoC	Standard Of Care
TEAE	Treatment-emergent Adverse Event
TEE	Thromboembolic Events
TMP	Trimethoprim
T_{max}	Elapsed time to C_{max}
VTE	Venous Thromboembolism
WOCBP	Women Of Childbearing Potential

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1 INTRODUCTION

Secondary immunodeficiency occurs, among other reasons, as a consequence of hematological malignancies. Infections are the main cause of morbidity and mortality in CLL patients. The pathogenesis of immune deficiency secondary to lymphoproliferative malignancy is multifactorial including disease- and treatment-related factors.[1] Patients with hematologic malignancies are at major risk for severe infections associated with substantial morbidity and mortality. Infections cause between 20 and 50% of deaths within the first year after diagnosis, depending on the underlying disease (CLL between 30 and 50%).[2-4] Hypogammaglobulinemia (low serum levels of IgG and IgA with variable IgM) contribute to the increased risk of infection in patients with hematologic malignancies like CLL. Upon diagnosis of hematologic malignancy, about 25% of patients present with hypogammaglobulinemia with incidence rates potentially increasing to up to 85% during course of disease,[2,3,5,6] and in particular during chemotherapy and/or immunomodulating treatments with recombinant monoclonal antibodies.

Recent advances in treatment have prolonged the duration of remission and the time between relapse phases in CLL patients. However, managing multiple relapses and the use of salvage therapies can lead to cumulative immunosuppression and a higher risk of infections. Supportive treatment, including early vaccination, anti-infective prophylaxis, and replacement immunoglobulin, plays a key role in preventing infections in CLL. Infection prevention by antibiotics is controversial due to potentially serious side effects such as increasing rates of multi-resistant pathogens,[7] but also due to untoward effect on the human microbiome.[8] Moreover, recent data reported at the 2019 Gastrointestinal Cancers Symposium suggested that cancer patients who received antibiotics within 60 days of starting immunotherapy were significantly less likely to respond to cancer treatment than those not receiving antibiotics.[9] Most anti-infectives exert toxic effects: quinolones are hepatotoxic,[10] TMP/SMX is hepatotoxic and allergenic,[11] antivirals are hepato- and hematotoxic,[12] and antifungals are hepatotoxic and prone to drug-drug interactions.[13] Vaccination is efficient in only some patients, but the strategy is underused, mostly because certain chemotherapy regimens hamper vaccine efficacy.[14]

Immunoglobulins have been used to provide antibodies for the prevention of viral and bacterial diseases in immunocompromised patients. Intravenous immunoglobulins (IVIGs) have exhibited an immunomodulatory effect in a wide variety of clinical conditions.[15-20] Panzyga is a 10% human normal immunoglobulin solution for intravenous administration (IVIG) developed by Octapharma. It is supplied as a ready to use liquid formulation.

The Panzyga manufacturing process achieves a significant viral reduction through a combination of two dedicated manufacturing process steps.[21,22] Panzyga complies with the latest international consensus on best practices for viral safety. The efficacy of the virus inactivation procedures has been extensively validated according to relevant international guidelines in place. Further information can be found in the current Investigator's Brochure.[23] ADRs reported for Panzyga were similar in type and intensity to those reported with other IVIG preparations. Panzyga is currently registered in [redacted], with the first marketing authorization granted in Germany in February 2016.[23]

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1.1 Rationale for Conducting the Study

IVIG are firmly established in secondary prophylaxis to reduce infectious complications in patients with hematological malignancies.[24-29] Several studies have proposed a role for IVIG prophylaxis in hypogammaglobulinemic patients with lymphoproliferative disorders,[25,28-36] but no randomized study has established IVIG efficacy as primary prophylaxis in CLL patients with SID. A systematic review and meta-analysis of randomized-controlled studies comparing prophylaxis with polyvalent IVIG vs. control in CLL and multiple myeloma reported a significant decrease in the occurrence of major infections, relative risk (RR) 0.45 (95% confidence interval [CI] 0.27–0.75) and a significant reduction in clinically documented infections, RR 0.49 (95% CI 0.39–0.61).[31]

In primary prophylaxis, IVIGs have not been systematically evaluated in well-designed clinical studies, and there is no gold standard for primary infection prophylaxis in CLL patients. For CLL patients, a 4-fold reduction of infections is expected.[26,28,37] Griffiths et al. showed a 1.8-fold reduction of serious infections in CLL patients (from 91.7% to 50.0% in 12 patients treated with placebo and IVIG).[27] These data result from a randomized crossover study with only 12 patients. Evaluating IVIGs in primary prophylaxis could not only extend the time to the first severe infection and reduce infection rates, but also antibiotic consumption.

Based on previous clinical evaluations, the most common major infections detected in CLL patients are pneumonia, upper respiratory tract infection, and septic shock.[29,38-42] Moreover, investigation of IVIG therapy in immunocompromized patients with fungal infections is limited to observational studies,[43] hence the choice of limiting investigations to bacterial and viral infections. Both microbiologically- and clinically-documented infections will be included in our analyses,[44] in order to ensure that a wide scope of infections are included (in clinical practice, microbiological pathogenesis is not proven in all cases or is often inaccessible to examination).[39,40]

The major causes of SID are hematological malignancies and their treatment,[1] inducing neutropenia, T-cell, and dendritic cell and natural killer cell disorders. Of note, B-cell dysfunction leads to hypogammaglobulinemia.[1,45-47] One strategy to reduce the risk of infection is the administration of immunoglobulins. Current guidelines promote the use of IVIG in CLL patients with hypogammaglobulinemia and recurrent infections,[48] but no IVIG is currently licensed for primary infection prophylaxis. We, therefore, propose CLL patients with secondary hypogammaglobulinemia as the population to be addressed by the primary endpoint within an evaluation of the benefit of primary prophylaxis by Panzyga.

This double-blind, randomized, placebo-controlled, prospective, multicenter, interventional Phase III clinical study will compare the number of patients with CLL undergoing CLL antineoplastic treatment and with secondary hypogammaglobulinemia who develop major infections with or without receiving prophylactic Panzyga in addition to SoC prophylaxis. Major infections or infection severity will not be graded based on the route of administration of antibiotic drugs or the need for hospitalization.[29,38,41] These criteria may not cover the range of infections considered important in assessing serious infections in CLL undergoing antineoplastic treatment. Patients undergoing chemotherapy may be unable to tolerate oral therapies for a variety of reasons that may be unrelated to the severity of the infection

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(nausea/emesis, gastrointestinal malabsorption, mucositis). Additionally, these criteria to categorize the severity of infections may not adequately cover the range of potential infections in this patient population. Therefore, an alternate grading system relevant to our study population and the definition of our endpoint was used. Infection severity will be graded by Investigators and then confirmed by an IEAB of clinical experts in a blinded manner. In order to cover the range of infections considered important in CLL patients undergoing chemotherapy, major infection for this trial is defined as (i) bacterial and/or viral infections resulting in death (confirmed cases of COVID-19 are excluded), (ii) MDI or CDI bacterial and/or viral infections requiring treatment with anti-infectives; upper respiratory tract infections, bronchitis, lower urinary tract infections, localized skin infections and stomatitis (MDI or CDI) are considered major only if they require treatment with anti-infectives AND hospitalization or hospitalization prolongation (confirmed cases of COVID-19 are excluded), (iii) FUO in requiring hospitalization or hospitalization prolongation.

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.

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1.2 Dose Rationale

According to published literature, patients with CLL respond to IVIG doses of 0.2 g/kg to 0.5 g/kg.[25,29,30,33] Egerer et al. consider IVIG replacement in patients with marked hypogammaglobulinemia (IgG <400 mg/dL) with more than two recent severe infections.[30] Low doses of IVIG were shown to be as effective as high doses in protecting CLL patients against infections, although a control group was not included.[33] In CLL patients with hypogammaglobulinemia (IgG <600 mg/dL), 0.3 g/kg IVIG every 4 weeks for 6 months resulted in a significantly lower incidence of infectious episodes.[29] According to Sklenar et al., the dosage recommendation in CLL patients is 0.4 g/kg every 3 weeks until week 12, when steady state is reached. The maintenance dose is 0.4 g/kg every 5 weeks.[25]

In the current study, patients in the Panzyga arm will receive 0.4 g/kg (4 mL/kg) per single infusion every 4 weeks in addition to SoC prophylaxis.

1.3 Benefit-Risk Statement

The risks of IVIG administration are well documented. In general, the incidence of AEs associated with IVIG tends to increase with the rate of infusion, and thus the recommended dosage, infusion rates, and monitoring procedures should be adhered to. Patients that are naïve to IVIG are more at risk than those that are well maintained and on regular therapy.

Patients with pre-existing risk factors for thrombotic events (such as advanced age, obesity, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilization, severely hypovolemic patients, patients with diseases which increase blood viscosity) may be at increased risk of developing TEEs.[23] Overdose is possible in overweight

and elderly patients and in those who have impaired renal function. In patients with signs of cerebral or cardiac ischemia, the increase in viscosity caused by an immunoglobulin infusion may be a risk.[23]

Patients with CLL may be at higher risk of developing TEEs.[49-54] Since 2013, IVIG products have carried a boxed safety warning about the risk of TEEs,[55] with TEEs reported in 0.5% to 15% of patients treated with IVIG (reviewed by Ammann et al.[49]). The risk of venous thromboembolism (VTE) and its effect on survival in CLL patients remains unclear. Gade et al. investigated the impact of patient-related factors, CLL prognostic markers, and CLL treatment on the risk of VTE and assessed OS relative to VTE based on data from the Danish National CLL Registry. During a median follow-up of 2.6 years, 92 VTEs occurred among 3609 CLL patients, corresponding to a total incidence rate of 8.2 VTEs per 1000 person-years (95% CI, 6.7–10.1). A history of VTE or second primary cancer was associated with hazard ratios (HRs) of VTE of 5.09 (95% CI, 2.82–9.17) and 3.72 (95% CI, 2.15–6.34), respectively. CLL patients with VTE had marginally higher mortality, which was most pronounced among patients <60 years of age (HR, 7.74; 95% CI, 2.12–28.29).[50] In a meta-analysis and systematic review, Wu et al. reported an incidence rate of VTE from 72 prospective studies comprising 9,061 patients of 5% (95% CI, 4–6%). The incidence rate of VTE in CLL was 3% (95% CI, 2–5%).[54]

Simkovic et al. retrospectively analyzed clinical and laboratory data of 346 consecutive patients with CLL followed up at one center and diagnosed between 1999 and 2011 (males, 64%; median age, 64 years; low/intermediate/high Rai modified risk in 41/47/12%). After a median follow-up of 72 months (range, 26–138), at least one episode of VTE occurred in 38 patients (11%). VTE developed after a median of 34 months from CLL diagnosis. Incidence of VTE was 1.67% per patient year of follow-up. There was a high proportion of unfavorable prognostic factors (advanced Rai stages, unmutated immunoglobulin variable heavy chain genes, and unfavorable cytogenetics) in patients with VTE. The most common risk factors for VTE besides age were corticosteroid therapy, other malignancies, and obesity.[51]

A retrospective cohort study of older patients with CLL or multiple myeloma identified from the Surveillance, Epidemiology, and End Results-Medicare Linked Database, assessed rates of clinically serious TEEs in 2724 new users of IVIG and a propensity-matched comparison group of 8035 non-users. The authors observed a transient increased risk of arterial TEE during the day of an IVIG infusion and the day afterward (HR 3.40; 95% CI, 1.25–9.25); this risk declined over the remainder of the 30-day treatment cycle. When considered in terms of absolute risk averaged over a 1-year treatment period, the increase in risk attributable to IVIG was estimated to be 0.7% (95% CI, -0.2%–2.0%) compared with a baseline risk of 1.8% for the arterial TEE end point. A statistically non-significant risk increase of 0.3% (95% CI: -0.4%, 1.5%) compared with a baseline risk of 1.1% was observed for venous TEE.[49]

Whittle et al. calculated the incidence rates for VTE in an unselected United Kingdom CLL clinic population at 1.45% per patient year.[53] Therefore, special emphasis will be given to the occurrence of TEEs.

Since 2011, the US Food and Drug Administration (FDA) has received increased reports of HTRs subsequent to IVIG therapy from health care providers.[56] Hemolytic anemia is caused by passive transfer of anti-A and anti-B hemagglutinins.[56,57] The exact incidence of hemolytic

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anemia induced by high-dose IVIG is uncertain. Hemagglutinins are normally present in donors of A, B, and O blood groups used for IVIG production, with the exception of group AB donors. Since O and A blood groups together form ~70%–80% of the world population, most of the plasma used in IVIG production is from these donors. In addition, plasma donations intended for Panzyga production are selected to keep anti-A and anti-B hemagglutinin titers to a minimum. However, IVIG contain blood group antibodies that may react with individuals of blood groups A, B, and AB. In such individuals, IVIG administration can potentially lead to HTRs similar to a blood transfusion mismatch.[58] Low-dose IVIG used in replacement therapy of primary and secondary immunodeficiency disorders is generally safe with a very low risk of hemolysis.[59] The incidence of IVIG-associated hemolysis is approximately 1 per 1000 IVIG treatment episodes, with most occurring within 48 hours of exposure.[60] The majority of such hemolytic episodes are unnoticed or self-limiting with positive direct antiglobulin test and mild decrease in hemoglobin.[61] Occasionally, hemolysis may lead to a clinically significant drop in hemoglobin, with severe cases requiring packed red blood cell transfusion.[62]

The safety profile of Panzyga based on clinical studies and long-term post-marketing experience is well documented,[63-65] detailed in the Full Prescribing Information for Panzyga.[66] Adverse drug reactions (ADRs) such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure, and moderate low back pain occur occasionally. These adverse effects are mostly transient and mild. However, some very rare adverse effects, including renal impairment, thrombosis, arrhythmia, aseptic meningitis, hemolytic anemia, and transfusion-related acute lung injury (TRALI), are serious.[67] They are rarely disabling or fatal, treatment involves supportive measures, and the majority of affected patients have a good prognosis. Reactions to IVIGs tend to be related to the dose and the rate of infusion. Rarely, human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration. Cases of reversible aseptic meningitis and rare cases of transient cutaneous reactions have been observed with human normal immunoglobulin. Reversible hemolytic reactions have been observed in patients, especially those with blood groups A, B, and AB.[23]

When medicinal products prepared from human blood or plasma are given to a patient, the transmission of infectious agents cannot be totally excluded. This applies also to hitherto unknown pathogens. However, specific virus inactivation procedures are implemented in the manufacturing process of Panzyga which are described in detail in the Investigator's Brochure (IB).[23]

For Panzyga, the same types of adverse reactions have been seen as for other IVIG products. No new or unknown safety problems are expected to emerge which are not already described in the IB.[23]

Guidelines published by the iwCLL state that secondary prophylactic use of IVIG decreases the rate of bacterial infections and prolongs the time to first infection, but does not produce differences in survival or other outcome parameters.[48] Therefore, the use of IVIG should be reserved to individual situations of hypogammaglobulinemia and repeated infections.[48] Many studies assessing the use of IVIG in patients with SID have included patient mortality among

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their primary outcome measures, and a lack of improvement of OS has been interpreted as a negative result. However, these were not recent studies; currently, patients with hematologic malignancies respond well to their primary treatment and have prolonged life expectancies. In this context, IVIG may provide an opportunity to improve morbidity and health-related QoL. In future studies, quality-of-life measures should be included together with measurements of morbidity and mortality as outcome measures.[68]

It can reasonably be assumed that Panzyga exhibits the same effectiveness in secondary infection prophylaxis as other IVIG brands. Thus, based on available data on secondary infection prophylaxis, we postulate that primary infection prophylaxis outweighs potential disadvantages of IVIG.

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2 STUDY OBJECTIVES

The primary and secondary objectives will be tested in the fixed sequence described below.

2.1 Primary Objective

The primary objective of this study is to demonstrate the benefit of Panzyga administration compared with placebo as primary infection prophylaxis in CLL patients with SID undergoing CLL antineoplastic therapy.

2.2 Secondary Objectives

The secondary objectives of this study are to compare the following aspects in CLL patients with SID treated with and without primary Panzyga prophylaxis:

- Overall infection rate
- Frequency of prophylaxis with anti-infectives (antibacterials and antivirals)
- Duration of prophylaxis with anti-infectives (antibacterials and antivirals)

2.3 Exploratory Objectives

The exploratory objectives of this study are to compare the following aspects in CLL patients with SID treated with and without primary Panzyga prophylaxis:

- Time to first major infection
- Overall mortality and mortality attributed to infection
- Duration of anti-infective treatment
- EQ-5D QoL assessments
- Relationship between efficacy outcome (major infections, overall infection rate) and infection risk factors
- Infections by the categories used in the primary endpoint definition
- Proportion of subjects with one or more microbiologically-documented infection, overall as well as by infection type (Viral/Bacterial).

To determine the PK profile of Panzyga in CLL patients with SID.

To evaluate the minimum target IgG trough level for infection prophylaxis in CLL patients with SID.

2.4 Safety Objective

- To evaluate the product safety of Panzyga administration

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2.5 Pharmacoeconomic Objectives

- To compare health economic effects in CLL patients with SID treated with and without primary Panzyga prophylaxis for the study duration. Secondary data usage is planned for pharmacoeconomic modeling.

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3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

Since the study objective is to show the benefit of Panzyga administration as primary infection prophylaxis, the primary endpoint is not the major infection rate but occurrence of at least one major infection in CLL patients with or without primary infection prophylaxis with Panzyga. Therefore, although patients will stay in the study regardless of the number of major infections, each patient will be counted only once for the primary endpoint calculation. Each potential infection will be assessed by an IEAB consisting of clinical experts. All adjudications will be conducted in a blinded manner and the IEAB will be provided with all relevant details. The IEAB will have the right to downgrade/upgrade any infections based on the agreed process. A detailed description of the information to be provided to the IEAB will be developed with the clinical experts and will be included in an IEAB charter.

Major infection for this trial is defined as:

- Bacterial and/or viral infections resulting in death. Confirmed cases of COVID-19 are excluded.
- Bacterial and/or viral infections, which are microbiologically documented (MDI) or clinically documented (CDI) requiring treatment with anti-infectives; upper respiratory tract infections, bronchitis, lower urinary tract infections, localized skin infections and stomatitis (MDI or CDI) are considered major only if they require treatment with anti-infectives AND hospitalization or hospitalization prolongation. Confirmed cases of COVID-19 are excluded.
- FUO requiring hospitalization or hospitalization prolongation

3.1.2 Secondary Endpoints

- Overall infection rate: infection rate for all infections.
- Frequency of prophylaxis with anti-infectives (antibacterials and antivirals).
- Duration of prophylaxis with anti-infectives (antibacterials and antivirals).

3.1.3 Exploratory Endpoints

[redacted]

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[redacted]

3.1.4 Safety Endpoints

[redacted]

3.1.5 Pharmacoeconomic Endpoints

[redacted]

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[redacted]

3.2 Overall Study Design and Plan

The study is planned to start in Q3 2020 and to be clinically completed by Q4 2024. The study will be a double-blind, randomized, placebo-controlled, prospective, multicenter, interventional phase III clinical study in a minimum of 240 adult patients of both genders with treatment-naïve or relapsed/refractory CLL and secondary hypogammaglobulinemia (IgG levels <5 g/l) undergoing CLL antineoplastic treatment.

About 50 sites are projected to participate in United States, Europe, Israel, and Russia.

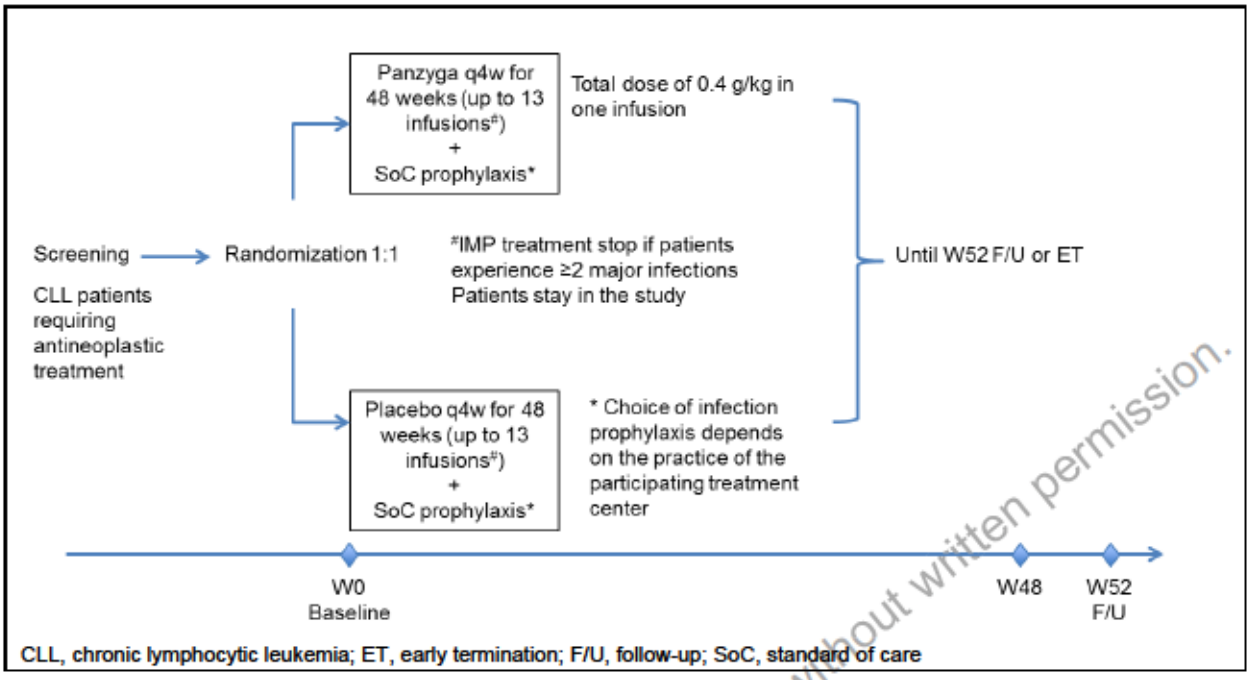
After Screening, eligible patients will be randomized 1:1 to receive either up to 13 infusions of Panzyga plus SoC prophylaxis or up to 13 infusions of placebo plus SoC prophylaxis. The choice of SoC infection prophylaxis depends on the practice of the participating center, including, but not limited to SARS-CoV-2 vaccine, influenza vaccine, pneumococcal vaccine, hematopoietic growth factors, antimicrobials, and antivirals. Patients will receive infusions every 4 weeks for 48 weeks. In the event that patients experience ≥2 major infections (based on the Investigator´s assessment according to major infection definition in section 7.3.5.1), IMP treatment will be stopped and they will receive secondary infection prophylaxis according to local standard of care, as recommended in clinical practice guidelines.[69,70] Such patients will stay in the study till Week 52 regardless at what visit they stopped treatment with IMP. The study schedule will remain unchanged for these patients (except IMP infusions and related safety evaluations.), for more details please review the Flow Chart of Assessments.

Approximately 40 patients will take part in the PK sub-study (at least 18 patients from the Panzyga arm). The assignment will be done based on the agreement of the patients (separate optional informed consent will be provided) and with the help of an IRT system in order to keep blind treatment assignment (once the goal of 18 patients from the Panzyga arm with evaluable data is reached (there will be a continuous review of PK data by a qualified PK-Expert on study to identify noteworthy values indicative of possible constraints on the evaluability of the PK profiles), recruitment into PK sub-study will be closed regardless of the number of patients from the placebo arm).

Figure 1 depicts the study design.

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Figure 1: *Scheme of Study Design*



CLL, chronic lymphocytic leukemia; ET, early termination; F/U, follow-up; SoC, standard of care

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

3.3.1 Study Design

The double-blind, randomized, placebo-controlled, prospective, multicenter, interventional phase III clinical study design for this study includes all major scientific, state-of-the-art interventions needed to demonstrate the benefit of adding Panzyga to SoC in primary infection prophylaxis in CLL patients with SID undergoing CLL antineoplastic therapy, and conform to the guidelines outlined by the European Medicines Association (EMA) and the FDA on the clinical investigation of IVIG (as described in section 7.5).[55,70]

In order to obtain valid results and because of differences in treatment approaches in different countries, the study population will be prospectively balanced by geographic region as follows: United States, Western Europe, and Central/Eastern Europe. Similarly, as the pathogenesis of immune deficiency secondary to lymphoproliferative malignancy is partly due to treatment-related factors,[1] the study population will be prospectively balanced according to treatment-naïve (in case patient is randomized at the start of or during the first line CLL antineoplastic therapy) or relapsed/refractory status, and into the following CLL treatment groups:

- Chemoimmunotherapy and anti-CD20 containing regimens, e.g. fludarabine, cyclophosphamide, and rituximab [FCR], bendamustine and rituximab [Benda-R]), obinutuzumab, rituximab;
- Small molecule inhibitors (Bruton's tyrosine kinase inhibitor, B-cell lymphoma-2 inhibitor, phosphoinositide 3-kinase (PI3K) inhibitor), e.g. ibrutinib, venetoclax, idelalisib;
- Other treatment.

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For CLL patients, a 4-fold reduction of infections is to be expected in secondary prophylaxis.[26,28,37] Griffiths *et al.* showed a 1.8-fold reduction of serious infections in CLL patients (from 91.7% to 50.0% in 12 patients treated with placebo and IVIG).[27] Based on this clinical experience and on FDA guidance,[71] IVIG treatment cycles at 4 week intervals for a 12 month study duration are necessary to be documented for a proper assessment of efficacy, hence the chosen study duration of 52 weeks from the Baseline Visit to the Follow-up Visit.

3.3.2 Control Group(s)

In the absence of a licensed IVIG treatment for primary infection prophylaxis, the control group in the study will receive placebo plus SoC infection prophylaxis, depending on the practice of the participating center, including, but not limited to SARS-CoV-2 vaccine, influenza vaccine, pneumococcal vaccine, hematopoietic growth factors, antimicrobials, and antivirals. Moreover, to exclude any potential bias, an IEAB will be set up for this study.

3.3.3 Study Parameters

The study parameters selected in the study are appropriate to verify the clinical efficacy of Panzyga plus SoC primary prophylaxis in treatment-naïve or relapsed/refractory CLL patients with SID (hypogammaglobulinemia secondary to CLL and/or antineoplastic treatment) undergoing CLL antineoplastic therapy.

The outcome measures in this study are consistent with previous studies of other IVIG products, and are also in compliance with guidance from the EMA and FDA.[70,71]

The EQ-5D QoL questionnaire is a standard, validated, instrument that has been widely used in clinical studies, including hematological malignancies and immunodeficiency disorders.[72-74]

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4 STUDY POPULATION

4.1 Population Base

In total, at least 240 adult patients of any gender with treatment-naïve or relapsed/refractory CLL undergoing treatment and with secondary hypogammaglobulinemia will be enrolled into the study. For a subgroup of approximately 40 patients (at least 18 patients from the Panzyga arm) additional PK samples will be collected (separate optional informed consent will be provided).

4.1.1 Inclusion Criteria

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

1. Treatment-naïve or relapsed/refractory CLL patients undergoing CLL antineoplastic treatment. Diagnosis of B-cell CLL established according to iwCLL criteria and documented within medical records.
2. Hypogammaglobulinemia (IgG levels <5 g/l as confirmed by the Central Laboratory).
3. ≥18 years of age.
4. Voluntarily given, fully informed written and signed consent obtained before any study-related procedures are conducted.

4.1.2 Exclusion Criteria

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

1. IgG treatment within 3 months prior to Screening.
2. Antibiotic prophylaxis and/or treatment within 7 days prior to Baseline (with the exception of trimethoprim-sulfamethoxazole [TMP/SMX], diaminodiphenyl sulfone [dapsone] and pentamidine inhalation).
3. Current major infection or >1 major infection in the previous 6 months before Baseline.
4. History of anaphylaxis or severe systemic response to immunoglobulin, blood or plasma-derived products or any Panzyga component.
5. History of a non-CLL malignancy or other medical condition with life-expectancy of less than two years.
6. Severe liver disease, with signs of ascites and/or hepatic encephalopathy.
7. Severe kidney disease (as defined by eGFR <30 mL/min/1.73 m^2).
8. Body weight >140 kg.
9. Eastern Cooperative Oncology Group (ECOG) performance score of >2 (Appendix 1: Eastern Cooperative Oncology Group Performance Status).
10. Female patients of childbearing potential unwilling to use a protocol-required method of contraception (as per protocol section 7.3.9 b) from the Screening Visit throughout the study treatment period and for 30 days following the last dose of study drug.

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11. HIV infection at Screening (defined for the study as positive HIV antibody test).
12. Patients found to be chronic carriers of hepatitis B virus (HBV), defined by positive surface antigen (HBsAg), positive Hepatitis B core antibodies (HBcAb) and/or low HBV titers, who will not receive targeted antiviral therapy while undergoing CLL therapy, and patients with active HBV, defined as high HBV titers.
13. Uncontrolled hepatitis C infection at Screening (defined for the study as positive HCV PCR).
14. Pregnant and lactating women.
15. Subjects with a history of TEE such as deep vein thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease (Fontaine IV) within 6 months before Baseline.
16. Planned or ongoing immunosuppressive treatment (other than for CLL or corticosteroids) or other forbidden medication during the entire study duration after study enrollment.
17. Participation in another interventional clinical trial that is either blinded or involves an investigational (not approved) product within 3 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.
18. Known IgA deficiency with antibodies to IgA (as part of the patient´s medical history).
19. Known blood hyperviscosity, or other hypercoagulable states.
20. Patients unable or unwilling to understand or comply with the study protocol

4.2 Prior and Concomitant Therapy

Details on medications taken prior to enrollment and any concomitant medications taken during the study will be recorded in the electronic case report form (eCRF). The data that will be collected are summarized in Table 2.

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Table 2: Categories of Concomitant Therapy

Category	Details to be collected	Timelines
CLL therapy* ended prior to enrollment	Names, date of administration	Any CLL therapy
CLL therapy* ongoing at enrollment and during the study	Names, dose, unit, route, frequency, date of administration	Any CLL therapy
Therapy of interest with potential impact on endpoints (e.g. antibiotics, corticosteroids, G-CSF, immunoglobulins)**	Names, indication, dose, unit, route, frequency, date of administration	6 months before enrollment and during the study
Vaccines	Name, date of administration	5 years before enrollment and during the study
Other concomitant medication, including premedication	Names, indication, dose, unit, route, frequency, date of administration	3 months before enrollment and during the study

*Allowed chemotherapy treatments include but not limited to chemoimmunotherapy and anti-CD20 containing regimens, e.g. FCR, Benda-R, obinutuzumab, rituximab; small molecule inhibitors (Bruton's tyrosine kinase inhibitor, B-cell lymphoma-2 inhibitor, phosphoinositide 3-kinase (PI3K) inhibitor), e.g. ibrutinib, venetoclax, idelalisib.

** After the stopping of IMP treatment in case ≥2 major infections

4.2.1 Permitted Concomitant Therapy

Permitted concomitant treatments include any CLL therapy. Patients are enrolled during the CLL antineoplastic treatment (during the period starting from 1 week before the 1st cycle till 2 weeks after start of the last cycle of a treatment line). For the study purposes cycle is defined as 28 calendar days in case continuous treatment.

Patients may also use corticosteroids as therapy for comorbid conditions.

The routine use of premedication to alleviate potential side effects should be avoided. However, if a subject experiences 2 consecutive infusion-related AEs that are likely to be prevented by premedication, then pre-medication is allowed prior to infusion of study drug. All data concerning pre-medication therapy will be collected in the eCRF. TEE prophylaxis, if deemed necessary by the Investigator, is allowed as a precautionary measure and should follow standard of care. Its use must be documented.

Prophylaxis of treatment-induced febrile neutropenia and/or treatment with granulocyte-colony stimulating factor (G-CSF) is allowed according to the current guidelines.

4.2.2 Forbidden Concomitant Therapy

The following medications or therapies are not permitted during participation in this study:

- Immunosuppressive agents other than CLL treatment or corticosteroids;
- Treatment with Lenalidomide;
- Immunoglobulin treatment other than Panzyga. Patients will be withdrawn from the study if IgG preparations other than Panzyga are administered; once the patients stop IMP treatment due to ≥2 major infections – any immunoglobulin treatment is allowed;
- Monoclonal antibodies other than those used as CLL therapy (exception: anti-SARS-CoV-2 monoclonal antibodies are permitted);

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- Other blood or plasma-derived products, except blood or platelet transfusions due to patient medical condition;
- Plasma exchange procedures, plasmapheresis;
- Live attenuated vaccines such as measles, rubella, mumps and varicella;
- Any experimental drug.

4.3 Withdrawal and Replacement of Patients

4.3.1 Premature Patient Withdrawal

Patients eligible after screening will be randomized 1:1 to receive either up to 13 infusions of Panzyga every 4 weeks in addition to SoC prophylaxis or placebo plus SoC prophylaxis throughout the planned study duration. 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 noninterpretable, 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 drop-outs. The Investigator has to organize the ET Visit, which is identical to the Follow-up Visit procedures.

Other reasons for premature termination of patients may be:

- Withdrawal of patient's consent.
- Pregnant 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 according to the study protocol.
- Occurrence of a condition or disease that interferes with the study treatment or represents an exclusion criterion.
- Immunoglobulin treatment other than Panzyga, except in cases where the patients stop IMP treatment due to ≥2 major infections.
- Patients do not comply with the study protocol.

4.3.2 Patient Replacement Policy

There will be no patient replacement in this study, but enrollment will continue until the number of patients required (according to the revised sample size determined at the interim analysis) for the evaluation of the primary endpoint in the intent-to-treat (ITT) population has been

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achieved with the currently enrolled patients. All randomized patients will be included in the primary analysis, in case of missing data by means of a multiple imputation method.

4.4 Assignment of Patients to Treatment Groups

All patients qualified to participate in the study at Baseline (Week 0) will be randomized to one of the two treatment arms by an electronic interactive response technology (IRT) tool and thereby enrolled into the double-blind treatment period. The randomization will assign each patient to one of 2 treatment groups:

- SoC treatment plus regular infusions of Panzyga
- SoC treatment plus regular infusions of placebo (0.9% w/v sodium chloride)

The randomization scheme for this trial will not be realized by means of randomization lists, but a baseline adaptive randomization procedure will be deployed to consider a number of co-variates that have been identified as potentially relevant for the primary endpoint:

- Differences in SoC treatment (infection prophylaxis) approaches in different regions:
  - North America
  - Western Europe
  - Central and Eastern Europe
- The pathogenesis of immune deficiency secondary to lymphoproliferative malignancy is partly due to treatment-related factors; the following CLL treatment groups will be considered:
  - Chemoimmunotherapy and anti-CD20 containing regimens, e.g. fludarabine, cyclophosphamide, and rituximab [FCR], bendamustine and rituximab [Benda-R]), obinutuzumab, rituximab;
  - Small molecule inhibitors (Bruton's tyrosine kinase inhibitor, B-cell lymphoma-2 inhibitor, phosphoinositide 3-kinase (PI3K) inhibitor), e.g. ibrutinib, venetoclax, idelalisib;
  - Other treatment.
- The patient's CLL treatment status:
  - Treatment-naïve (in case patient is randomized at the start of or during the first line CLL antineoplastic therapy)
  - Relapsed/refractory

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4.5 Protocol Deviations

Deviations from the protocol should be avoided. 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 is to be compiled and regularly updated by the Project Manager and provided for preparation of the CSR.

Examples of critical/major protocol deviations that will be addressed 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).
- Missing visits (for example, cases in which a visit within the treatment period is delayed for more than 20 days).
- Patients who received forbidden concomitant medication.

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

4.6 Subsequent Therapy

All patients who leave the study – be it prematurely or per-protocol (PP) – will continue with CLL treatment and an infection prophylaxis regimen as per the discretion of the Investigator.

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5 INVESTIGATIONAL MEDICINAL PRODUCT(S)

5.1 Characterization of Investigational Product(s)

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 validated manufacturing steps. The composition with the most important ingredients and the biochemical characteristics are summarized in the IB.[23]

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

5.2 Packaging and Labeling

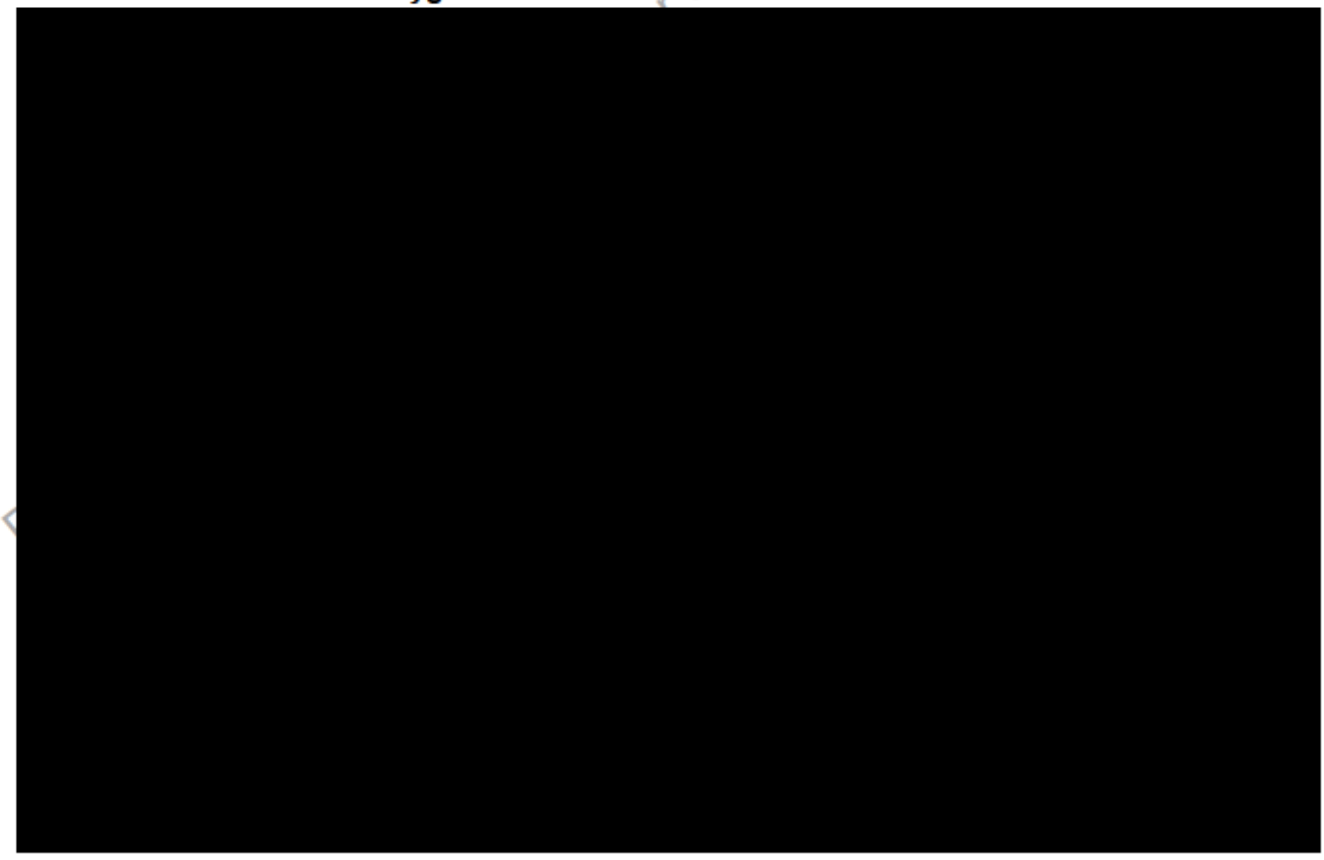
The IMP will be labeled per each kit (container) with unique kit identifiers.

Panzyga is delivered as ready-to-use solution in glass bottles. Each Panzyga bottle will be labeled as follows:

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EU Master Label – Panzyga:



Marketed sodium chloride 0.9% w/v solution for intravenous infusion that can be used in the respective countries in which the study will be conducted, will be purchased and provided to the local pharmacies. Each bottle will be labeled as follows:

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US Master Label – Sodium Chloride 0.9% w/v solution:



EU Master Label – Sodium Chloride 0.9% w/v solution:



Final labeling will be in compliance with the national requirements of each country where the study is to be conducted.

[redacted]

[redacted]

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Final labeling will be in compliance with the national requirements of each country where the study is to be conducted.

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.

Sodium chloride 0.9% w/v 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, as stated on the label.

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

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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.

If a patient is randomized to receive placebo (0.9% w/v isotonic sodium chloride solution), the same volume with the same infusion rate as would have been applied in case the patient would have been randomized to 0.4 g/kg Panzyga, will be used. Therefore, patients randomized to the placebo treatment arm will receive a dose of 4 mL/kg 0.9% w/v sodium chloride solution given in one day.

Body weight is to be measured at each visit (or within 7 days prior to IMP administration) on calibrated equipment, and reported to the IRT, as it is needed for the calculation of the required IMP dose, which will be adapted in case of body weight change. Body weight is to be reported to the IRT to the full kilogram values by rounding up or down as per normal guidance (last decimal is < 5 round down, last decimal ≥ 5 round up).

All patients should be clinically assessed for being adequately hydrated prior to IMP administration. TEE prophylaxis 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.

Infusion rates in the first 3 infusions (Visits 2, 3 and 4) will be:

- The initial infusion rate for each infusion will be 0.01 mL/kg/min (60 mg/kg/h) for the first 30 minutes;
- if tolerated, advanced to 0.02 mL/kg/min (120 mg/kg/h) for the next 30 minutes;
- if tolerated, advanced to 0.04 mL/kg/min (240 mg/kg/h) for the next 30 minutes;
- if tolerated, advanced to 0.08 mL/kg/min (480 mg/kg/h) for the remainder of the infusion

If this is tolerated, infusion rates in the next infusions (Visits 5-14) will be:

- The initial infusion rate for each infusion will be 0.01 mL/kg/min (60 mg/kg/h) for the first 30 minutes;
- if tolerated, advanced to 0.02 mL/kg/min (120 mg/kg/h) for the next 15-30 minutes;
- if tolerated, advanced to 0.04 mL/kg/min (240 mg/kg/h) for the next 15-30 minutes;
- if tolerated, advanced to 0.08 mL/kg/min (480 mg/kg/h) for the next 15-30 minutes;
- if tolerated, advanced to ≤0.12 mL/kg/min (≤720 mg/kg/h) for the remainder of the infusion, if any.

The interval of 30 minutes may be prolonged as per the discretion of the Investigator.

In patients at risk for thromboembolic adverse reactions and acute renal failure (such as advanced age, hypertension, history of thrombotic episodes, patients with prolonged periods of immobilization, concomitant nephrotoxic medication, diabetes mellitus, overweight, hypovolemia), IMP should be administered at lower rate of infusion, i.e. lowest rate of infusion that deemed practicable and safe by the Investigator.

Infusions should be given in one day. Total dose for an infusion will be 0.4 g/kg. The infusions will be given continuously. During the study period, patients will receive double-blinded treatment of up to 13 infusions of 0.4 g/kg (4 mL/kg) Panzyga plus SoC prophylaxis or up to 13 infusions of placebo (4 mL/kg) plus SoC prophylaxis at 4-week intervals.

If an AE occurs during the infusion, the rate is to be reduced to half the rate at which the event occurred, or the infusion is to be interrupted until symptoms subside. The infusion may then be resumed at a rate tolerated by the patient. The rest of the assigned volume can be infused

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on the same day or within next two days. In such a case, vital signs should be measured before, during and after each infusion. Additional IMP will be assigned by IRT in such case.

5.5 Preparation and Method of Administration

Each bottle of Panzyga must be examined visually by the site staff for particulate matter and discoloration prior to IMP administration. Non-homogenous solutions or those that have a deposit must not be used. The same procedures should also be performed for sodium chloride 0.9% w/v solution.

Panzyga must be allowed to warm to room or body temperature prior to administration. The same holds true for sodium chloride 0.9% w/v solution for patients in the placebo arm.

Patients must be monitored before IV infusion and observed for any symptoms at least once throughout the infusion period and at least 1 hour after the first infusion, and at least 20 minutes after subsequent infusions.

Panzyga solution for IV infusion must not be mixed with other medicinal products or sodium chloride. For other IV products, a separate IV line must be used. Panzyga can be administered on the same day as CLL treatment, at the discretion of the Investigator.

The special warnings and precautions for use (see IB) of Panzyga must be respected.[23]

5.6 Blinding, Emergency Envelopes, and Breaking the Study Blind

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 during the study period, infusions will be given in blinded infusion bags (corresponding to a volume of 0.4 g/kg (4 mL/kg) Panzyga or sodium chloride 0.9% w/v solution). Thus, the original unblinded vial/ bottle /container where the unblinded label is on, will be discarded, and a new label will be fixed onto the infusion bag and on non-transparent over pouch by the hospital pharmacist or designee. The over pouch (normally used for light protection) will be put over the infusion bag to maintain blinding. The new labels will be identical for both Panzyga and sodium chloride 0.9% w/v solution, so that the content of the bags is only known to the unblinded hospital pharmacist or designee. An example of this label can be found in section 5.2.

The hospital pharmacist or designee will send the infusion bag(s) per patient to the ward. IMP administration will be done by site staff assigned to this task. For blinding reason, the following study assessments must not be done by the same person who performs the infusion: re-obtaining of ICF in case updates, physical examination, Wells scales assessment, AEs assessments, concomitant medication assignment, patient diary and EQ-5D collection. Staff administrating IMP should not also have unblinded IRT access and be involved in IMP storage and/or preparation.

Patients and blinded site staff will be blinded with respect to study treatment throughout the study. Because of the non-transparent infusion line and over pouches, patients will not be able to see the medication he/she is treated with.

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Blinding will only be broken under the following circumstances:

- Occurrence of serious and presumably related AEs, if the Investigator needs to know the assigned treatment for a proper clinical management of the patient.
- If unblinding is required by the local regulatory authorities.

Whenever possible, the Investigator should notify the Sponsor prior to unblinding.

In order to maintain the blind, IgG plasma level results performed at the Central Laboratory will not be revealed to the Sponsor, the Investigator, and other blinded personnel at the study site.

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 amount of IMP received and assigned to each patient and the remaining quantity.

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

IMP can be destroyed at the study site or returned to the Sponsor depot for destruction. IMP containers (vials, bottles, bags) that were already used for preparation of the infusion can be destroyed after preparation. 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 Monitor and destruction or return must be confirmed in written 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 in the eCRF. Unique kit numbers and batch number(s) will be available in IRT and will be checked regularly by the unblinded Study Monitor.

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6 STUDY CONDUCT

Patients have to be informed about the study details and have to give their written informed consent. A full written informed consent must be available before the start of any screening activities.

The Flow Chart of assessments by study visit is displayed in Table 1.

Prior to randomization, patients will have to be screened for eligibility (inclusion and exclusion criteria).

Screening should be completed within 3 weeks. Based on the screening results, the patients' eligibility for the study is determined. In case of screening test delays for any reason, each patient will be individually addressed by the Sponsor.

If a patient does not meet inclusion criterion 2, it is allowed to perform one retest of IgG during the Screening period in the Central Laboratory. In this case, the Screening period could be prolonged up to 8 weeks. In case of eligibility, the patient should be randomized within 3 weeks after retest.

If retest is performed >21 days after Screening, the following tests should be repeated together with IgG test and assessed before randomization: clinical chemistry, hematology and pregnancy test (see section 7.3.6).

Screening failures will be entered into the eCRF. If a patient screen failed, the patient can be rescreened at a later date. Similarly, if a patient experiences CLL treatment delay and cannot be randomized within specified timelines, the patient will also be rescreened. In these cases, the patient will be given a new patient number. Rescreening for each patient will only be possible once. Patients who completed the study must not be rescreened.

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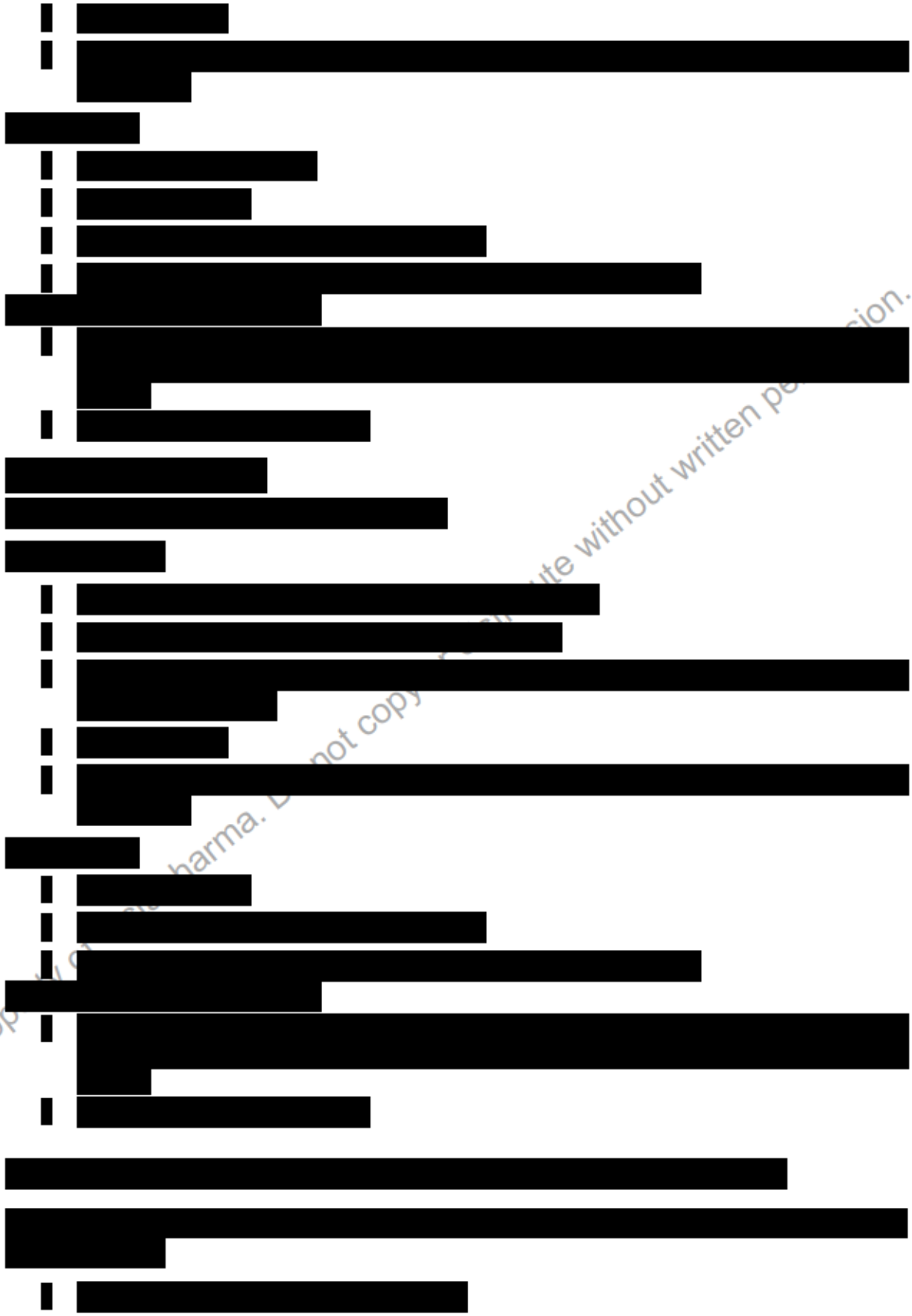
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6.1.16 Assessments for patients who experience ≥2 major infections

In the event that patients experience ≥2 major infections, they will stop their treatment with IMP, the procedures specified in the ET visit should be performed and the patient will stay in the study until Week 52. Regardless at what visit they stop the treatment with IMP, the study visit schedule will remain unchanged and continue according to Flow chart of Assessments.

The following procedures are not required at visits Visit 3-Visit 15 for such: infusion of IMP, weight measurement, Wells criteria assessment, chemistry panel, IgG, additional safety panel 1, additional safety panel 2. Physical examination/targeted physical examination should include vital signs measurement. Retention samples should be collected at next visit after last IMP administration (and not required then at Visit 15).

If a patient disagrees to further participate in the trial, the ET visit should be performed.

6.1.17 Time Windows Used in this Study, including Tolerances

In this study, the following time windows and tolerances apply:

Table 3: Time Windows Allowed in this Study

Time point	Time stated	Tolerance
Interval between Visits (starting at interval between Visit 2 and Visit 3) – exception for PK patients see below	4 weeks	± 7 days, (not less than 15 days between two consecutive infusions)
Vital signs	Before IMP administration	≤ 60 minutes
	At the end of the first IMP administration	≤15 minutes before the end of infusion or ≤ 15 minutes after end of infusion
	After first IMP administration	≥ 60 minutes, but ≤120 minutes
	After subsequent IMP administrations	≥ 20 minutes, but ≤60 minutes
Body weight	Before IMP administration	Within 7 days
Time window between Visit 9 and Visit 10 for patients participating in optional PK assessment	4 weeks	± 2 days
PK samples between Visit 9 and Visit 10	15 minutes post infusion	± 5 minutes
	1 hour post infusion	± 15 minutes
	4 hours post infusion	±15 minutes
	24 hours post infusion	± 1 hour
	72 hours post infusion	± 1 hour
	7 days post infusion	± 1 day
	14 days post infusion	±1 day
	21 days post infusion	± 2 days
Total duration of IMP infusion	As calculated	+/- 5% of calculated total time

Patients are enrolled during the CLL antineoplastic treatment (during the period starting from 1 week before the 1st cycle till 2 weeks after start of the last cycle of a treatment line, ±2 days). For the study purposes cycle is defined as 28 calendar days in case continuous treatment.

In case a visit is delayed within the acceptable time frame or outside the visit window, the next scheduled visit has to revert to the original visit schedule (calculated from Baseline Visit).

In each treatment arm, if a visit within the treatment period is delayed for more than 20 days, the visit should be skipped and major protocol deviation should be registered (see section 4.5).

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6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The duration of the entire study for each patient will be approximately 52 weeks from the Baseline Visit to the Follow-up Visit.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed when all patients have completed per the planned observation period/Final Examination Visit.

The estimated start of the study (enrollment of first patient) is Q3 2020, and the estimated end of the study (last visit of last patient) is Q4 2024.

6.2.3 Premature Termination of the Study

Both the Investigator and the Sponsor reserve the right to terminate the study at any time for any reason. In this event, any necessary procedure will be arranged on an individual study basis 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.

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

Early termination of the study as a whole or by center may apply for the following reasons:

6.2.3.1 Early Termination of the Entire Clinical Study

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

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

In addition to the ongoing safety monitoring and the IDMC data review, the following stopping rules will be implemented to apply temporary suspension of study drug administration, pending a safety investigation:

- For both groups the risk of major infection will be calculated as (# of patients with major infections)/(# of patients). If the lower limit of the 95% Wald confidence interval for the risk difference (Panzyga–Placebo) is above 0 at the interim analysis, the study will be stopped for futility. Remark: The same rule will be applied whenever the IDMC reviews data in an unblinded fashion, and at least 50 patients are available for the review.
- An unacceptable increased TEE risk in the Panzyga group compared to the Placebo group: Whenever an unblinded evaluation is done, and a total of 100 or more infusions have been administered in the context of this study the following will be applied: For both groups the TEE risk will be calculated as (# of TEEs reported)/(# of infusions), and the 95% confidence interval for the resulting risk ratio (RPanzyga/RPlacebo) will be determined by means of the /relrisk option of the SAS procedure FREQ. In case no TEEs are observed in the Placebo group, 1 will be added to each cell in the 2x2 table to enable this risk ratio evaluation. The study will be stopped if the lower confidence limit is greater than 1.1. The threshold of 1.1 is chosen to reflect that the TEE risk may be further augmented by IGIV administration.

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6.2.3.2 Early Termination at an Individual Study Center

At any time, the study can 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 by 16 weeks after initiation of the center.
- The required recruitment rate is not met.

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

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7 ASSESSMENTS AND METHODS

7.1 Demographic and Baseline Information

The following information will be recorded during the Screening Visit:

7.1.1 Demographic and baseline characteristics

The demographic and baseline characteristics are sex, age, ethnic origin, height, weight, and Body Mass Index (BMI). Height is to be recorded at Screening only. Body weight is to be measured at each visit (or within 7 days prior to IMP administration).

7.1.2 Medical history and prior/concomitant medications

The medical history will be obtained by interviewing the patient. Records of past diseases and treatments (e.g., hospital discharge letters) will be obtained for the study files, if available.

Prior and concomitant medications will be obtained by interview. Comorbidities, vaccination history, including booster vaccinations, treatment course, CLL treatment history and clinical staging[75,76] (Appendix 2) will be recorded.

7.1.3 Physical examination

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems.

Any abnormality identified at Baseline Visit should be recorded on the General Medical History and Baseline Conditions eCRF. As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

Targeted physical examinations should be limited to systems of primary relevance, i.e. cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment (lymph nodes, liver, and spleen).

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

7.1.4 Laboratory parameters

Required screening laboratory data (within 3 weeks prior to randomization) are provided in the table below. In case of Screening prolongation up to 8 weeks because of the IgG retest, clinical chemistry, hematology and pregnancy test should be repeated within 3 weeks before Baseline in the Central Laboratory. Values should be obtained within the screening period and should generally be the most recent measurement obtained. Patients with any degree of neutropenia, thrombocytopenia, or anemia due to CLL or prior therapy may be enrolled.

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Table 4: Required Screening Laboratory Values

Organ System	Parameter	Required Value
Renal	eGFR*	≥30 mL/min/1.73 m^2
Immune	IgG	<5 g/L
Infection	HIV	Negative HIV antibody
	HCV	Negative HCV PCR
	HBV	Low titer HBV PCR or negative
Pregnancy	Human chorionic gonadotropin	Negative

*According to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[77]

Negative HCV PCR serves as confirmation of the exclusion criterion "uncontrolled hepatitis C (defined for the study as positive HCV PCR)".

In the event of a positive urine pregnancy test, a serum pregnancy test will be performed in the Central Laboratory.

7.2 Efficacy Assessments

7.2.1 Assessments for Primary Efficacy Endpoint

To study the effectiveness of Panzyga primary prophylaxis of infections, the following measurements will be recorded throughout the study: number of major infections as assessed by the IEAB, along with type and severity of infection, and time to resolution. Major infection for this trial is defined as described in section 7.3.5.1.

7.2.2 Assessments for Secondary Efficacy Endpoints

To study the effectiveness of Panzyga primary prophylaxis of infections, the following measurements will be recorded throughout the study:

- Overall infection rate for all recorded infections between Baseline and Follow-up/ET Visits, with type and severity of infection, and time to resolution.
- Use and number of days of use of anti-infective prophylaxis (oral, parenteral, oral plus parenteral, and dose).

7.2.3 Assessments for Exploratory Efficacy and PK Endpoints

[redacted]

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[redacted]

7.2.4 Assessments for Pharmacoeconomic Endpoints

[redacted]

[redacted]

For the collection of the above measurements, each patient will be provided with an individual diary to be filled in by the patient during the time in between site visits. After having checked the accuracy of the data, the Investigator will transfer the data to the appropriate pages in the eCRF.

Below is the list of possible questions for the resource utilization data collection:

- How many times have you seen your family physician related to your condition or as a result of an infection?
- How many times have you seen a specialist related to your condition or as a result of an infection?
- How many times have you been to an emergency room related to your condition or as a result of an infection?
- How many times have you been hospitalized related to your condition or as a result of an infection?
- Since your last visit, have you or a caregiver had to take any time off from paid employment as a result of your condition or as a result of an infection related to your condition?

7.3 Safety Assessments

7.3.1 Assessments for Safety Endpoints

[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 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

The condition of the patient will be monitored throughout the study. At 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?" In addition, the Investigator will check the patient diaries (if applicable) for any documented event. Adverse events should be collected from the Baseline Visit for both treatment arms.

Any AE or ADR which occurs during the study will be noted in detail on 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 confirmed 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 the first administration of IMP will not be considered AEs unless an exacerbation in intensity or frequency (worsening) occurs.

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:

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- **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 under the reference safety information section or other Reference Safety Information.
- **Unexpected:** an ADR that is not listed in the current edition of the IB or other RSI, 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

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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 4 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:

a) 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)

b) IMP-related actions taken in the event of an AE

- None
- Product withdrawn
- Dose interrupted

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.

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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.

Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness.

Prolongation of existing hospitalizations for non-medical reasons, and hospitalization due to social, situational (i.e., no place to stay, live too far away to come for hospital visits, respite care), or administrative reasons will not be considered inpatient hospitalizations.

Adverse Events of Special Interest (AESIs) such as major infections, TEEs, and confirmed HTRs are to be reported as SAEs (see section 7.3.5). If no other seriousness criteria apply, AESIs are to be reported as important medical events.

Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

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.

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7.3.4 SAE Reporting Timelines

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 [redacted] or 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
[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. 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
[redacted]

In parallel, 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:

- Emergency room or urgent care visit without hospital admission
- Hospitalization for a procedure planned before signing informed consent, or for elective treatment of a pre-existing condition

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- Prolongation of existing hospitalizations for non-medical reasons
- Hospitalization due to social, situational, or administrative 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 competent authorities in all participating countries concerned as well 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 an additional eight days.

All other SUSARs will be reported to the FDA and all applicable competent authorities in all participating countries concerned as well 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.

The requirements above refer to the requirements relating to the investigational medicinal product.

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7.3.5 Adverse Events of Special Interest (AESI)

The following AEs are defined as AESI:

- Any major infection;
- 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 7.3.3. HTR should be reported as SAE only if it meets criteria for confirmed hemolysis (see section 7.3.5.3).

7.3.5.1 Major Infections

Major infections for this trial are defined as follows:

- Bacterial and/or viral infections resulting in death. Confirmed cases of COVID-19 are excluded.
- Bacterial and/or viral infections, which are microbiologically documented (MDI) or clinically documented (CDI) requiring treatment with anti-infectives:
    - MDI can include both (1) blood stream infection, either with a single organism or polymicrobial infection, but without definable other site of infection, and (2) a microbiologically defined site of infection (e.g., pneumonia, cellulitis) with or without concomitant blood stream infection[44] or (3) viral infection confirmation.

- CDI is designated when a site of infection is diagnosed (e.g., pneumonia, cellulitis) but its microbiologic pathogenesis either cannot be proven or is inaccessible to examination.[44]
- The upper respiratory tract, bronchitis, lower urinary tract, localized skin infections and stomatitis (MDI or CDI) are considered major only if they require treatment with anti-infectives AND hospitalization or hospitalization prolongation. Confirmed cases of COVID-19 are excluded.

- FUO requiring hospitalization or hospitalization prolongation.

  Fever is defined as measured orally of ≥38.3°C (100.9°F) once or ≥38.0°C (100.4°F) lasting for at least 1 h or being measured twice within 12 h or a method shown to be equivalent to these results may be used to define fever.[78] For the study purposes the following equivalents are defined:

  - Oral temperature 38.3°C (100.9°F) equals rectal temperature/ear (tympanic) scanner 38.6°C (101.4°F) and forehead (temporal)/armpit (axillary) temperature 38.0°C (100.4°F)
  - Oral temperature 38.0°C (100.4 F) equals rectal temperature/ear (tympanic) scanner 38.3°C (100.9°F) and forehead (temporal)/armpit (axillary) temperature 37.7°C (99.9°F)

  In case fever is registered within 24 hours after the end of the IMP infusion or another concomitant medication assignment, which could possibly cause pyrexia, another episode of fever should be registered at least once out of the 24 hours.

  The minimum diagnostic evaluations required for a case to qualify as classical FUO are the following:[78,79]

  1. Physical examination
  2. Laboratory tests should include a complete blood cell count with differential leukocyte count and platelet count; measurement of serum levels of creatinine and blood urea nitrogen; and measurement of electrolytes, hepatic transaminase enzymes, and total bilirubin.
  3. At least 2 sets of blood cultures, with a set collected simultaneously from each lumen of an existing central venous catheter, if present, and from a peripheral vein site; 2 blood culture sets from separate venipunctures should be sent if no central catheter is present
  4. Culture specimens from other sites of suspected infection should be obtained as clinically indicated.
  5. A chest radiograph is indicated for patients with respiratory signs or symptoms.

In case patients have bacterial and/or viral infections or FUO and are not hospitalized/hospitalization is not prolonged due to limited hospital access, the higher possible risk of COVID-19 infections or an overall trend to avoid hospitalizations due to the pandemic,

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such adverse events should be still reported as major infections if they meet other above-mentioned criteria.

Infections recurring within the time frames specified in Table 5 should not be reported as a separate infection.

Table 5: Definitions for Same Infection

Bacterial	Viral
≤ 7 Days • Any bacteria **≤ 30 Days** • Clostridium difficile **≤ 365 Days** • Helicobacter pylori	**≤ 14 Days** • Adenovirus • Enterovirus • Herpes zoster • Influenza • Parainfluenza • Rhinovirus • Respiratory syncytial • Varicella zoster **≤ 30 Days** • Human herpes virus - 6 **≤ 60 Days** • Cytomegalovirus • Epstein-Barr virus • Herpes simplex • Polyomavirus

Reproduced from Center for International Blood & Marrow Transplant Research Comprehensive Baseline & Follow-Up Manuals, Infection Q428-440, available from: https://www.cibmtr.org/manuals/fim/1/en/topic/f2100-q428-440 (accessed 10 October 2019).

Special attention should be paid during each visit to detect any symptoms of tuberculosis. If tuberculosis is suspected at any time during the study, appropriate examinations according to local standards should be performed (e.g. chest imaging, as well as either a tuberculin skin test or interferon-gamma release assay) and the results documented. Therapeutic measures managing suspected tuberculosis shall be initiated according to local clinical practice.

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7.3.5.2 Thromboembolic Events (TEEs)

There is clinical evidence of an association between IVIG administration and TEEs,[23] 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.

TEEs will be monitored as follows:

- For the patients, receiving prophylactic anti-coagulation treatment, in case any clinical signs of DVTs, Doppler screening of leg veins for DVT will have to be completed (recommended: Doppler using color duplex sonography). In case Doppler Screening for DVT is not possible to be performed within 24 hours – blood sample should be taken

for D-Dimers (in local or central lab). In case positive D-Dimer test Doppler screening for DVT should be performed as soon as possible in order to exclude DVT.

- For the patients, who are not receiving prophylactic anti-coagulation treatment ,Wells criteria for assessment of probability for possible DVTs at each visit[80] modified according to NICE Clinical Guideline 144, 2012):

Present		Score
☐	Active cancer (treatment ongoing, within 6 months, or palliative)	+1
☐	Paralysis, paresis or recent plaster immobilization of the lower extremities	+1
☐	Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anesthesia	+1
☐	Localized tenderness along the distribution of the deep venous system	+1
☐	Entire leg swollen	+1
☐	Calf swelling at least 3 cm larger than asymptomatic side	+1
☐	Pitting edema confined to the symptomatic leg	+1
☐	Collateral superficial veins (non-varicose)	+1
☐	Previously documented DVT*	+1
☐	An alternative diagnosis is at least as likely as DVT	-2
Clinical Probability Simplified Score	DVT likely ≥2 points DVT unlikely ≤1 point	

*Note: This is also an exclusion criterion if it´s within 6 months before the Baseline.

- If the Well's DVT probability score is ≥2, then a Doppler screening of leg veins for DVT will have to be completed (recommended: Doppler using color duplex sonography). In case Doppler Screening for DVT is not possible to be performed within 24 hours – blood sample should be taken for D-Dimers (in local or central lab). In case positive D-Dimer test Doppler screening for DVT should be performed as soon as possible in order to exclude DVT.

- Wells criteria for assessment of probability for possible PE at each visit[81] modified according to NICE Clinical Guideline 144, 2012) for all patients:

Present		Score
☐	Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
☐	An alternative diagnosis is less likely than PE	3
☐	Heart rate > 100 beats per minute	1.5
☐	Immobilization for more than 3 days or surgery in the previous 4 weeks	1.5
☐	Previous DVT/PE*	1.5
☐	Hemoptysis	1
☐	Malignancy (on treatment, treated in the last 6 months, or palliative)	1
Clinical Probability Simplified Score	PE likely >4 points PE unlikely ≤4 point	

*Note: This is also an exclusion criterion if it´s within 6 months before the Baseline.

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Therapeutic measures managing suspected TEEs shall be initiated according to local clinical practice (e.g. anticoagulation).

7.3.5.3 ***Hemolytic Transfusion Reactions (HTRs)***

HTRs can develop subsequent to IVIG therapy. IVIG-related hemolysis is associated with passive transfer of anti-A and anti-B hemagglutinins.

Autoimmune complications are well recognized in CLL, occurring in 5% to 10% of patients at some time during their disease course.[82] Autoimmunity in CLL predominantly targets blood

constituents, and autoimmune hemolytic anemia is the most common form of autoimmune disorder.[83] Although modern treatment minimizes the risk of its development,[84-88] it is planned to perform similar tests in both treatment arms at Baseline Visit since differential diagnosis between autoimmune hemolytic anemia and HTR is complicated.

HTRs will be monitored quarterly from Baseline (see Flow Charts of Assessments):

- Additional safety panel 1 before infusion: serum haptoglobin, plasma-free hemoglobin, and Direct Coombs' test. If a positive result is obtained, the antibodies responsible for the positive test result will be eluted to investigate their specificity (anti-A, anti-B or anti-D). Of note, hemoglobin and LDH will be done as part of the hematology/chemistry tests at every visit before IMP infusion.
- Additional safety panel 2 after infusion: serum haptoglobin, hemoglobin, plasma-free hemoglobin, LDH, and Coombs' test.

Additional Safety panel 2 tests will be performed 24-48 hours following the initial administration of IMP.

Suspected hemolysis will be considered in case of a fall (from the previous regular visit) in serum hemoglobin of >1 g/dL within 28 (± 7) days of last IMP administration, in the absence of non-phlebotomy blood loss, together with a positive Coombs' test.

Confirmed HTRs will be considered in case of fall (from the previous regular visit) in serum hemoglobin of >2 g/dL within 28 (± 7) days of last IMP administration, in the absence of non-phlebotomy blood loss, together with a positive Coombs' test. Confirmed hemolysis cases should satisfy these criteria and meet at least one additional criterion from among the following:

- fall in serum haptoglobin to below the lower limit of normal,
- rise in LDH to above the upper limit of normal,
- rise in indirect or total bilirubin to above the upper limit of normal, or
- rise in plasma-free hemoglobin above the upper limit of normal.

In case a treatment-emergent fall in hemoglobin by >1 g/dL from previous visit is detected, the investigator should evaluate this event and if, according to the investigator's judgement, this drop in hemoglobin is clinically significant, patients should be invited as soon as possible (preferably within 48 hours) to the investigational site and blood should be collected for the Additional Safety Panels 2 tests.

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 for managing suspected and confirmed 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.

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For Italy only: urine pregnancy tests are to be done in WOCBP at every visit starting from Visit 1 before IMP infusion based on local regulations requirements. If positive, a serum pregnancy test will be performed in the Central Laboratory.

7.3.6.1 Central Laboratory

The following laboratory tests will be done at a central laboratory:

- Clinical chemistry: Na+ (sodium), K+ (potassium), glucose, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), LDH, total bilirubin, blood urea nitrogen or urea, creatinine, albumin.
- Hematology: hematocrit, hemoglobin, complete blood count with differential (red blood cell counts, white blood cell counts (neutrophils, eosinophils, basophils, lymphocytes, monocytes, platelets).
- In case **hemoglobin laboratory results from a previous visit** are not available (due to clotting or hemolyzation, etc.), either local or central laboratory retest results for hemoglobin should be available before the next IMP infusion. 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. Any clinically significant abnormal value will be reported as an AE.
- Additional safety panel 1: serum haptoglobin, plasma-free hemoglobin, and Direct Coombs' test.
- Potential risk factors panel: absolute CD4 and CD8 count, CD4/CD8 lymphocyte ratios, immunoglobulin levels (IgG, IgA, IgM), and IgG subclasses at study start.
- Direct Coombs' test: if a positive result is obtained, the antibodies responsible for the positive test result will be eluted in the Central Laboratory to investigate their specificity (anti-A, anti-B or anti-D; no extra visit to the investigational site is required).
- Additional safety panel 2: serum haptoglobin, hemoglobin, plasma-free hemoglobin, LDH, Direct Coombs' test.
- Serum IgG, including all PK samples (results will be blinded for the study duration).
- Viral markers: details see section 7.3.7.
- Pregnancy test: Urine pregnancy test; if positive, a serum pregnancy test will be performed in the Central Laboratory.
- Urinalysis: protein, pH, glucose, ketones, leukocytes, hemoglobin and blood
- D-dimers.

Blood sampling will take place according to the time points given in section 6.1. The methods used for each parameter and the normal ranges of each determination will be provided in the CSR. A laboratory manual detailing blood sampling and shipment procedures will be provided to each study site.

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7.3.6.2 Local Laboratory

The following laboratory tests could be done at a local laboratory:

- D-dimers.

Standard laboratory tests will be done by the local laboratories of each study site if clinically indicated.

7.3.7 Viral Safety Tests

Viral marker samples will be taken at Screening and at the Follow-up/ET Visit. The samples from the Screening Visit will be tested for HIV antibody, HCV PCR, HBsAg, HBc antibodies and HBV PCR in Central Laboratory.

The samples from Baseline will be tested for cytomegalovirus CMV quantitative PCR, CMV IgG and CMV IgM) in Central Laboratory. In case CMV PCR test is positive at the Baseline visit it will be repeated at Visits 5, 8 and 11 in order to detect CMV reactivation. In case of clinical suspicion of CMV infection PCR test to be done for all patients at any visit.

The samples from Baseline will be tested for Epstein-Barr-Virus viral capsid antigen IgG (VCA IgG), VCA IgM, and EBNA-1 IgG in Central Laboratory. In case Epstein-Barr-Virus [EBV] tests are negative at Baseline - EBV PCR will be performed Visits 5, 8 and 11 or in case of clinical suspicion of EBV infection at any visit, in case EBV tests are positive at Baseline - EBV PCR will be performed in case of clinical suspicion EBV infection at any visit.

Screening and Follow Up/ET Visit retention samples will be collected and stored frozen at ≤70°C at the Central Laboratory for possible future testing.

7.3.8 Vital Signs and Physical Examination

The vital signs obtained at the time points specified in section 6.1 are blood pressure, body temperature, pulse rate, and respiratory rate. Measurements will be carried out within 1 hour before, during and 1 to 2 hours after infusion at the Baseline Visit, and 20 minutes to 1 hour after each infusion for subsequent visits. Additionally, vital signs to be measured at the end of the infusion at the Baseline visit. Vital sign abnormalities qualify as AEs and only then will be reported in the eCRF as such. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g. dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the Investigator's judgment

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.

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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 on the Adverse Event eCRF.

Physical examinations will be performed at the visits specified in section 6.1. Both height and weight will be measured at Screening. In addition, body weight is to be measured at each visit (or within 7 days prior to IMP administration). Physical examinations will be performed before administration of any treatment at Screening, Baseline, every 12 weeks, and at Follow-up/ET Visits. A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

Targeted physical examinations should be limited to systems of primary relevance – that is, cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment (lymph nodes, liver, and spleen). Changes from baseline abnormalities at subsequent visits should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

7.3.9 Other Relevant Safety Information

a) Post-study related safety reports

Any SAE which occurs up to 4 weeks after the last IMP administration should be reported by the Investigator to the Sponsor in case the Investigator becomes aware of it. 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 4 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.

Every effort will be made to avoid a pregnancy during the use of an IMP. For WOCBP, not willingness to use a protocol-recommended method of contraception from the Screening Visit throughout the study treatment period and for 30 days following the last dose of study drug is an exclusion criterion. Pregnancies occurring during the study (fetal exposure to the IMP) need to be reported. Pregnancy tests will be completed at Screening Visit.

A WOCBP is defined as a fertile woman, from the beginning of menstruation until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include documented hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A

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postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

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
- 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 the Medpace Clinical Safety (see section 7.3.4).

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

Overdose, interaction, and medication error

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

c) 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.

d) 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.

e) 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.

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7.4 Other Assessments

7.4.1 Drug Concentration Measurements

The trough level IgG concentrations will be measured at each visit (prior to IMP administration) in order to potentially correlate the IgG levels with responder classification.

7.4.2 Blood Sample for Biomarkers, Genotyping and Expression analysis

A biorepository blood samples will be taken at the Baseline Visit in order to investigate potential biomarkers of disease activity (e.g. cytokine, chemokine), genotyping and expression analysis, including blood for DNA, ribonucleic acid (RNA) and protein isolation (patients may choose to not provide DNA sample – separate Inform Consent to be provided).

7.4.3 Quality of Life Assessment

The EQ-5D QoL questionnaire is a standard, validated, instrument that has been widely used in clinical studies, including hematological malignancies and immunodeficiency disorders.[72-74]

The EQ-5D consists of a descriptive system and the EQ visual analog scale (VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ visual analog scale (VAS) records the patient's self-rated health on a vertical visual analogue scale. This can be used as a quantitative measure of health outcome that reflects the patient's own judgment. The scores on these five dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preferability compared to other health profiles.

7.5 Appropriateness of Measurements

The study design includes all major scientific, state-of-the-art interventions needed to assess the efficacy, safety and tolerability of therapeutic treatments in CLL patients with secondary hypogammaglobulinemia. The measurements selected in this study are appropriate to verify the clinical efficacy of IVIG primary infection prophylaxis in treatment-naïve or relapsed/refractory CLL patients with SID.

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.[70,71]

AEs will be evaluated with regard to the infusion rates. Renal function will be monitored, particularly in patients at risk.[70,71]

Retention samples from each patient will be stored at -70°C for possible future testing.[70]

The effect of passive transmission of hemagglutinins and hemolysins (anti-A/anti-B), and anti-D will be evaluated by searching for hemolysis and performing a direct antiglobulin test (direct Coombs' test) in the patient at Baseline and Follow-up Visits.[70,71]

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In addition, routine hematology, serum chemistry tests, and urinalysis will be obtained at Baseline and at the Follow-up Visit.[71] Secondary endpoints include overall infection rate and frequency and duration of prophylaxis with anti-infective treatment.

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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.

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 or an authorized sub-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 entry or change eCRF data must be listed in the Delegation of Authority Log.

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8.1.3 Changes to Electronic Case Report Form (eCRF) Data

Study 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 a 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.

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8.2 Information to Investigators

An IB will be handed out 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.

Monitoring will be done by a CRO.

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, 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 eCRFs, 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 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 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 Study Committees

8.6.1 Independent Endpoint Adjudication Board

An IEAB will be established by the Sponsor. The IEAB will be composed of five permanent members who shall have – as a group – experience in the fields of hematology and infections. The members of the IEAB must not actively recruit patients.

The responsibility of the IEAB will be to review individual case histories and to assess disease infection severity in a blinded manner. An IEAB charter will be developed before study start to serve as the central reference document for the IEAB process and its participants. The charter will define, at a minimum, the purpose of the IEAB, member requirements and qualifications, event definitions, adjudication rules, and voting scheme that will document how events will be adjudicated and how final IEAB decision will be reached.

8.6.2 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established by the Sponsor. The IDMC will be composed of recognized experts in the fields of hematology and infection who are not actively recruiting patients, and an unblinded statistician.

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The IDMC will review relevant data periodically during the study and will give advice on the continuation, modification, or termination of the study.

The IDMC will have the following responsibilities:

- to review relevant safety data periodically;
- to review TEEs and HTRs in a timely fashion;
- to advise on the futility (see section 9.1), 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 hematology, infection diseases and SID not otherwise involved into this study 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. The Steering Committee will also be responsible for any decision with regard to the biorepository blood samples as defined in section 7.4.2.

The Steering Committee will be kept blinded until the blind is officially broken.

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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

The reported incidence of infections in patients with hematologic malignancies ranges between 20 and 50%. Of note, infection rates in patients with hypogammaglobulinemia are much higher and reported to be between 25 and 85% in CLL patients.

Most studies suggest a 4-fold reduction of infectious complications by IVIG. From this, our initial expectations for the proportions of patients with a primary infection would be around 20% for patients without prophylactic Panzyga, and between 5% and 10% for patients with prophylactic Panzyga. Our goal is to demonstrate superiority of Panzyga prophylaxis in preventing serious infections with an overall α of 0.025 (1-sided test) and a power of 80%. Because of the wide range of infection rates reported in patients with hypogammaglobulinemia mentioned above, an adaptive study design with an interim analysis after 100 patients have provided evaluable data (i.e. have either experienced one major infection or have completed the study without any major infection) will be performed. The interim analysis is only intended for sample size recalculation.

Assuming the proportion of patients with a major infection is 7.5% in the Panzyga arm (i.e. in the middle of the 5-10% range derived from literature), and a Lan-DeMets implementation of the O'Brien-Fleming type I error spending function leads to an overall sample size of 240 patients (120 per arm) at the final stage to provide 80% power to detect the difference at 1-sided 0.025 level.

The following clinical stopping rule will be implemented:

- If the lower limit of the 95% Wald confidence interval for the risk difference (Panzyga–Placebo) is above 0 at the interim analysis, the study will be stopped for futility. Remark: The same rule will be applied whenever the IDMC reviews data in an unblinded fashion, and at least 50 patients are available for the review.

At the interim stage, sample size will be re-estimated using the methodology described by Cui et al.[89] Please refer to the SAP for details and formulae.

The updated sample size will be capped at 450 patients, a limit imposed by operational constraints.

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9.2 Statistical Analysis

A formal SAP describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to the start of the statistical analysis.

The primary endpoint parameter in this study is the occurrence of major infection in CLL patients with or without primary infection prophylaxis with Panzyga. Although patients will stay in the study regardless of the number of major infections, each patient for the primary endpoint

calculation will be counted only once. The proportion of patients with such a major infection will be determined in both randomized treatment groups, and the following hypotheses will be tested:

$$H0: \pi c - \pi o \leq 0 \text{ vs. } Ha: \pi c - \pi o > 0$$

where πo and πc are the proportion of patients with a major infection in the Panzyga + SoC and the placebo + SoC respectively.

The Z approximation will be used for statistical comparison of the proportions observed. One-sided 97.5% CI will be provided. Please refer to the SAP for the calculation details.

Analyses of the primary efficacy variable will be performed for subgroups of patients based on baseline characteristics for the following:

- Age group (<65 years, ≥65 years)
- Sex (male versus female)
- Race (white versus not white)

Additional subgroups may be considered.

9.2.1 Populations for Analysis

The following populations will be considered for the statistical analysis:

The **Intent-to-Treat (ITT)** Population will include all randomized patients, regardless of whether the patient actually received study drug.

The **full analysis set (FAS)** will include all randomized patients who received at least part of one infusion of Panzyga or placebo. The FAS will coincide with the safety set (see below).

The **per-protocol set (PP)** consists of all patients of the FAS, excluding those with protocol deviations that may have an impact on the evaluation of the primary study outcome parameter. Only significant protocol deviations with the potential to affect the study results significantly, or to invalidate the interpretation of the data obtained, will lead to exclusion of patients from the PP set; protocol deviations to be considered will include (but will not be limited to):

- Violations of the study entry criteria
- Withdrawal criteria that developed during the study
- Wrong treatment or incorrect dose
- Prohibited concomitant medication

All protocol deviations documented during the conduct of the study or identified at the data review process prior to DB lock will be reviewed and classified as minor or major and with respect to their significance for the planned analyses. This classification of protocol deviations is the joint responsibility of the clinical study manager, the study statistician, and Octapharma's responsible medical expert, and will be agreed and documented before the database is locked and the statistical analyses are performed.

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For this study, no separate safety population is defined as the FAS coincides with all patients who received at least part of one infusion of Panzyga or placebo. All safety data will thus be analyzed using the FAS. In the event that a subject takes the wrong study drug (*i.e.* did not take the randomized study drug), the actual treatment received will be used for safety analyses.

All efficacy analyses will be based on the ITT population. All efficacy analyses will follow the intent-to-treat principle, i.e. patients will be analyzed according to the group they were originally assigned, regardless of what treatment they actually received. Selected efficacy analyses (at least the primary and secondary efficacy analyses) will be repeated for the FAS and PP population.

Screening failures will only be accounted for in the overall subject disposition, and individual data will be listed.

9.2.2 Efficacy Analysis Plan

The primary efficacy evaluation is based on the comparison of major infections (see section 7.3.5.1) in CLL patients with or without primary infection prophylaxis with Panzyga. The difference between these proportions will be statistically tested in the ITT population (see section 9.2.1). The Z approximation will be used for statistical comparison of the proportions observed. One-sided 97.5% confidence interval (CI) will be provided.

For analyses based on the ITT population, patients with missing data who are randomized but not treated, or who are lost to follow-up, missing endpoint data will be imputed using the multiple imputation method assuming that missing at random (MAR).

Sensitivity Analyses

- Sensitivity 1: Conservative approach. This sensitivity analysis assumes the patients who drop out from the study as an occurrence of major infection, taking the worst-case approach.
- Sensitivity 2: Primary endpoint analyzed using the stratified logistic regression model with treatment as the main effect and the three stratification factors as the covariates.

Secondary efficacy endpoints will be evaluated as follows. The secondary efficacy endpoints included in the hierarchical step-down testing procedure include the following parameters in a fixed sequence of: (1) Overall infection rate, (2) Frequency of prophylaxis with anti-infectives, and (3) Duration of anti-infective prophylaxis:

1. Overall infection rate: infection rate for all infections. The infection rate is defined to be the number of infections per person-year. The overall infection rate will be presented for both treatment groups. It will be tested using Poisson regression model including the overdispersion correction with the number of infections observed per person-year as dependent variable, treatment group as the main effect and the three stratification factors as covariates. Estimate for treatment difference, p-value together with the associated one-sided 97.5% confidence intervals will be provided.

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A sensitivity analysis will include an adjustment for the period of IVIG other than Panzyga. The overall infection rate will be tested using Poisson regression model including the overdispersion correction with the number of infections observed per person-year as dependent variable, treatment group as the main effect, the number of days on IVIG as a factor, and the three stratification factors as covariates. Estimate for treatment difference, p-value together with the associated one-sided 97.5% confidence intervals will be provided

2. The frequency of prophylaxis with anti-infectives (antibacterials and antivirals) is defined as the number of occurrences for each patient who receive prophylaxis with anti-infective treatment including antibacterials and antivirals. It will be tested using Poisson regression model including the overdispersion correction with the number of occurrences for each patient who receive prophylaxis with anti-infectives as dependent variable, treatment group as the main effect and three stratification factos as covariates. Estimate for treatment difference, p-value together with the associated two-sided 95% confidence intervals will be provided. A sensitivity analysis will include an adjustment for the period of IVIG other than Panzyga.
3. The duration of anti-infective prophylaxis (antibacterials and antivirals) is defined as the sum of the number of days of the patients who receive prophylaxis with anti-infective treatment including antibacterials and antivirals. It will be tested using a Poisson regression model including the overdispersion correction with the duration of anti-infective prophylaxis as dependent variable, treatment group as the main effect and three stratification factors as covariates. Estimate for treatment difference, p-value together with the associated two-sided 95% confidence intervals will be provided. A sensitivity analysis will include an adjustment for the period of IVIG other than Panzyga.

The secondary efficacy analysis will be repeated for the FAS and PP population.

The exploratory efficacy endpoints of the following parameters will be summarized descriptively by treatment groups with no hypothesis testing:

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

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[redacted]

Pharmacokinetic parameters will be determined in a subgroup of patients (PK sub-study):

Blood samples for the PK profiles of total IgG will be taken at the following 10 time points during and after Visit 9:

- Before the start of infusion (trough level)

Of note, the IgG sample taken prior to infusion at Visit 9 is considered as pre-dose/baseline sample for the PK sub-study.

- After the end of infusion:
  - 15 minutes ±5 minutes
  - 1 hour ±15 minutes
  - 4 hours ±15 minutes
  - 24 hours ±1 hour
  - 72 hours ±1 hour
  - 7 days ±1 day
  - 14 days ±1 day
  - 21 days ±2 days
  - 28 days ±2 days (trough level prior to subsequent infusion).

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Of note, IgG sample taken at Visit 10 is considered as PK sample Day 28. Visit 10 IMP infusion cannot proceed without this sample. If Visit 10 is delayed for more than 2 days, sites should schedule an extra visit to collect the 28-day post-dose PK sample in a timely manner.

The following parameters will be assessed for patients treated with Panzyga.

- Half-life ($T_{1/2}$)
- Area under the curve (AUC_{0-t}; $AUC_{0-infinity}$)
- Volume of distribution (V_d)
- Concentration maximum (C_{max}; T_{max})
- Clearance (Cl)

For patients treated with Placebo, no PK parameters will be estimated, as the underlying assumptions for exponential modelling are not fulfilled.

PK parameters will be estimated with both, baseline-corrected and uncorrected values. All individual IgG values will be listed and presented graphically, individual PK profiles will be presented as rectilinear and semi-logarithmic plots. Descriptive statistics of IgG concentrations per time point will be presented. The derived PK parameters will be listed by patient, and summarized by descriptive statistics, in total as well as by subgroups of interest, including age (<65 years, ≥65 years).

All available IgG trough concentration data will be presented per patient, and compared between treatment groups by descriptive statistics, including plots of IgG troughs over time and summary statistics by time points. The number and proportion of patients above/below the target level will be presented by time point as well. IgG trough level data will be summarized for the Panzyga treatment arm for the whole study duration and in addition separately during the steady state (after 5 estimated half-lives – starting from Visit 8).

The relationship between the occurrence of major infections to the latest IgG trough measurement preceding the onset of infection will be evaluated to identify possible patterns, and to evaluate the predefined minimum target IgG level for infection prophylaxis.

The minimum target IgG level of 6g/L for infection prophylaxis was selected based on the international guidelines on secondary infection prophylaxis with immunoglobulins in CLL patients[91,92,93] and available clinical trial data[94].

Univariate statistics for trough IgG preceding the occurrence of major infections will be presented alongside the same statistics for infusion periods without such infection.

Pharmacoeconomic evaluation for the study duration will be summarized descriptively by treatment group and overall for the following parameters:

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

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Additional pharmacoeconomic modeling will be conducted by a specialist in the field to evaluate the cost effectiveness of Panzyga as an add-on treatment to SoC treatments. This modeling will be described in a separate plan at a later time and reported separately from the CSR standard output.

9.2.3 Safety Analysis Plan

Safety data will be summarized by actual treatment received (and in total for selected analyses) based on the FAS. Safety data will be present before and after the time point when IMP treatment was stopped due to infections and medically relevant additional concomitant medication was introduced.

Adverse Events (AEs)

AEs will be captured from Baseline through to study completion. All AEs will be coded to system organ class and preferred term using the latest version of MedDRA. Treatment-emergent adverse events are defined as AEs that start after the first dose of study drug but not more than 28 days after the last dose of study drug. Nevertheless, all AEs will be collected throughout the observation period, and included in the analyses of infections and adverse events of special interest.

An overview of AEs will be provided including counts and percentages of subjects (and event counts) with the following:

- Any TEAEs (overall and by maximum severity)
- Any study drug related TEAEs (overall and by maximum severity)
- Any SAEs
- Any TEAEs leading to discontinuation of study drug
- Any study drug related TEAEs leading to discontinuation of study drug
- Any AEs leading to death
- AEs that occur during or within: (a) 1 hour, (b) 24 hours, and (c) 72 hours following an infusion, regardless of other factors that may impact the causality assessment

Counts and percentages of subjects (and event counts) will also be presented by system organ class and preferred term for each of the categories in the overview.

A list of subjects who have SAEs, and a list of subjects who discontinue from study drug will be provided. All adverse events will be listed.

Clinical Laboratory Tests

All laboratory data will be converted to standard units during the Data Management process. The laboratory data will be listed with suitable flags indicating abnormal values (L=Lower than reference range, H=Higher than reference range).

Summary statistics for the laboratory values as well as their changes from baseline will be tabulated for all laboratory parameters. The tables on changes in lab parameters will feature columns for each study drug and a total column in a side-by-side fashion.

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Vital Signs

To evaluate short-term tolerance, monitoring of vital signs including blood pressure, body temperature, pulse and respiratory rate will be performed before, during and after end of each infusion at time points specified in the protocol. These measurements will however not be entered into the clinical database, but only reported in case of vital sign abnormalities that qualify as AE according to the definition given in the protocol.

Physical Examinations

General physical examination will be performed throughout the study at visits specified in the protocol. All documented abnormalities will be listed.

9.2.4 Handling of Missing Data

Multiple imputation method will be used for missing data in the primary endpoint analyses.

In cases of missing or incomplete data (e.g. dates of AEs and concomitant medications), the missing component(s) will be assumed as the most conservative value possible. For example, AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of study drug or ended prior to the start of study drug. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered as treatment-emergent. Actual data values as they appear in the original eCRF will be presented in the data listings.

Missing values for other variables will not be imputed and only observed values will be used in data analyses and presentation.

9.3 Randomization, Stratification, and Code Release

All patients qualified to participate in the study at Baseline (Week 0) will be randomized to one of the two treatment arms by an electronic IRT tool and thereby enrolled into the double-blind treatment period. The randomization will assign each patient to one of the 2 treatment groups: SoC treatment plus regular infusions of Panzyga or SoC treatment plus regular infusions of placebo (0.9% w/v sodium chloride).

The randomization scheme for this trial will not be realized by means of randomization lists (except for the first 16 patients), but a baseline adaptive randomization procedure will be deployed to consider a number of co-variates that have been identified as potentially relevant for the primary endpoint (see section 4.4). An attempt will be made to balance the randomization with respect to these patient characteristics of interest; the planned randomization procedure to achieve this is an extended implementation of the baseline adaptive randomization presented by Smoak and Cheney[90]:

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- The first 16 patients will be randomized in a 1:1 ratio without considering the covariates, by means of a single initial randomization list featuring a block size of 4. After that, a pre-defined block size will be applied.
- From the 17th randomization onwards, for each covariate, treatment imbalance (or deviation from the desired treatment allocation ratio) with the given level of the covariate is evaluated by Pearson's chi-square test statistic for goodness-of-fit.
- A new patient is initially assigned to the treatment group that results in the smallest maximum deviation, given that the particular treatment assignment is available in the current block. If the maximum statistic is the same for both assignments, the system 'tosses a coin' to determine the initial assignment for this patient.
- In case the initial treatment assignment determined in the previous step is not available in the current block, the patient is assigned to the alternative treatment, otherwise the initial assignment becomes the final one.

The actual randomization and the status of the above-mentioned program will only be available to the responsible, unblinded statistician, and the programmer implementing the scheme into the IRT system. No information on treatment assignment will be communicated to the Sponsor or any CRO personnel responsible for the conduct of the study or the analysis of data.

The result of randomization, i.e. the treatment group assignment of individual patients will only be reported to the hospital pharmacist or designee by a defined manner that no other trial personnel will have access to.

Blinding will only be broken in circumstances described in section 5.6 of the protocol.

Only after completion of all procedures related to data cleaning, the medical review of the data, the finalization of the SAP, the agreement on the final patient disposition, and the formal database lock, the blind will be broken and the individual treatment assignment will be added to the clinical database for analysis.

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9.4 Interim Analysis

Because published data on incidences of infections in CLL patients with hypogammaglobulinemia are scarce, varying and only partly applicable to the current study setup, we plan for an interim analysis to verify the initial assumptions with respect to the proportions of patients with major infections in the two treatment groups, and to allow for a sample size re-estimation to achieve the desired power of 80% while maintaining the overall type 1 error rate of 2.5%.

The interim analysis will be conducted once at least 100 patients are available for evaluation of the primary endpoint in the ITT population (see section 9.2.1). Enrollment will continue while the interim analysis is conducted which is in line with our initial expectation that the study will be continued after the interim analysis. At the interim stage a clinical stopping rule on basis of the risk difference with respect to major infections will be applied. The sample size will be re-estimated, and that the adjusted maximum total number of patients to be enrolled will be 450,

a maximum imposed by operational constraints. The interim analysis is only intended for sample size recalculation.

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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 will obtain freely given written consent from each patient after 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. 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.

The Investigator 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 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. An optional and separate informed consent will be provided for the purpose of the biorepository for genotyping and expression analysis.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Investigator (Co-ordinating Investigator in multi-center studies) and the Sponsor prior to its implementation. Any such

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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.

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11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The Study Monitor will contact and visit the Investigator periodically to review study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of eCRF entries compared to source data. Risk Based Monitoring approach will be implemented in this study. The Investigator will co-operate with the Study Monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take place shortly after the inclusion of the first patient. Thereafter, monitoring frequency will depend on study progress.

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.

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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.

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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 Appendix 1: Eastern Cooperative Oncology Group Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Reproduced from Oken MM, *et al*. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-55.

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15.2 Appendix 2: Rai classification and Binet staging systems for CLL

Rai stage (simplified 3-stage)	
0 (low risk)	Lymphocytosis in blood and marrow only
I and II (intermediate risk)	Lymphadenopathy, splenomegaly +/− hepatomegaly
III and IV (high risk)	Anemia, thrombocytopenia
Binet group	
A	Fewer than 3 areas of lymphadenopathy; no anemia or thrombocytopenia
B	More than 3 involved node areas; no anemia or thrombocytopenia
C	Hemoglobin < 100 g/L platelets < 100 × 10 g/L

Based on Rai KR, *et al*. Clinical staging of chronic lymphocytic leukemia. *Blood* 1975;46:219-34 and Binet JL, *et al*. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer* 1981;48:198-206

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