octapharma®
For the safe and optimal use of human proteins

Statistical Analysis Plan

Version: 5.0

Date: 02-Sep-2025

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

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

Copying or distribution of this document is only permitted with the written permission of Octapharma. Any commercial use of the information is subject to the permission of Octapharma and a license fee.

MEDPACE

STATISTICAL ANALYSIS PLAN

Protocol 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)
Protocol Number:	NGAM-12
Protocol Version/Date:	Version 7.0, 14 November 2022
Investigational Product:	Panzyga
Sponsor:	Octapharma Pharmazeutika Produktionsges.m.b.H. Oberlaaer Str. 235, 1100 Vienna, Austria
SAP Version/Date:	Version 5.0, 02 September 2025
Doc-Id:	3076

Property of Octapharma. Do not copy or distribute without written permission.

[redacted]

The information in this document [redacted] is not to be disclosed without the written consent of Octapharma except to the extent that disclosure would be required by law and for the purpose of evaluating and/or conducting a clinical study for Octapharma. You are allowed to disclose the contents of this document only to your Institutional Review Board or Independent Ethics Committee and study personnel directly involved with conducting this protocol. Persons to whom the information is disclosed must be informed that the information is [redacted] proprietary to Octapharma and that it may not be further disclosed to third parties.

SIGNATURE PAGE

Protocol 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)
Protocol Number:	NGAM-12
SAP Version/Date:	Version 5.0, 02 September 2025

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	**Date**
signatures on the file	
[redacted] Medpace, Inc.	
[redacted] Medpace, Inc.	
[redacted] Octapharma	
[redacted] Octapharma	

Property of Octapharma. Do not copy or distribute without written permission.

VERSION HISTORY

Version	Version Date	Author	Description
Final 1.0	11 November 2019	[redacted]	Original signed version
Final 2.0	11 December 2019	[redacted]	• Remove of treatment switch, but continued follow-up after IMP withdrawal • Revision of clinical stopping rule for futility • Adding a stopping rule for TEEs • Inclusion of ITT population • Additional analysis by infection type (viral/ bacterial) • Revised method for sample size re-estimation • Definition of suspected adverse drug reactions
Final 3.0	22 June 2020	[redacted]	• Updated the objectives/endpoints per protocol updates • Revised determination of sample size • Revised Populations for analysis • Revised statistical methodology • Removed the stopping boundary for interim analysis
Final 4.0	31 July 2023	[redacted]	• Sections 2.1.3, 2.3.3, 3.4.3: Exploratory endpoints updated based on changes in protocol versions 6.0 and 7.0. • Section 2.2.1: SARS-CoV-2 vaccine was added to SoC treatment options. • Section 2.2.2: IRT stratification details updated to match protocol V.7.0. • Sections 2.2.3: Sample Size Determination and 7.1 Interim Analysis: updated to include further details on the sample size re-estimation method and to specify validation will be performed by an independent consultant. • Section 2.3.1: Definition of "Major Infection" updated to match protocol V.7.0 – definition now excludes confirmed cases of COVID-19.
Final 5.0	02 September 2025	[redacted]	• Section 3.4.3: Added the analyses of 'frequency of anti-infective treatment of infections'. • Section 3.2: Added the Pharmacokinetic (PK) analysis populations. • Section 3.3: Added the baseline summary analyses for the risk factors. • Section 3.5.1: Added the summary analyses of adverse events of special interest (AESI).

Property of Octapharma. Do not copy or distribute without written permission.

TABLE OF CONTENTS

1 Introduction 7
2 Study Overview 7
2.1 Study Objectives 7
2.1.1 Primary Objective 7
2.1.2 Secondary Objectives 7
2.1.3 Exploratory Objectives 7
2.1.4 Safety Objective 8
2.1.5 Pharmacoeconomic Objectives 8
2.2 Study Design 8
2.2.1 Overview 8
2.2.2 Randomization, stratification and Blinding 9
2.2.3 Sample Size Determination 10
2.3 Study Endpoints 11
2.3.1 Primary Efficacy Endpoint 11
2.3.2 Secondary Efficacy Endpoints 12
2.3.3 Exploratory Efficacy Endpoints 12
2.3.4 Safety Endpoints 13
2.3.5 Pharmacoeconomic Endpoints 13
3 Statistical Methodology 13
3.1 General Considerations 13
3.1.1 Analysis Day 13
3.1.2 Definition of Baseline 14
3.1.3 Summary Statistics 14
3.1.4 Handling of Dropouts and Missing Data 14
3.2 Analysis Populations 14
3.2.1 Intent-to-Treat (ITT) 14
3.2.2 Full Analysis Set (FAS) 14
3.2.3 Per-Protocol Set 14
3.2.4 Pharmacokinetic Population 15
3.2.5 Pharmacokinetic Sub-Study Population 15
3.2.6 Pharmacokinetic Sub-Study Evaluable Population 15
3.2.7 Analysis of Safety 15
3.2.8 Analysis of Efficacy 15
3.3 Patient Data and Study Conduct 15
3.3.1 Patient Disposition 15
3.3.2 Protocol Deviations 16
3.3.3 Demographic and Baseline Characteristics 16
3.3.4 Medical History 17
3.3.5 Concomitant Medications 17
3.3.6 Measurement of Treatment Compliance 17

Property of Octapharma. Do not copy or distribute without written permission.

3.4 Efficacy Assessment 17
3.4.1 Primary Efficacy Endpoints 18
3.4.2 Secondary Efficacy Endpoints 18
3.4.3 Exploratory Efficacy Endpoints 19
3.4.4 Pharmacoeconomic Endpoints 21
3.4.5 Subgroups 21
3.5 Safety Assessment 21
3.5.1 Adverse Events (AEs) 21
3.5.2 Clinical Laboratory Tests 22
3.5.3 Vital Signs 22
3.5.4 Physical Examinations 22
4 Independent Endpoint Adjudication Board 23
5 Independent Data Monitoring Committee 23
6 Steering Committee 23
7 Sequence of Planned Analyses 23
7.1 Interim Analysis 23
7.2 Final Analyses and Reporting 24
8 Changes From Protocol-Specified Statistical Analyses 24
9 Programming Specifications 25
10 References 25

Property of Octapharma. Do not copy or distribute without written permission.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Events of Special Interest
ATC	Anatomical Therapeutic Chemical
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
BMI	Body Mass Index
CDI	Clinically Documented Infection
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CSR	Clinical Study Report
C_{max}	Maximum observed plasma concentration
DB	Database
eCRF	Electronic Case Report Form
ET	Early Termination
FAS	Full Analysis Set
FUO	Fever of Unknown Origin
HTR	Hemolytic Transfusion Reactions
IDMC	Independent Data Monitoring Committee
IEAB	Independent Endpoint Adjudication Board
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IVIG	Intravenous Immunoglobulin
MAR	Missing at Random
MDI	Microbiologically Documented Infection
MedDRA	Medical Dictionary for Regulatory Activities
OS	Overall Survival
PP	Per-Protocol
PK	Pharmacokinetic
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SID	Secondary Immunodeficiency
SoC	Standard of Care
TEAE	Treatment-Emergent Adverse Events
TEE	Thromboembolic Event
T_{max}	Elapsed time to C_{max}
WHO	World Health Organization

Property of Octapharma. Do not copy or distribute without written permission.

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number NGAM-12. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

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

2.1.2 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)

2.1.3 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 quality of life (QoL) assessments
- Relationship between efficacy outcomes (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.

Property of Octapharma. Do not copy or distribute without written permission.

2.1.4 Safety Objective

- To evaluate the product safety of Panzyga administration

2.1.5 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.

2.2 Study Design

2.2.1 Overview

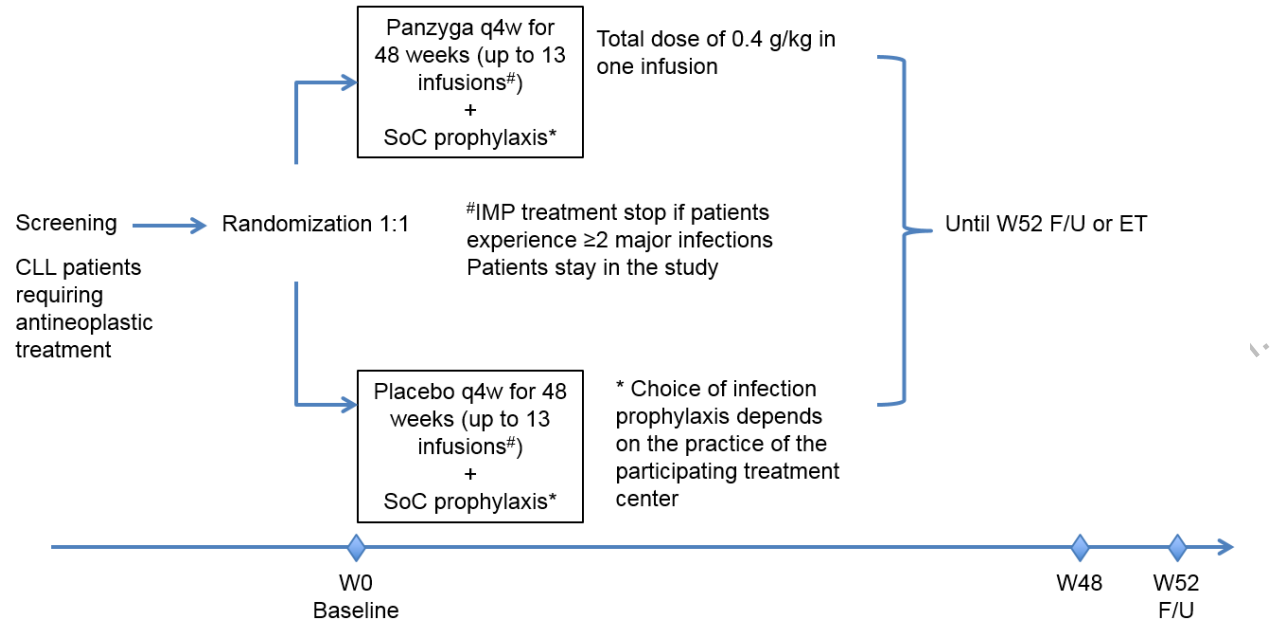
The study will be a double-blind, randomized, placebo-controlled, prospective, multicenter, interventional phase III clinical study in a minimum of 240 adult patients of both genders with treatment-naïve or relapsed/refractory CLL and secondary hypogammaglobulinemia (IgG levels <5 g/l) undergoing CLL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

About 50 sites are projected to participate in United States, Western Europe and Central/Eastern Europe.

After Screening, eligible patients will be randomized 1:1 to receive either up to 13 infusions of Panzyga plus standard of care (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), will stop their treatment with IMP and will start getting non-study secondary infection prophylaxis according to the local standards of care, as recommended in clinical practice guidelines. Such patients will stay in the study till Week 52 regardless at what visit they stop the treatment with IMP. The study schedule will remain unchanged for these patients (except IMP infusions), for more details please go to the Protocol Flow Chart.

The overall study design can be depicted as follows:

Property of Octapharma. Do not copy or distribute without written permission.



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

2.2.2 Randomization, stratification and Blinding

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
- 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.

Property of Octapharma. Do not copy or distribute with

- 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

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[1].

- 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) within the given level of the covariate is evaluated by Pearson's chi-square test statistic for goodness-of-fit.
- A new subject 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 abovementioned 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 in 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.

2.2.3 Sample Size Determination

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 intravenous immunoglobulin (IVIG).

From this, our initial expectations for the proportions of patients with a major 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 IVIG prophylaxis in preventing major 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

Property of Octapharma. Do not copy or distribute without written permission.

after 100 patients have provided evaluable data (i.e. have either experienced one infection or have completed the study without any infection) will be performed. For the purposes of the interim analysis "completed the study" is defined as having been under observation for at least 350 days since treatment start. The interim analysis is intended for sample size recalculation.

Assuming the proportion of patients with a major infection is 7.5% in the IVIG arm (i.e. at the middle of the 5 percentage points 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:

At interim analysis N=100 (information fraction 0.417), Z statistics (Z_1) will be calculated. If Z_1 is above - 0.176, the study will be stopped for futility.

The interim analysis will be based on patients qualifying for the ITT Population.

At the interim stage sample size will be re-estimated using the methodology described in Cui, Huang and Wang (1999), Mehta and Pocock (2010) and Kieser (2020). The infection rates $\boldsymbol{P_E}$ and $\boldsymbol{P_C}$ are defined as follows:

1) **Treatment group ($\boldsymbol{P_E}$)**: SoC treatment plus regular infusions of Panzyga;
2) **Placebo group ($\boldsymbol{P_C}$)**: SoC treatment plus regular infusions of placebo.

Conditional power will be calculated using $CP(z_1, \widetilde{n_2}) = 1 - \Phi\left(\frac{Z_{\alpha 2}\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{\widetilde{n_2}}} - \frac{z_1\sqrt{\widetilde{n_2}}}{\sqrt{n_1}}\right)$, where α_2 = 0.024. When CP is within 40% and 80%, sample size will be calculated using $N'(z_1) = n_1 + \left[\frac{n_1}{z_1^2}\right]\left[\frac{Z_{\alpha 2}\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{n_2 - n_1}} + z_\beta\right]^2$.

- Z_1 is test statistics of the treatment difference at interim analysis, $z_1 = -\left(\frac{\widehat{p_E} - \widehat{p_C}}{\sqrt{\frac{\widehat{p_E}(1-\widehat{p_E})}{\widehat{N_E}} + \frac{\widehat{p_C}(1-\widehat{p_C})}{\widehat{N_C}}}}\right)$.
- n_1 is total sample size from treatment group and control group at interim or $\widehat{N_E} + \widehat{N_C}$.
- $\widehat{p_E}$ and $\widehat{p_C}$ are estimated major infection rates from treatment group and control group.
- n_2 is planned sample size, 240.
- $\widetilde{n_2}$ is incremental sample size after interim or $n_2 - n_1$.
- Z_{a2} and Z_β are 1.98 and 0.84.

The updated sample size N′ will then be given by the minimum of (Nmax, N'(z_1)), Nmax being the maximum sample size in this trial imposed by operational constraints, which is 450. If the re-estimated sample size N' from the interim analysis is smaller than the initial planned sample size N, the sample size adjustment will not be needed.

Property of Octapharma. Do not copy or distribute without written permission.

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoint

Since the study objective is to demonstrate 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 for the primary endpoint calculation will be counted only once. 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 infection 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).
- MDI or CDI bacterial and/or viral infections requiring treatment with anti-infectives; upper respiratory tract infections, MDI or CDI bacterial and/or viral infections requiring treatment with anti-infectives; upper respiratory tract 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.

2.3.2 Secondary Efficacy 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).

2.3.3 Exploratory Efficacy Endpoints

[redacted]

Protocol and data property of Octapharma. Do not copy or distribute without written permission.

[redacted]

2.3.4 Safety Endpoints

[redacted]

2.3.5 Pharmacoeconomic Endpoints

[redacted]

Property of Octapharma. Do not copy or distribute without written permission.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

The primary confirmatory efficacy analysis will be a straightforward comparison of proportions to demonstrate superiority, and secondary efficacy endpoints will be included in a hierarchical step-down testing procedure; please refer to section 3.4 for details.

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Definition of Baseline

Baseline is defined as the last measurement prior to the first dose of study drug.

3.1.3 Summary Statistics

Categorical data will generally be summarized with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

3.1.4 Handling of Dropouts and Missing Data

Multiple imputation method will be used for missing data in the primary and secondary endpoints analyses.

In cases of missing or incomplete dates (e.g. AE 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 electronic Case Report Form (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.

3.2 Analysis Populations

The following two populations will be considered for the statistical analysis:

3.2.1 Intent-to-Treat (ITT)

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

3.2.2 Full Analysis Set (FAS)

The full analysis set (FAS) will include all randomized patients who received at least part of one infusion of Panzyga or placebo.

3.2.3 Per-Protocol Set

The per-protocol set (PP) consists of all patients of the FAS, excluding those with protocol deviations which may have an impact on the evaluation of the primary study outcome parameter(s). 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

Property of Octapharma. Do not copy or distribute without written permission.

All protocol deviations documented during the conduct of the study or identified at the data review process prior to database (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.

3.2.4 Pharmacokinetic Population

The Pharmacokinetic (PK) population consists of all patients who received at least 1 dose of study drug and have at least 1 quantifiable post-dose IgG concentration.

3.2.5 Pharmacokinetic Sub-Study Population

The PK sub-study population consists of all patients enrolled in the PK sub-study who received at least 1 dose of study drug and have at least 1 quantifiable post-dose IgG concentration within the PK sub-study.

3.2.6 Pharmacokinetic Sub-Study Evaluable Population

The PK sub-study evaluable population consists of all patients enrolled in the PK sub-study who received at least 1 dose of Panzyga and have at least 1 quantifiable post-dose IgG concentration within the PK sub-study.

3.2.7 Analysis of Safety

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 be 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.

3.2.8 Analysis of Efficacy

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, but 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.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Counts and percentages of patients who were screened (signed informed consent), discontinued early during screening (screen failures), and randomized will be summarized in total based on all screened subjects. Reasons for early discontinuation will also be summarized.

Counts and percentages of patients who were randomized, discontinued early from the study drug, discontinued early from the study, completed the study treatment, and completed the study will be summarized by treatment and in total based on all randomized subjects. Reasons for early discontinuation will also be summarized.

Property of Octapharma. Do not copy or distribute without written permission.

Counts and percentages of subjects in each analysis population will be summarized by treatment and in total based on all randomized subjects. Reasons for exclusion from each analysis population will also be summarized.

Patient disposition data will be presented in a data listing.

3.3.2 Protocol Deviations

Protocol deviations as defined in the Medpace Protocol Deviation Plan will be summarized for the ITT. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall, by treatment group and total. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol deviation will be counted once in the overall summary.

A data listing will be provided by patient.

3.3.3 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (<65 years, ≥65 years)
- Sex
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2) and BMI categories (<30 kg/m^2, ≥30 kg/m^2)
- Countries/regions (North America, Western Europe, Central and Eastern Europe)
- CLL treatment groups (Chemoimmunotherapy and anti-CD20 containing regimens, Small molecule inhibitors and Other treatment)
- CLL treatment status (Treatment-naïve (in case patient is randomized at the start of or during the first line CLL antineoplastic therapy) and Relapsed/refractory)
- Current clinical stage of CLL (Rai stage 0, Rai stage I , Rai stage II , Rai stage III, Rai stage IV)
- Neutrophils (10^9/L)
- Lymphocytes (10^9/L)

[redacted]

Property of Octapharma. Do not copy or distribute without written permission.

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by treatment and in total for all randomized subjects and each defined analysis population.

3.3.4 Medical History

Medical history will be coded to system organ class and preferred term using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Counts and percentages of subjects with medical history by system organ class and preferred term will be summarized by treatment and in total based on ITT Population.

3.3.5 Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class Level 2 and Level 4 using the latest version of World Health Organization (WHO) Drug Dictionary. For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug and concomitant medications if they were taken at any time after the first dose of study drug (i.e. started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).

Counts and percentages of subjects taking prior and concomitant medications by ATC class Level 2 and Level 4 will be summarized by treatment and in total based on the ITT Population.

Counts and percentages of patients who received prior IVIG other than Panzyga and duration of the prior IVIG period (days) will be summarized by treatment and in total based on the ITT Population.

3.3.6 Measurement of Treatment Compliance

The following parameters will be listed and summarized per subject and/or per infusion cycle:

- Body weight
- Actual dose (total and per kg body weight, based on the latest available weight measurement)
- Total dose administered
- Total number of infusions administered
- Infusion times
- Overall amount of product administered (only included in data listings)

Deviations from the planned treatment schedule will be summarized by counting the number of infusion cycles that deviate from the scheduled intervals by more than the allowed intervals, and by listing all cases with more than two days deviation individually.

3.4 Efficacy Assessment

The efficacy analysis will be performed 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.

Whenever applicable, analyses will be performed twofold to address the issue of data collected for patients who stopped IMP treatment due to infections: once considering all available data, and once censoring data at the time point when medically relevant additional concomitant medication was introduced. For the analysis of the primary endpoint these two approaches do obviously coincide.

Property of Octapharma. Do not copy or distribute without written permission.

3.4.1 Primary Efficacy Endpoints

Primary 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:

$$H_0: \pi_c - \pi_o \leq 0 \quad \text{vs.} \quad H_a: \pi_c - \pi_o > 0$$

where π_o and π_c 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 (Panzyga–Placebo) of the proportions observed. One-sided 97.5% confidence interval (CI) will be provided (the lower bound of the two-sided 95% CI is the same as the lower bound of the one-sided 97.5% CI).

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 data is 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.

Supportive Analyses

The primary analysis will be repeated for the FAS and the PP Population.

3.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints included in the hierarchical step-down testing procedure include the following parameters in a fixed sequence at level α by the order of the hypotheses based on clinical importance of: (1) Overall infection rate, (2) Frequency of prophylactic with anti-infectives, and (3) Duration of prophylaxis with anti-infectives.

- 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.

  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 other than Panzyga 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.

- Frequency of prophylaxis with anti-infectives (antibacterials and antivirals).

Property of Octapharma. Do not copy or distribute without written permission.

The frequency of prophylaxis with anti-infectives (antibacterials and antivirals) is defined as the number of times for each patient who receive prophylaxis with anti-infective including antibacterials and antivirals. It will be tested using a 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 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.

- Duration of prophylaxis with anti-infectives (antibacterials and antivirals).

  The duration of prophylaxis with anti-infectives (antibacterials and antivirals) is defined as the sum of the number of days of the patients who receive prophylaxis with anti-infectives 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.

As with the primary efficacy endpoints, secondary efficacy analysis analyses based on the ITT Population will employ a multiple imputation method assuming missing endpoint data is missing at random (MAR) for patients with missing data who are randomized but not treated, or who are lost to follow-up. The secondary efficacy analysis will be repeated for the FAS and the PP Population.

3.4.3 Exploratory Efficacy Endpoints

[redacted]

Proprietary information. Do not distribute without written permission.

Pro

[redacted]

3.4.4 Pharmacoeconomic Endpoints

[redacted]

3.4.5 Subgroups

Analyses of 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)

Any additional subgroup may be considered.

3.5 Safety Assessment

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.

3.5.1 Adverse Events (AEs)

AEs will be captured from the date of informed consent through study completion. All AEs will be coded to system organ class and preferred term using the latest version of MedDRA. Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug but not more than 28 days

Property of Octapharma. Do not distribute without written permission.

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 (AESI).

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 AESIs
- Any AEs leading to death
- AEs (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
- Suspected adverse drug reactions (ADRs), i.e. possible or probable related TEAEs whose incidence in the Panyzga treatment arm exceeds that in the placebo arm by 2%

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, AESIs, and a list of subjects who discontinue from study drug will be provided. All AEs will be listed.

3.5.2 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.

3.5.3 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.

3.5.4 Physical Examinations

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

Property of Octapharma. Do not copy or distribute without written permission.

4 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 grades 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.

5 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.

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 give advice on the continuation, modification, or termination of the study.

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

6 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.

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

7 SEQUENCE OF PLANNED ANALYSES

7.1 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 a grade 3 infections in the two

Property of Octapharma. Do not copy or distribute without written permission.

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 100 patients are available for evaluation of the primary endpoint in the ITT Population, where evaluable data entails having either experienced one infection or have completed the study without any infection. For the purposes of the interim analysis "completed the study" is defined as having been under observation for at least 350 days since treatment start. 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 the basis of the risk difference with respect to major infections will be applied. The sample size will be re-estimated, and the total number of patients to be enrolled may be increased up to the maximum of 450 imposed by operational constraints.

The interim analysis is only intended for sample size recalculation; the trial will not be stopped for superior efficacy. The sample size re-estimation will be validated by an independent statistical consultant (contact details will be documented in a separate memo uploaded to the TMF).

7.2 Final Analyses and Reporting

Once the last patient has completed the study, data validation will be completed and the database will be locked according to the applicable standard operating procedures. This process includes a data review, the identification and classification of any protocol deviations, and thus the patient disposition with respect to the analysis populations. All final, planned, analyses identified in the protocol and in this SAP will be performed only after the last patient has completed the study, the subject disposition has been agreed and documented, and the final SAP has been approved.

Key statistics and study results will be made available to the study team following database lock and prior to completion of the final CSR by means of tables, figures and listings (TFLs).

A list of all TFLs prepared for sections 14 and 16 of the CSR will be supplied in a separate document later when all feedback from authorities will be available.

Any additional, post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in the final SAP, will be documented and reported in appendices to the CSR. Any results from such unplanned analyses will also be clearly identified in the text of the CSR.

Deviations from the analyses described in the protocol, this SAP or its appendices will also be described and justified in a protocol amendment and/or the final CSR.

8 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

- The stopping rule employed at the interim analysis has been adjusted from that specified in version 7.0 of the protocol to be consistent with the Lan-DeMets implementation of the O'Brien-Fleming type I error spending function; the rule described in the protocol does not take account of the alpha-adjustment.
- An additional exploratory analysis of the frequency of anti-infective treatment of infections was added in Section 3.4.3.
- Additional PK-related populations such as PK Population, PK Sub-Study Population, and PK Sub-Study Evaluable Population were added in Section 3.2.

Property of Octapharma. Do not copy or distribute without written permission.

9 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

10 REFERENCES

1. Smoak, C. G., and Lin, J.-S, 2001, A SAS program to perform adaptive randomization. SAS Institute Inc., Proceedings of the Twenty-Sixth Annual SAS® Users Group International Conference, Paper 242-226.
2. Cui, L, HM Hung, and SJ Wang, 1999, Modification of Sample Size in Group Sequential Clinical Trials, *Biometrics*, Sep 1; 55(3):853–857.
3. Mehta, C. R., Pocock, S. J., 2010, Adaptive Increase in Sample Size when Interim Results are Promising: A Practical Guide with Examples. *Statistics In Medicine.*
4. Kieser, M., 2020, *Methods and Applications of Sample Size Calculation and Recalculation in Clinical Trials*, Springer Series in Pharmaceutical Statistics

Property of Octapharma. Do not copy or distribute without written permission.