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Title page

A Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of copanlisib in combination with rituximab in patients with relapsed indolent B-cell non-Hodgkin's lymphoma (iNHL) – CHRONOS -3

(Protocol Version 8.0, dated 09 FEB 2023)

SAP (incl. Version no. and date):
Main SAP, Version 6.0, dated 26 AUG 2020
SAP Supplement, Version 1.0, dated 02 AUG 2021
SAP Supplement 2.0, dated 02 SEP 2022

Clinical study phase:	III	**Date:**	05 SEP 2023
Study No.:	17067	**Version:**	Supplement 3.0
Author:	PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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List of Abbreviations

AE	Adverse event
CMV	Cytomegalovirus
CSR	Clinical study report
DRS-P	Disease-related symptoms – physical
ECOG	Eastern Cooperative Oncology Group
FL	Follicular Lymphoma
iNHL	indolent non-Hodgkin's lymphoma
OS	Overall survival
PI3K	Phosphatidylinositol 3-kinase
PRO	Patient-reported outcome
SAP	Statistical Analysis Plan
TLF	Tables, Listings, and Figures

1. Introduction

This Statistical Analysis Plan (SAP) Supplement 3 is used for the analyses of 3-year follow-up after the primary completion. The data cut-off date is 31 AUG 2023. Evaluations of selected analyses will be performed using data up to the cut-off date.

The analyses performed 2 years after the primary completion will be repeated in this analysis plan. All subgroup analyses for the time to event endpoints will be done on non-stratified Cox model and log-rank test.

There are a few changes in this 3-year follow-up analysis after the primary completion:

- To align with the latest TransCelerate clinical study report (CSR) template, Section 14 (TLFs) and Section 16.2 (Listings) will be renumbered to Section 8 and Section 10.2. In addition, subject listings listed below in the original Section 14 will be moved to the new Section 10.2.
    - Subject listing, subjects with COVID-19 related protocol deviations in Section 14.1.1
    - Subject listing, copanlisib/placebo: dose delay ≥60 days due to COVID-19 in Section 14.2.1
    - Section 14.3.2, listing of deaths, other serious and significant AEs
    - Section 14.3.3, listing of pregnancy test
- As the number of death events increases, the following subgroup analysis will be conducted for the efficacy endpoint overall survival (OS). Forest plot of the hazard ratios will be provided.
    - iNHL histology (FL vs. other iNHL histology)
    - Entry criterion (progression-free and treatment-free interval following the last rituximab-containing treatment ≥ 12 months vs. considered unwilling/unfit to receive chemotherapy for age or comorbidities)
    - Presence of bulky disease (yes vs. no)
    - Previous treatment with PI3K inhibitors (yes vs. no)
    - Prior lines of systemic anti-cancer therapy (1 vs. 2 vs. 3 vs. ≥4)
    - Age (<65 vs. ≥ 65)
    - ECOG performance status (0 vs. 1 vs. 2)
- Subgroup analyses for time to deterioration in DRS-P of at least 3 points, and time to improvement in DRS-P of at least 3 points will not be performed as sufficient patient-reported outcome (PRO) data analyses have been provided.
- Summary of participants with cytomegalovirus (CMV) infections will be displayed descriptively.

2. References

(1) Statistical Analysis Plan, version 6.0, BAY 80-6946 / 17067, dated 26 AUG 2020

(2) Statistical Analysis Plan TLF Specifications, version 1.0, BAY 80-6946 / 17067, dated 14 SEP 2020

(3) Statistical Analysis Plan Supplement, version 1.0, BAY 80-6946 / 17067, dated 02 AUG 2021

(4) Statistical Analysis Plan TLF Specifications supplement, version 1.0, BAY 80-6946 / 17067, dated 02 AUG 2021

(5) Statistical Analysis Plan Supplement 2.0, BAY 80-6946 / 17067, dated 02 SEP 2022

Title page

A Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of copanlisib in combination with rituximab in patients with relapsed indolent B-cell non-Hodgkin's lymphoma (iNHL) – CHRONOS -3

(Protocol Version 7.0, dated 22 MAY 2020)

SAP (incl. Version no. and date):
Main SAP, Version 6.0, dated 26 AUG 2020
SAP Supplement, Version 1.0, dated 02 AUG 2021

Clinical study phase:	III	**Date:**	02 SEP 2022
Study No.:	17067	**Version:**	Supplement 2.0
Author:	PPD		

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List of Abbreviations

SAP	Statistical Analysis Plan
TLF	Tables, Listings, and Figures

1. Introduction

This Statistical Analysis Plan (SAP) Supplement 2 is used for the analyses of two years after the primary completion. The data cut-off date will be 31 AUG 2022. Evaluations of selected analyses will be performed using data up to the cut-off date.

All the analyses performed one year after the primary completion will be repeated in this analysis plan. The details of the analyses are described in the main SAP, version 6.0, dated 26 AUG 2020 for the analyses at the primary completion, and SAP Supplement, version 1.0, dated 02 AUG 2021 for the analyses at one year after the primary completion. The list of tables and figures will be identical to the ones in TLF Specifications Supplement, version 1.0, dated 02 AUG 2021. The layout and specifications of the tables and figures will be the same as in the main TLF Specifications, version 1.0, dated 14 SEP 2020. No new TLF Specification document will be prepared for this analysis plan.

2. References

(1) Statistical Analysis Plan, version 6.0, BAY 80-6946 / 17067, dated 26 AUG 2020

(2) Statistical Analysis Plan TLF Specifications, version 1.0, BAY 80-6946 / 17067, dated 14 SEP 2020

(3) Statistical Analysis Plan Supplement, version 1.0, BAY 80-6946 / 17067, dated 02 AUG 2021

(4) Statistical Analysis Plan TLF Specifications supplement, version 1.0, BAY 80-6946 / 17067, dated 02 AUG 2021

Title page

A Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of copanlisib in combination with rituximab in patients with relapsed indolent B-cell non-Hodgkin's lymphoma (iNHL) – CHRONOS -3

(Version 7.0, dated 22 MAY 2020)

SAP (incl. Version no. and date):
SAP for study 17067, Version 6.0, dated 26 AUG 2020

Clinical study phase:	III	**Date:**	02 AUG 2021
Study No.:	17067	**Version:**	1.0
Author:	PPD		

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List of Abbreviations

AEs	Adverse events
CRR	Complete response rate
CTCAE	Common Terminology Criteria of Adverse Event
DCR	Disease control rate
DOR	Duration of response
DRS-P	Disease-related symptoms - physical
MedDRA	Medical Dictionary for Regulatory Activities
MLG	MedDRA labelling group
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall survival
ODWG	Organ Dysfunction Working Group
PFS	Progression-free survival
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA Query
TEAEs	Treatment-emergent adverse events
TLF	Tables, Listings, and Figures
TTP	Time to progression

1. Introduction

This Supplement Statistical Analysis Plan (SAP) is used for the analyses one year after the primary completion. The data cut-off date will be AUG 2021. Evaluations of selected analyses in all sections will be performed using data up to the cut-off date.

This Supplement SAP version 1.0 is a supplement of SAP version 6.0 dated 26 AUG 2020. A list of tables and figures to be generated based on this SAP will be provided in a separate document (TLF specifications supplement). The layout and specifications of the tables and figures will be the same as in the main TLF specifications version 1.0, dated 14 SEP 2020.

2. Study Objectives

Refer to main SAP, Version 6.0 dated 26 AUG 2020.

3. Study Design

Refer to the main SAP v6.0 dated 26 AUG 2020.

4. General Statistical Considerations

Refer to the main SAP v6.0 dated 26 AUG 2020.

5. Analysis Sets

Refer to the main SAP v6.0 dated 26 AUG 2020.

6. Statistical Methodology

6.1 Population characteristics

Analyses on disposition, concomitant medication, and treatment duration and exposure will be performed.

Analysis of time to end of study treatment will be conducted. Kaplan-Meier plot for 'Time to end of study treatment' will be provided by treatment group, and by histology subgroup.

Treatment duration and dosage will be summarized for overall safety population and by histology subgroup.

6.2 Efficacy

Primary analysis based on the independent assessment on the primary efficacy endpoint progression-free survival (PFS) will be conducted. Analysis of PFS based on the investigator’s assessment will also be conducted.

Overall survival (OS) will be analyzed using the data up to AUG 2021. For other secondary efficacy endpoints, i.e., tumor objective response rate (ORR), complete response rate (CRR), disease control rate (DCR), duration of response (DOR), and time to progression (TTP), analyses based on the independent assessment and investigator’s assessment will be provided.

Analysis of time to deterioration and time to improvement in DRS-P at least 3 points will be performed.

Subgroup analysis by histology subgroup will be conducted for PFS, OS, ORR, CRR, DCR, DOR, and time to deterioration and time to improvement in DRS-P at least 3 points.

6.3 Safety

6.3.1 Adverse Events (AEs)

Analyses of adverse events for overall safety population and by histology subgroup will be conducted. In addition, the following subgroup analyses of AEs including death will be conducted by baseline renal function and baseline hepatic function using National Cancer Institute's Organ Dysfunction Working Group (NCI-ODWG) criteria:

- Overview of treatment-emergent AEs (TEAEs)
- Incidence rates of TEAEs
- Incidence rates of treatment-emergent serious AEs
- drug-related TEAEs (copanlisib/placebo or rituximab-related)
- TEAEs leading to treatment (copanlisib/placebo or rituximab) discontinuation
- Summary of deaths

6.3.2 Adverse Event Groupings

The table below presents definitions of adverse event groupings. The overall strategy for the MedDRA Searches is aimed at achieving high specificity. Wherever considered appropriate, narrow versions of SMQs will be used. Additional Bayer-specific MedDRA search groups will be used for searches where SMQs would not adequately cover the targeted search. The Bayer-specific MedDRA search groups include MedDRA Labelling Groupings (MLG). These groupings are created and centrally maintained by a dedicated coding group, according to requests by end-users from the medical and statistical functions. They are therefore potentially subject to change e.g. through MedDRA up-versioning.

Table 6–1: Adverse Event Groupings

Adverse Event Grouping	MedDRA Search criteria
Arterial hypertension	MLG: Hypertension
Hyperglycemia	MLG: Hyperglycemia
Non-infectious pneumonitis	SMQ: Interstitial lung disease (narrow, i.e. category 2A)

For each of the above listed groupings of adverse events, the following will be presented for treatment-emergent events and copanlisib/placebo-related treatment-emergent events:

- Incidence proportions, by worst CTCAE grade, by seriousness, by outcome, and by action taken; 95% Clopper Pearson (exact) confidence interval for the overall incidence proportion and for the category of serious adverse events.
- Incidence proportions by the specific reported preferred terms (within each grouping)
- Exposure-adjusted incidence rate, which is defined as the number of patients with the specific event divided by the sum of exposure-time among the patients in the study group; 95% exact confidence interval for the overall rate (assuming the first occurrences of an event follow a Poisson process with constant rate). Exposure time is defined as follows: if

the event occurred, exposure time is the time to first occurrence of the event. If the event did not occur, then exposure time is the treatment duration plus time at risk after treatment end, where time at risk is the minimum of 30 days and day of death relative to last treatment.

6.3.3 Clinical Laboratory Parameters

Summary tables for clinical laboratory parameters for overall safety population will be provided.