STATISTICAL ANALYSIS PLAN

PO-3887 (PO-CL-MM-PI-003887)

A MULTICENTER, OPEN LABEL, RANDOMIZED PHASE III STUDY OF POMALIDOMIDE-DEXAMETHASONE (Pom-dex) versus POMALIDOMIDE-CYCLOPHOSPHAMIDE-DEXAMETHASONE (Pom-cyclo-dex) IN MULTIPLE MYELOMA (MM) PATIENTS WHO EXPERIENCE BIOCHEMICAL (EARLY TREATMENT) OR CLINICAL RELAPSE (LATE TREATMENT) DURING LENALIDOMIDE MAINTENANCE TREATMENT

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1 Document Information

1.1 Revision History

Version	Date	Comments	Revised section(s)
1.0		First version	

1.2 List of Abbreviation

AE	Adverse Event
ASCT	Autologous Stem Cell Transplantation
AST	Aspartate Aminotransferase
Bj	Bence Jones
CI	Confidence Interval
CR	Complete Response
CTCAE	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
eCRF	Common Terminology Criteria for Adverse Events
FISH	Fluorescence In Situ Hybridization
ICF	Informed Consent Form
IQR	inter-quartile range
ISS	International Staging System score
ITT	Intention-To-Treat
Ldh	Lactate dehydrogenase
LTFU	Long-term Follow-up
MM	Multiple Myeloma
PD	progressive disease
PR	Partial Response
SAE	Seriuos Adverse Event
SAP	Statistical Analysis Plan
sCR	stringent Complete Response
SD	Stable Disease
VGPR	Very Good Partial Response

2 Introduction

2.1 Background and rationale

This Statistical Analysis Plan (SAP) provides details for the analysis for the PO-3887 trial, and it was produced according to Guidelines for the Content of Statistical Analysis Plans in Clinical Trials (JAMA. 2017;318(23):2337-2343. doi:10.1001/jama.2017.18556).

Since the study was interrupted due to low enrolment, the primary objectives could not be met and not tested. For the same reason, some endpoint will not be evaulabel according to le lower sample size.

2.2 Research hypothesis

The null and alternative hypotheses for primary secondary endpoints are:

H_0: OS in CPd arm = OS in Pd arm

H_1: OS in CPd arm > OS in Pd arm

The null and alternative hypotheses for primary secondary endpoints are:

H_0: OS in Early arm = OS in Late arm

H_1: OS in Early arm > OS in Late arm

2.3 Objectives

The first primary objective of this trial is to determine the efficacy, in term of Overall Surival of the combination of Pomalidomide-Cyclophosphamide-Dexamethasone (CPd) versus Pomalidomide-Dexamethasone (Pd).

The second primary objective of this trial is to determine the efficacy, in term of Overall Surival of the Early treatment versus Late treatment.

Secondary objectives are:

- Compare the best therapy, CPd vs Pd in terms of PFS
- Compare the best strategy, Early treatment versus Late treatment, in terms of PFS
- Compare the best therapy, CPd vs Pd in terms of PFS2
- Compare the best strategy, Early treatment versus Late treatment, in terms of PFS2

- Compare the best therapy, CPd vs Pd in terms of PFS2
- Evaluate quality of life (QoL) and health related costs in the two therapies, CPd versus Pd, and in the two strategies, Early treatment versus Late treatment.
- Explore the presence of clinically meaningful interactions between therapies and strategies.
- Determine whether tumor response, PFS, PFS2 and OS might significantly change in particular subgroups of patients defined by prognostic factors (such as International Staging System, chromosomal abnormalities) and by performance status.
- Evaluate the safety and tolerability of the strategy and of the combination CPd vs Pd

3 Study Methods

3.1 Trial design

This is a multicenter, randomized, open label phase III study designed to assess the safety and the efficacy of two different pomalidomide combinations as salvage treatment in multiple myeloma (MM) patients after biochemical relapse during Lenalidomide maintenance.

Patients will be evaluated at scheduled visits in up to 3 study periods: pre-treatment, treatment and long-term follow-up (LTFU).

The pre-treatment period includes screening visits, performed at study entry. After providing written informed consent to participate in the study, patients will be evaluated for study eligibility.

After confirmation of eligilibty patients was randomized to (random 1):

- ARM I: Early treatment
    - The randomization between Arm A and B (random 2) was disclosed at biochemical relapse, this patient start treatment at enrollment
- ARM II: Late treatment
    - The randomization between Arm A and B (random 2) was disclosed at clinical relapse, this patient started treatment when CRAB critirea was met

After confirmation of eligilibty patients was randomized to (random 2):

- ARM A: Pom-dex (Pd)
    - Pomalidomide: at the dose of 4 mg/daily as oral administration (PO) on days 1-21.
    - Dexamethasone: at the dose of 40 mg as oral administration (PO) on days 1, 8, 15, 22.
- ARM B: Pom-cyclo-dex (CPd)
    - Pomalidomide: at the dose of 4 mg/daily as oral administration (PO) on days 1-21.
    - Cyclophosphamide: 50 mg every other day as oral administration (PO) on days 1-28.
    - Dexamethasone: at the dose of 40 mg as oral administration (PO) on days 1, 8, 15, 22.

Each cycle will be repeated every 28 days until progression or intolerance.

3.2 Randomization

All patients eligible will be randomized at enrolment in a 1:1:1:1 ratio for the 2 comparison. Patients was randomized using blocks of sizes 12 by the eCRF; this procedure is completely concealed to study participants.

3.3 Study endpoints

3.3.1 Primary endpoints

The primary endpoint of the study is Overall Survival for the comparison CPd vs Pd (OS_A_B) and for the comparison Late vs Early (OS_I_II).

Overall survival for che comparison CPd vs Pd (OS_A_B) is defined as the time from the date of random disclosure to the date of death from any cause.

Overall survival for che comparison Late vs Early (OS_I_II) is defined as the time from the date of random disclosure to the date of death from any cause.

3.3.2 Secondary endpoints

PFS for che comparison CPd vs Pd (OS_A_B) will be measured from the date of random disclosure to the date of first observation of PD, or death from any cause as an event. Subjects who have not progressed or who withdraw from the study will be censored at the time of the last complete disease assessment. All subjects who were lost to FU will also be censored at the time of last complete disease assessment

PFS for che comparison Late vs Early (OS_I_II) will be measured from the date of random disclosure to the date of first observation of PD, or death from any cause as an event. Subjects who have not progressed or who withdraw from the study will be censored at the time of the last complete disease assessment. All subjects who were lost to FU will also be censored at the time of last complete disease assessment

PFS2 for the comparison CPd vs Pd (PFS2_A_B) will be measured from the date of randomization disclosure to the date of first observation of PD in second line therapy, or death from any cause as an event. Subjects who have not progressed or who withdraw from the study will be censored at the time of the last complete disease assessment. All subjects who were lost to FU will also be censored at the time of last complete disease assessment

PFS2 for the comparison Late vs Early (PFS2_I_II) will be measured from the date of randomization disclosure to the date of first observation of PD in second line therapy, or death from any cause as an event. Subjects who have not progressed or who withdraw from the study will be censored at the time of the last complete disease assessment. All subjects who were lost to FU will also be censored at the time of last complete disease assessment

Time to Clinical Progression will be defined as the time from random assignment to the early or late strategy to the date of onset of CRAB symptoms or death. Subjects who have not clinically progressed or who withdraw from the study will be censored at the time of the last complete disease assessment. All subjects who were lost to FU will also be censored at the time of last complete disease assessment

Overall Response Rate (ORR) for the Comparison CPd vs Pd and I vs II in terms of partial response (PR), very good partial response (VGPR), complete response (CR) stringent complete response (sCR).

Quality of Life With EORTC-QLQ-C30 and QLQ-MY24 for the comparison B vs A and I vs II.

Incidence of hematologic and non-hematologic adverse events (AEs) for the comparison CPd vs Pd.

3.4 Sample size

This is a 2x2 factorial randomized study. The sample size of the study has been calculated in order to demonstrate both the primary objectives, assuming no major interaction between the 2 factors.
The sample size calculation has been performed on the basis of the following assumptions:

- Median OS in the Late treatment group: 14 months
- Median OS in the Early treatment (experimental) group: 21 months (HR 0.67)
- Two sided α= 0.05
- β= 0.20
- Accrual time: 36 months
- Follow-up: 24 months
- Rate of expected losses during follow up: 5%
- Allocation ratio: 1:1:1:1 (2x2 design)

The total sample size needed for the study is 256 patients (rounded to 260) and the final analyses will be performed when at least 191 deaths will be recorded.

This sample size is based on the Early vs Late strategy because it is the maximum sample size required; it should be also sufficient to assess a similar OS advantage of CPd vs Pd with the same statistical assumptions.
Since the study was interrupted due to low enrolment, the primary objectives could not be met and not tested. For the same reason, some endpoint will not be evaulabel according to le lower sample size.

3.5 Framework

The trail testing the superiority of CPd vs Pd and of Early vs Late treatment in term of OS.

3.6 Statistical interim analyses and stopping guidance

Toxicity will be evaluated for the entire duration of the study according to the NCI CTCAE, version 4.0. Arm specific stopping rules for toxicity during the first 3 cycles of therapy are pre-specified to assure safety of treatments.
A toxicity rate of ≤45% is considered acceptable, otherwise the treatment will be stopped for excessive toxicity.
Any of the following toxicities occurring during the first 3 cycles will be considered for safety monitoring and stopping rules:

1. Hematologocal toxicities ≥ grade 4
2. Non-hematological toxicities ≥ grade 3

The stopping bundarie are calculated using the Bayesian approach of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998) (43, 44, 45).
For each arm, the following table describes the toxicity stopping boundary for cohorts of 10 patients (boundaries calculated with a posterior probability ≥ 0.95 that the experimental treatment toxicity is more than 45%).

# Patients (in complete cohorts of 10)	# Toxicities (inclusive) The trial will be stopped if there are at least this many toxicity
10	8
20	14
30	19
40	25
50	30
60	36
70	41
80	46
90	52
100	57
110	62
120	68
130	Always stop with this many patients

Results of interim analyses will be presented to the principal investigators and to an independent data monitoring committee.

Since the study was interrupted due to low enrolment, also the interim analysis was not procuded since the total sample size is only 9 patients, lower than the required patients for arm to analyze it.

3.7 Timing of final analysis

The first main publication of the trial can be prepared when 191 OS events will be met. Since the study was interrupted due to low enrolment, the analysis will be done when the sponsor closed the study.

4 Statistical Principles

4.1 Confidence intervals and P values

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level; all confidence intervals (CIs) presented will be 95% and two-sided. P-values will be rounded to 3 decimal places. P-values that round to 0.000 will be presented as '<0.001'

4.1.1 Mutiplicity

Since was assuming no major interaction between the 2 comparison, multiplicity adjustment was not requiered.

4.2 Analysis populations

4.2.1 Treatment strategy population

The treatment strategy population includes all patients who was randomised to the Early or Late strategy arm.

4.2.2 Therapy population

The Therapy population according to ITT principe includes:

- all patients of Early strategy who are simultaneously randomised to the CPd or Pd arm
- all patients of Late strategy who has disclose the randomization between CPd or Pd arm

4.2.3 Safety population

Safety population consider all patients of the therapy population who received at least one dose of study drugs.

4.3 General principles

No methods of handling with missing data will be adopted. Discrete variables will be tabulated as numbers and percentages, continuous variables will be summarized using median and inter-quartile range (IQR) or Range.

5 Trial Population

5.1 Screening data

The total number of eligible patients was not collected during the study. Only recruited patients was included. Only in case of patients initially randomized but considered ineligible afterwards based on information that should have been available before randomization, patients will be excluded from the trial.

5.2 Eligibility

5.2.1 Inclusion Criteria

- Patients >18 years and <80 years.
- Patient is, in the investigator(s) opinion, willing and able to comply with the protocol requirements.
- Patient has given voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to their future medical care.
- Male patient agrees to use an acceptable method for contraception (i.e. condom or abstinence) for the duration of the study.
- Female of childbearing potential agrees to use two acceptable methods for contraception [implant, levonorgestrel-releasing intrauterine system (IUS), medroxyprogesterone acetate depot, tubal sterilization, sexual intercourse with a vasectomised male partner only (vasectomy must be confirmed by two negative semen analyses), ovulation inhibitory progesterone-only pills (i.e. desogestrel)] or absolute and continuous sexual abstinence.
- Patient has measurable disease, defined as follows: any quantifiable serum monoclonal protein value (generally, but not necessarily, ≥ 0.5 g/dL of M-protein) and, where applicable, urine light-chain excretion of >200 mg/24 hours; only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels must be > 10 mg/dL. Less than 10% of oligo- or non-secretory MM patients with free light chains will be admitted to this study in order to maximize interpretation of benefit results.
- Patient receiving lenalidomide maintenance therapy as part of first line treatment (concomitant use of prednisone is accepted) and has experienced a biochemical relapse, with evidence of progressive disease defined as an increase of 25% from lowest response value in any one or more of the following: serum M-component (absolute increase must be ≥0.5 g/100 ml) and/or urine M-component (absolute increase must

be ≥200 mg per 24 hours) only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels must be >10 mg/dL (35).

- Patient who received as first line treatment a bortezomib-based therapy, including lenalidomide maintenance during the same line of therapy, can be included in the trial.
- Patient has a life-expectancy > 3 months
- Patient has not a currently active malignancy, other than non melanoma skin cancer and carcinoma in situ of the cervix, and has not invasive malignancies within the past 5 years.
- No history of allergic reactions attributed to study agents
- Patient has the following laboratory values within 28 days before baseline day 1 of the cycle 1:
  a. absolute neutrophil count (ANC) > 1 x 10^9/L
  b. platelet count > 75 x 10^9/L
  c. haemoglobin > 8 g/dl.
  d. aspartate transaminase (AST): < 2 x the upper limit of normal (ULN).
  e. alanine transaminase (ALT): < 2 x the ULN.

5.2.2 Exclusion Criteria

- Pregnant or lactating females.
- Patient with Creatinine Clearance (CrCl) < 45 mL/minute
- Patient with peripheral neuropathy ≥ Grade 2
- Subject with any one of the following:
  a. Congestive heart failure (NY Heart Association Class III or IV)
  b. Myocardial infarction within 12 months prior to starting study treatment
  c. Unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris
- Any significant medical disease or conditions (e.g. pulmonary disease, infection) that, in the investigator's opinion, may interfere with protocol adherence or subject's ability to give informed consent or could place the subject at unacceptable risk.
- Clinical active infectious hepatitis type A, B, C or HIV
- Acute active infection requiring antibiotics or infiltrative pulmonary disease
- Contraindication to any of the required drugs or supportive treatments.
- Known allergy to any of the study medications, their analogues, or excipients in the various formulations.

5.3 Recruitment

A CONSORT flow diagram (Appendix B: Consort Diagram) will be adopted for the analysis to summarise:

- Randomided patients to the comparison Late vs Early treatment
- Randomided patients to the comparison CPd vs Pd
- Patients who start induction phases and number and causes of early discontinuation
- Patients who are on treatment at data of analysis and number and causes of early discontinuation

Early discontinuation will be summarized as:

- Progressed
- Death
- Discontinued treatment due to AEs (and SPM)
- Lost to Follow-up
- Other causes of discontinuation

Median follow-up will be also reported.

5.4 Withdrawal/follow-up

The reason for withdrawal from treatment will be documented in the eCRF. Post-treatment follow-up for disease status and survival will continue until death unless any of the criteria for early study withdrawal are met. Patients who drop-out for reasons other than PD except conset withdrawl are followed until PD for response assessment.

5.5 Baseline patient characteristics

Patients baseline characteristics will be summarized separately for the treatment strategy population, and for the therapy population.

Demographics:

- Age(years) as continuous
- Age [≤ 60 vs > 60]
- Sex [Male vs Female]

Disease characteristics:

- Isotype [IgA vs IgG vs IgD vs IgE vs IgM vs Bj vs NS]
- Light Chain [Kappa vs Lambda]

Prognostic factors

- International Staging System score (ISS) [I vs II vs III]
- Eastern Cooperative Oncology Group performance status score (ECOG) [0 vs 1 vs 2]
- Serum Ldh [≤ upper normal limit vs > upper normal limit]
- Albumin [g/dL]
- B2microglobulim [mg/L]

Previous Therapies

- ASCT
- Lenalidomide
- Bortezomib

Cytogenetics

- Deletion 17p13.1 [Yes vs No vs NE]
- Translocation 4;14 (p16.3;q32.3) [Yes vs No vs NE]
- Translocation 14;16 (q32.3;q23) [Yes vs No vs NE]
- Fonseca FISH risk [Standard vs High vs NE]

Fonseca FISH risk as defined High risk as presence of at least one of Deletion 17p13.1, Translocation 4;14 (p16.3;q32.3) or Translocation 14;16 (q32.3;q23).

The results of all characteristics will be summarized both overall and separately for the two arms for both comparisons.
Categorical data will be summarised by numbers and percentages. Continuous data will be summarised by median and interquartile range (IQR).
Tests of statistical significance will not be undertaken for baseline characteristics.

5.6 Study drug exposure

The following measures of drug exposure will be analyzed for safety popoulations.

Relative dose will be evaluated consider the ratio between the administred and the planned dose. Relative dose will be estimated for each study drugs.

Number of patients with at least one dose reduction and number of patients who discontinued the drug will be summarized by treatment arm and study drug.

6 Analysis

6.1 Outcome definitions

Since the study was interrupted due to low enrolment, some endpoints could not be met and not tested. For the same reason, some endpoint will not be evaulabel according to le lower sample size but only a descriptive analysis will be done.

6.1.1 Primary Endpoint

The Overall Survival (OS) is determined defined as the time from the date of random disclosure to the date of death from any cause for the comparisons CPd vs Pd and for the comparisons Early vs Late. Subjects who withdraw consent will be censored at the time of withdrawal. Subjects who are still alive at the cut-off date of final analysis will be censored at the cut-off date. Subjects lost to FU will also be censored at the time of last contact.

6.1.2 Secondary Endpoint

Time to Clinical Progression defined as the time from random assignment to the early or late strategy to the date of onset of CRAB symptoms or death.
Clinical relapse requires one or more direct indicators of progressive disease and end organ dysfunction (CRAB features). Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder: hypercalcaemia, renal insufficiency, anaemia, bone lesions or any one or more of the biomarkers of malignancy (clonal bone marrow plasma cell percentage ≥60%, involved/uninvolved serum free light chain ratio ≥100, >1 focal lesions on MRI studies [each focal lesion must be 5 mm or more in size])

Progression Free-survival (PFS) will be measured from the date of random disclosure to the date of first observation of PD, or death from any cause as an event. Subjects who have not progressed or who withdraw from the study will be censored at the time of the last complete disease assessment. All subjects who were lost to FU will also becensored at the time of last complete disease assessment

Progression Free-survival 2(PFS2) will be measured from the date of random disclosure to the date of observation of second disease progression (i.e. progression after the second line of therapy) or death to any cause as an event. In case of date of second progression is not available, date of start of third line treatment can be used. Subjects who have no progressed, and are still alive at the cut-off date of final analysis will be censored at the cut-off date. All subjects who were lost to follow-up prior to the end of the study, have no progressed, and are still alive will also be censored at the time of last contact.

Time to PR will be measured from the date of random disclosure to the date of first observation of PR (Partial Response). Subjects who achieved response better than PR will be consider that PR is achieved. Subjects who withdraw from the study will be censored at the time of the last complete disease assessment. Subjects have not achieved a PR, and are still alive at the cut-off date of final analysis will be censored at the cut-off date. All subjects who were lost to FU will also be censored at the time of last contact.

Time to VGPR will be measured from the date of random disclosure to the date of first observation of VGPR (Very Good Partial Response). Subjects who achieved response better than VGPR will be consider that VGPR is achieved. Subjects who withdraw from the study will be censored at the time of the last complete disease assessment. Subjects have not achieved a VGPR, and are still alive at the cut-off date of final analysis will be censored at the cut-off date. All subjects who were lost to FU will also be censored at the time of last contact.

Time to CR will be measured from the date of random disclosure to the date of first observation of CR (Complete Partial Response). Subjects who achieved response better than CR will be consider that CR is achieved. Subjects who withdraw from the study will be censored at the time of the last complete disease assessment. Subjects have not achieved a CR, and are still alive at the cut-off date of final analysis will be censored at the cut-off date. All subjects who were lost to FU will also be censored at the time of last contact.

Time to sCR will be measured from the date of random disclosure to the date of first observation of sCR (stringent Complete Partial Response). Subjects who withdraw from the study will be censored at the time of the last complete disease assessment. Subjects have not achieved a sCR, and are still alive at the cut-off date of final analysis will be censored at the cut-off date. All subjects who were lost to FU will also be censored at the time of last contact.

Duration of response (DOR) will be measured from the date of achievement of at least a partial response (PR) to the date of first observation of PD, with deaths from causes other than progression censored. Subjects who withdraw from the study will be censored at the time of the last complete disease assessment. Subjects who have no progressed, and are still alive at the cut-off date of final analysis will be censored at the cut-off date. All subjects who were lost to FU will also be censored at the time of last contact.

6.1.3 Safety Endpoints

Adverse events (AEs) will be summarized by treatment arm for safey population.

In case of study discontinuation. AE will be included in the analysis if the onset date occurring within 30 days after the last dose of the last study drug received in each specific phase.

AEs are documented on the eCRF together with their grade, according to the NCI CTCAE version 4.0.

In particular, AEs will be considered related if there is a relation with at least one study drugs.

Relation will be considered as following:

- Related (Unlikely to be related, Possibly related, Probably related, Definitely related)
- Not related (Not related)
- Unknown (Unknown)

with in brackets the value reported on eCRF. All AEs will be summarized by the following predefined event categories used in the AE CRF:

- Hematologic toxicity (Anemia, Neutropenia, Thrombocytopenia and Other)
- Cardiac disorders
- Vascular disorders
- Infections
- Gastrointestinal disorders
- Hepatic disorders
- Nervous disorders
- Respiratory disorders
- Renal disorders
- General disorders
- Dermatological disorders
- Investigations disorders
- Other toxicity

A subject having the same event more than once will be counted only once for the worst grade.

In the case that the adverse events or event frequencies are judged to be clinically important, an exact test will be used to analyze the difference between the treatment arms.

In addition, AE will be considered as proportion of patients experiencing at least one of:

- hematologic Adverse Event (AE)
- non-hematologic AE
- AE leading to death (Grade 5)
- Adverse Event leading to treatment discontinuation

- Adverse Event leading to treatment reduction

Cause of death was reported in the e-CRF by investigators:

- Progression Disease
- Adverse Event (SPM included)
- Unknown
- Other

All causes of death will be reported by treatment arm.

Time to discontinuation will be measured from the date of first dose of induction study drugs to the date of discontinuation due to AE or Death for AE/SPM. Subjects who discontinued drugs due to PD, or death for cause other than AE/SPM will be considered a competitive event. Subjects has not discontinued, and are still alive and on treatment at the cut-off date of final analysis will be censored at the cut-off date. All subjects who were lost to FU will also be censored at the time of last contact.

Relative dose will be evaluated consider the ration between the administred and the planned dose. Relative dose will be estimated for each study drugs.

6.2 Analysis methods

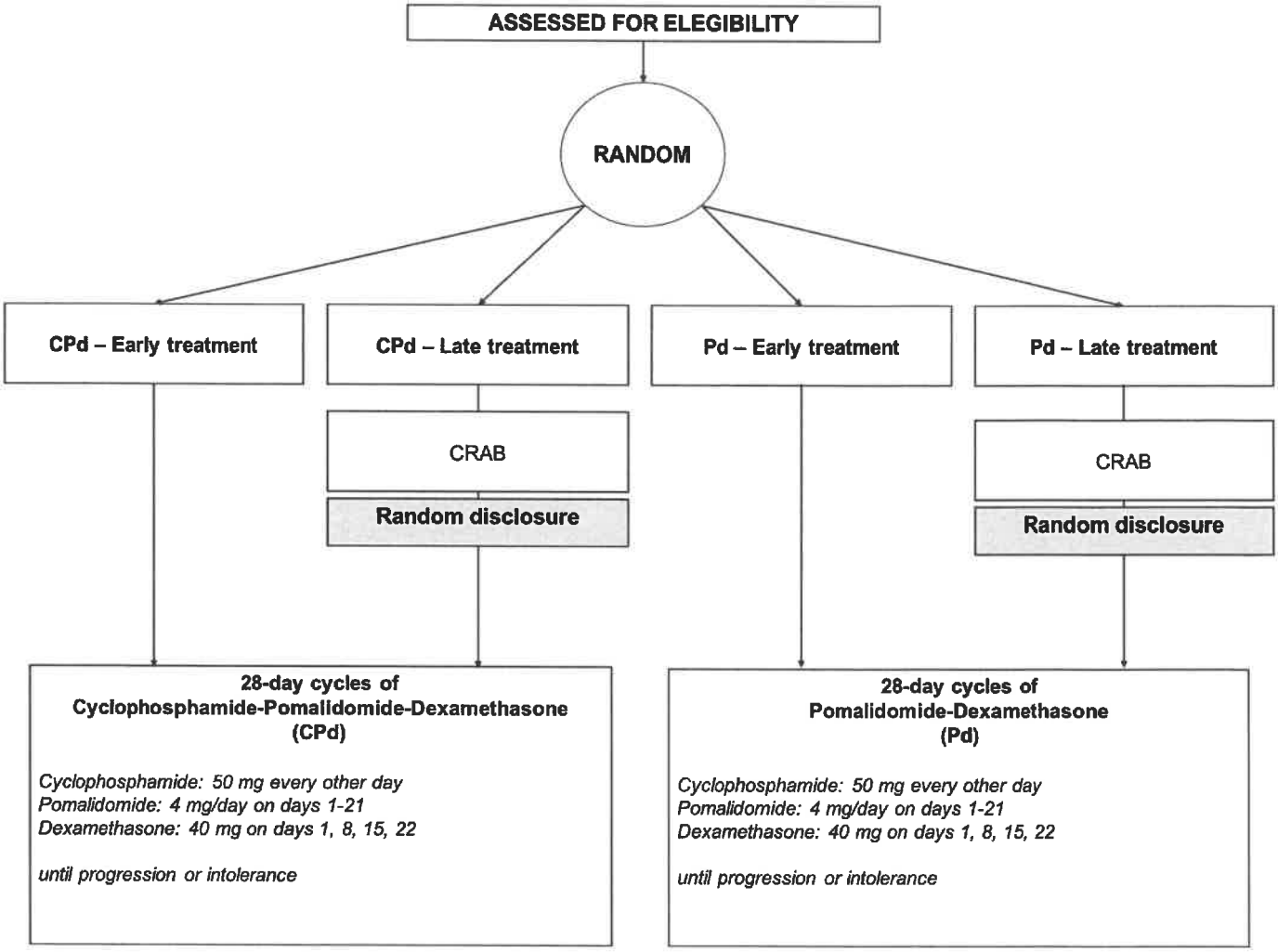
Since the study was interrupted due to low enrolment, some endpoints could not be met and not tested. For the same reason, some endpoint will not be evaulabel according to le lower sample size but only a descriptive analysis will be done.
Comparison between Adverse Event indicence will be done whitout testing.

6.3 Statistical software

Data were analyzed using R language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria - Version 3.6.0 or higher).

A. Appendix: Treatment Schema

Treatment schema



B. Appendix: Consort Diagram

Flow Diagram