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STATISTICAL ANALYSIS PLAN

A phase I, dose-finding study of the bromodomain (Brd) inhibitor OTX015/MK-8628 in haematological malignancies

Protocol OTX015_104/PN001, Version H, Amendment 7, 30 September 2014

SAP v2.0 10 March, 2017

Investigational Product: Bromodomain (Brd) inhibitor OTX015/MK-8628

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1. SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN APPROVAL
Version 2.0, 10 March 2017

A phase I, dose-finding study of the bromodomain (Brd) inhibitor OTX015/MK-8628 in haematological malignancies

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Version history

Version	Date	Main changes/Justification
v1.0	24October2014	Initial version
Draft2.0	18May2015	After OTD remarks on V1.0
V2.0	10March2017	For final analysis and after last Data review committee

	PPD	Date
CRO Medical Monitor **Sponsor representative**	[redacted]	14 MAR 2017
Statistician **eXYSTAT**	[redacted]	10 MAR 2017

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3. PROTOCOL SYNOPSIS

Title:

A phase I, dose-finding study of the bromodomain (Brd) inhibitor OTX015/MK-8628 in haematological malignancies

Study code: OTX015_104/PN001

Investigator(s), study site(s):

- PPD France
- PPD France
- PPD Italy
- PPD Switzerland
- PPD France
- PPD France
- PPD France
- PPD France
- PPD France
- PPD United Kingdom
- PPD Canada

Objectives

Primary:

To determine the recommended dose (RD) of OTX015/MK-8628 for further phase II studies, in patients with acute leukemia and in patients with other hematologic malignancies

Secondary:

- To assess the safety profile of OTX015/MK-8628 as a single agent in patients with hematologic malignancies
- To assess pharmacokinetics (PK) of OTX015/MK-8628 in patients with hematologic malignancies and PK/safety relationship
- To assess pharmacodynamics (PD) of OTX015/MK-8628 in patients with hematologic malignancies, PD/safety and PK/PD relationships
- To detect clues of clinical antitumor activity

Exploratory:

- To detect predictive factors of clinical activity

Study design: Multicenter, dose finding**,** open label**,** phase I b study in successive cohorts of 3 patients with cohort expansion.

Dose escalation part:

- Two dose escalation subsets will be assessed independently in parallel: patients with acute leukemia (AL) and patients with other hematologic malignancies (OHM).
- In each subset, patients will be enrolled by successive cohorts of 3 patients.
- Three patients will be initially treated at the starting dose level (DL) in each subset. If no dose limiting toxicity (DLT) is observed among these 3 patients during the first cycle of treatment (i.e. the first 21 days following study treatment initiation, regardless of the treatment schedule), the next 3 patients will be treated at the DL immediately above, according to the dose escalation schedule defined below. In the absence of DLT observed at the current DL, the dose will be doubled.
- At each DL in each subset, the second patient enrolled will not start the study treatment before the first treated patient of the cohort has completed at least 2 weeks of treatment (i.e. 14 consecutive daily administrations). The first patient enrolled into a higher DL cohort will not start the study treatment

before the last treated patient in the DL immediately below has completed one cycle of study treatment (21 days following study treatment initiation, regardless of the treatment schedule).

- If one 1 of 3 patients of a cohort experiences a DLT during the first cycle (i.e. the first 21 days following study treatment initiation, regardless of the treatment schedule), 3 additional patients will be entered at this DL. If no more than 1/6 treated and evaluable patient experience a DLT, the dose escalation will proceed to the DL immediately above. As soon as a DLT is observed, the magnitude of dose escalation will follow a Fibonacci-like model (see below). If more than 1 patient out of 6 (or more than 1 out of 3) experiences a DLT, the DL will be considered exceeding the maximum tolerated dose (MTD) for this subset.
- Patients not evaluable for DLT (i.e. those having received less than 85% of the intended cumulative dose during the first 21 days) and who have not experienced a DLT, will be replaced.
- The dose escalation will be stopped independently in each subset upon a decision of the Safety Monitoring Committee (SMC). This decision can be taken if one of the following conditions is met:
  - A DL exceeding the MTD has been reached
  - Biological activity (PD) or sustained biologically active concentrations (PK) of OTX015/MK-8628 have been achieved
  - Or any other unforeseen condition, which, in the judgment of the SMC, would prevent, or would not deserve, further dose escalation.
- In the absence of other data (PD or PK) suggesting a lower RD, the MTD will be considered the RD. At least 6 evaluable patients will be enrolled at the supposed RD (one DL below the dose exceeding the MTD) in each subset. The RD will be confirmed for each subset if no more than 1/6 patient experiences a DLT. Otherwise the DL immediately below will be explored with a minimum of 6 evaluable patients.

Expansion part

- Once the RD will be established with at least 3 patients having received at least 2 cycles of study treatment for each subset, the study will be prolonged with expansion cohorts in selected patients to confirm feasibility, safety, PK and PD at the RD. At least 12 evaluable patients with acute leukemia will be treated at the RD established for patients with acute leukemia. At least 12 evaluable patients with diffuse large B-cell lymphoma (DLBCL) or multiple myeloma (MM) will be treated at the RD established for patients with other hematologic malignancies. Additional expansion cohorts may be decided by the SMC, based upon the data collected during the dose escalation phase.
- The RD for expansion cohorts for both acute leukemia and other hematologic malignancies was established at 80 mg QD days 1 to 14 of 21-day cycles (2 weeks ON/one week OFF).

Inclusion criteria

1. Signed informed consent prior to beginning protocol specific procedures. Patients registered for this trial must be treated and followed at the participating centers.
2. Histologically or cytologically proven hematologic malignancy, or confirmed multiple myeloma using standard diagnosis criteria. For the dose finding part, any refractory/relapsing hematologic malignancy will be accepted. For the expansion cohorts, only patients with selected hematologic malignancies will be enrolled: acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), DLBCL and MM) and/or other diseases, as decided by the SMC after closure of the dose finding part.
3. Patient having failed all standard therapies or for whom standard treatment are contra-indicated:
   - For acute leukemia: patients < 60 years old in second or further relapse or relapsing after allogeneic stem cell transplantation (aSCT) regardless of number of relapses; patients ≥ 60 years old in first relapse with a disease-free interval (DFI) < 12 months, or further relapse ; irrespective of age, in patients relapsing after aSCT, the time elapsed since aSCT should be > 90 days. Patients with Philadelphia chromosome positive (Ph+) and/or bcr-abl+ B-cell ALL must have received at least two lines of therapy, including 2 bcr-abl tyrosine-kinase (TK) inhibitors (among imatinib, nilotinib and dasatinib), or only one line including one TK inhibitor, if the relapse/refractoriness is associated with the detection of a resistance mutation to these inhibitors.
   - For MM: patients adequately exposed to at least one alkylating agent, one corticosteroid, one immunomodulatory drug (IMiD) and bortezomib,
   - For lymphomas: Patients having failed 2 standard lines of therapy (at least one containing an anti-CD20 antibody if B-cell lymphoma), or for whom such treatment is contra-indicated.
4. Patients with evaluable disease
   - AL patients must have ≥ 5% bone marrow blasts at study entry, without alternative causality (e.g. bone marrow regeneration)

- Lymphoma patients must have at least one non-irradiated tumor mass ≥ 15 mm (long axis of lymph node) or ≥ 10 mm (short axis of lymph node or extranodal lesions) on spiral CT-scan.
- Patients with MM must have at least one of the following: serum monoclonal component ≥ 1g/dL (IgG), or ≥ 0.5g/dL (IgA), or Bence-Jones (BJ) proteinuria ≥ 200mg/24h, or measurable plasmacytoma (not previously irradiated).

5. Patients ≥ 18 years old.
6. Life expectancy of at least 3 months
7. ECOG performance status of 0 to 2
8. Off previous therapy for at least 3 weeks, or 5 half-lives of previously administered drug, whichever is longer, prior to first study treatment administration, except 1) hydroxyurea given to control hyperleukocytosis that should be stopped 48 hours prior to start study medication and 2) rituximab, which should be stopped for at least 3 weeks, regardless of half-life
9. Recovery from the non-hematologic toxic effects of prior treatment to grade ≤1, or baseline value, according to NCI-CTC classification, except alopecia.
10. Bone marrow function:
    - For patients with acute leukemia: No limitation
    - For patients with other hematologic malignancies: Neutrophils ≥ 1.0 x 10^9 /L and platelets ≥ 150 x 10^9 /L (without transfusion)
11. Calculated creatinine clearance ≥ 30 mL/min (Cockroft & Gault formula, or MDRD formula for patients aged ≥ 65 years).
12. Adequate LFTs: Total bilirubin ≤ the institutional upper normal limits (UNL); ALAT/ASAT ≤ 3 x UNL (or ≤ 5 x UNL in case of liver involvement).
13. Serum albumin ≥ 28g/L
14. Complete baseline disease assessment workup prior to first study treatment administration.

Exclusion criteria

1. History of prior malignancy other than those previously treated with a curative intent more than 5 years ago and without relapse (any tumor) or basal cell skin cancer, in situ cervical cancer, superficial bladder cancer, or high grade intestinal polyps treated adequately, regardless of the disease-free interval.
2. Pregnant or lactating women or women of childbearing potential not using adequate contraception. Male patients not using adequate contraception.
3. Patients with peripheral cytopenias (i.e. auto-immune hemolytic anemia or thrombocytopenia)
4. Patients with acute promyelocytic leukemia or with clinically uncontrolled (i.e. with bleeding) disseminated intravascular coagulation (DIC)
5. MM patients with POEMS syndrome or plasma cell leukemia.
6. Patient with chronic graft versus host disease (GVHD) or on immunosuppressive therapy for the control of GVHD
7. Uncontrolled leptomeningeal disease.
8. Other tumor location necessitating an urgent therapeutic intervention (palliative care, surgery or radiation therapy), such as spinal cord compression, other compressive mass, uncontrolled painful lesion, bone fracture, etc..)
9. Uncontrolled disease-related metabolic disorder (e.g. hypercalcemia)
10. Patients unable to swallow oral medications, or patients with gastrointestinal condition (e.g. malabsorption, resection…) deemed to jeopardize intestinal absorption.
11. Other serious illness or medical conditions, which, in the investigator's opinion could hamper understanding of the study by the patient, patient's compliance to study treatment, patient's safety or interpretation of study results. These conditions include (but are not restricted to):
    a) Congestive heart failure or angina pectoris except if medically controlled. Previous history of myocardial infarction within 1 year from study entry, uncontrolled hypertension or arrhythmias.
    b) Existence of significant neurologic or psychiatric disorders impairing the ability to obtain consent.
    c) Uncontrolled infection.
    d) Known HIV positivity
12. Concurrent treatment with other experimental therapies or participation in another clinical trial within 21 days prior to first study treatment administration, or 5 half-lives of previously administered drugs, whichever is longer.

13. Concurrent treatment or within 21 days prior to first study treatment administration with any other anticancer therapy, except hydroxyurea to reduced hyperleukocytosis.
14. Concomitant treatment with corticosteroids except if chronic treatment with corticosteroids ≤ 30 mg of methylprednisolone daily or equivalent.
15. Patients taking concomitant strong CYP3A4 interacting drugs.
16. Patients with prior irradiation on more than 30% of bone marrow reserves (including Total Body Irradiation), regardless of washout period, and patients having received high dose chemotherapy followed by autologous stem cell transplantation less than 90 days prior to first OTX015/MK-8628 dosing.

Treatment

- Patients should receive the study treatment within 7 days after registration.
- All patients will be hospitalized for at least 8 hours after the first study drug administration to check vital signs and ECG and collect PK blood samples around the anticipated T_{max}.
- Patients will take OTX015/MK-8628 orally, daily in a fasted state just before lunch, at least 3 hours after breakfast end (except outpatient who must take the study medication before breakfast at the hospital on day 1). The schedule of administration will initially depend on the indication:
  - AL patients will initially take OTX015/MK-8628, over 14 consecutive days followed by a 7-day rest period. Upon SMC decision, AL patients may take OTX015/MK-8628 continuously without planned rest period (as for OHM patients).
  - OHM patients will take OTX015/MK-8628 continuously without planned rest period
  - a cycle = 21 days by convention.
- The initial daily schedule of administration will be once a day (QD) at the first DL. Based upon PK and PD results, this schedule could be modified (e.g. to twice daily [BID] by SMC decision) for further patients. For the BID schedule, patients will take their medication in a fasted state around 8 a.m. (± 2 hours) and 8 p.m. (± 2 hours).
- Treatment will be interrupted in cases of toxicity according to specific guidelines (see dose and schedule adaptation).
- Enrolled patients will receive OTX015/MK-8628 at the DL they were assigned at study entry throughout the study, or at reduced dose according to toxicity encountered.
- However, in exceptional circumstances, intra-patient dose escalation could be allowed, provided all the following conditions are met: 1) The patient did not experience toxicity of grade > 1 while treated at the initial dose for at least 2 cycles; 2) The dose immediately above has already been tested and is considered safe (i.e. at least 3 patients were treated over 3 weeks and no DLT was observed, or at least 6 were treated over 3 weeks and no more than one of them has experienced a DLT); 3) the patient has experienced stable disease so far (no response and no progression); 4) the investigator considers that the patient could benefit from dose increment and 5) the SMC agrees.
- Treatment will be definitively discontinued upon patient's request, or in cases of disease progression, intolerable toxicity, treatment interruption > 2 weeks due to toxicity (except in cases of suspicion of hematologic DLT in acute leukemia, where treatment interruption for 3 weeks is allowed to confirm DLT), recurrence of the same toxicity despite dose reduction, lack of compliance, or major protocol deviation.
- Dosing not performed at the same time (± 2 hours) as the other days will be omitted.
- Omitted or vomited doses will not be replaced.

Dose & schedule adaptation

Study product dosing (OTX015/MK-8628) will be interrupted in case of:

Non-hematologic toxicities:

- any grade 3-4 non hematologic toxicity despite adequate medication, regardless of duration;
- grade 3-4 asymptomatic non hematologic laboratory abnormal values, deemed related to study medication, lasting > 7 days. This definition applies for patients with LFTs/creatinine clearance grade ≤ 1 at baseline. For patients with grade 2 values at baseline, only grade 4 lasting > 7 days will be considered DLT, unless the SMC considers the event clinically significant.
- Any prolonged grade 2 toxicity (lasting more than 2 weeks), leading to treatment interruption and/or dose reduction.

Hematologic toxicities:

-- *Patients with acute leukemia:*

- pancytopenia with a hypocellular bone marrow and no marrow blasts lasting for ≥ 6 weeks after the start of a cycle.

- *Patients with other hematologic malignancies:*

- any grade 3 neutropenia, with fever or infection; any grade 3 thrombocytopenia with bleeding,
- any grade 4 neutropenia or thrombocytopenia, lasting ≥ 3 days.

OTX015/MK-8628 dosing will be resumed when all toxic events have resolved to grade ≤ 1 (or to the baseline value) at reduced dose at the DL immediately below during the dose escalation phase.

During the cohort expansion phase, patients initially treated at 80 mg will have their dose reduced to 60 mg QD (2 weeks ON/1 week OFF) at the first occurrence of toxicity, then to 40 mg QD (2 weeks ON/1 week OFF) if the same toxicity recurs.

In all cases:

> Dosing interruption for > 2 weeks due to toxicity or recurrence of the same toxicity with the same severity despite one dose reduction will lead to definite study treatment discontinuation, unless the investigator thinks the patient's best interest is to pursue study treatment, with sponsor's agreement.

Premedication

No premedication is planned at the first cycle, in the first 3 patients. Decisions of further systematic premedication will be made by the SMC.

Dose escalation scheme

- The starting dose will be 10 mg/day (once a day, flat dose, without adaptation for body weight or surface area)
- DLTs will be collected during the first cycle (21 days after the first OTX015/MK-8628 administration)

The dose escalation scheme will be as followed for each patient subset (AL and OHM). The magnitude of dose escalation between two consecutive dose levels will depend upon the occurrence or not of DLT at the current DL.

Dose Level			
1 (starting dose) (mg)	**10**		
2	20		
3	30	40	
4	40	60	80
5	50	80	120
Dose escalation schedule: Doubling the dose in the absence of DLT (grey boxes). Fibonacci-like model once at least one DLT occurs (white boxes)			

- Dose escalation will be stopped by SMC decision separately and independently for the two patient subsets when the RD is deemed to be reached or exceeded.
- If and when the decision of exploring a BID schedule is taken by the SMC after the assessment of dose level X mg once-a-day, the first BID dose level explored will be X/2 mg twice-a-day (e.g. if the last once-a day dose level explored = 80 mg → the first BID dose level explored = 40 mg x 2/day).Further dose escalation with the BID schedule will proceed as described in the table above (e.g. if the first BID dose level explored= 40 mg x 2/day, then the next dose level explored will be 80 mg x 2/day if no DLT was observed at 40 mg x 2/day, or 60 mg x 2 if one DLT was observed).

  If a decision to deliver OTX015/MK-8628 continuously to AL patients is taken by the SMC, ongoing AL patients having received at least one intermittent cycle (14 days ON/7 days OFF) without DLT will be proposed to receive further cycles without planned interruption (21days ON) at the same daily dose. When sufficient safety data have been collected with the continuous schedule both in AL and OHM patients, the SMC may allow further cohorts of AL patients to receive continuous OTX015/MK-8628 treatment from cycle 1.
- The RD will be defined either by the MTD, or, in the absence of DLT, based upon PK and/or PD

considerations or other unforeseen condition (see Study Design).

The final decision of further escalating the dose and of stopping dose escalation, determining the RD and starting expansion cohorts enrollment will be left to the discretion of the SMC. According to the nature, suspected relationship to study drug, or other clinical considerations, the SMC will make *ad-hoc* decisions, such as replacing non-evaluable patients, adding more patients at the same DL, adding intermediate DLs, not considering a given DLT as clinically relevant for the determination of the RD. Serial assessments of PK/PD results will be forwarded to the SMC and taken into account for the determination of the RD, especially if no DLT occurs.

Safety Monitoring Committee (SMC)

The SMC will be composed of the principal investigators of each participating center, the pharmacokinetics (PK) specialist, the medical and safety representatives of the Sponsor and an independent expert in oncology/hematology phase I development. All decisions taken by the SMC and their rationale will be recorded in meeting minutes that will be integrated in the final clinical study report.

Definition of dose limiting toxicities (DLTs)

The DLTs are identical to the events leading to treatment interruption and dose adjustment (see dose & schedule adaptation), as well as any other unforeseen drug-related AE resulting in study drug discontinuation or interruption with/without dose reduction. But only such AEs occurring during cycle 1 (or the first 21 days following the first dosing of OTX015/MK-8628) are considered DLT, except for the hematologic DLT for patient with acute leukemia that must be confirmed after 6 weeks of treatment,

Treatment compliance

Patients will record daily in a specific diary, the number of capsules swallowed, time of intake, as well as possible reactions, including vomiting, and their time of occurrence. At each study visit the hospital pharmacist of the study center will provide the patient with the needed number of capsules for the visit interval and retrieve the unused capsules that will be kept until study end for accountability by the study monitor.

Number of subjects

The total number of patients enrolled will depend on the number of DLs explored and of DLT encountered.

Approximately 80 evaluable patients will be enrolled in the dose escalation part (40 by subset AL/OHM)

At least 12 evaluable patients by expansion cohorts will be enrolled in at least 3 expansion cohorts

Pharmacokinetics (PK)

Blood collection:

- Once-a-day schedule

Three patients by DL will have complete PK sampling, consisting of 7 blood draws of 3 mL each at days 1 and 2 (T0, T1h, T4h, T8h, T12h and T24h, plus one sampling ay either T10h or T16h). Complete PK sampling will preferably be performed in patients hospitalized due to medical reasons. All other patients enrolled at this DL will have limited PK sampling, consisting of 5 blood draws on day 1 (T0, T1h, T4h, T6h and T8h). Patients enrolled into the same DL across both dose escalation subsets (AL/OHM) will be considered for the selection of the 3 patients with complete PK sampling.

In addition, all patients will have blood sampling at T0 (just before drug intake) on days 8, 15 and 22.

- Twice-a-day (BID) schedule

All patients will have complete PK consisting of 8 blood draws of 3 mL each on days 1 and 2 (T0, T20min±5min, T1h±10min, T2h15min±10min, T3h15min±10min, T9h±1h, T12h±15min (before drug intake) and T24h (before drug intake)). Patients will be hospitalized for 24 hours for PK sampling.

In addition, all patients will have blood sampling at T0 (just before drug intake) on days 8, 15 and 22.

Fresh tumor collection:

OTX015/MK-8628 concentration will be measured in tumor cells.

- Patients with AL will have one bone marrow (3 mL) or one blood (7 mL) sample of at day 8.
- Patients with OHM* (optional): If a tumor is easily accessible to tumor cell collection using non-invasive method (i.e., skin or superficial lymph node deposits), optional tumor core biopsy will be strongly encouraged, with patient's express additional consent at baseline, and on D15 ± 7 days.

Assay method: Ultra Performance Liquid Chromatography with tandem Mass Spectrometry detection (UPLC-MS/MS).

Pharmacokinetic/safety correlations: The incidence and severity of AEs will be compared to Cmax, CL and AUC of OTX015/MK-8628.

Pharmacodynamics (PD)

Potential biomarkers will be explored in tumor cells, including c-MYC and BRD2, 3 and 4.

- Patients with AL will have 2 bone marrow (3 mL each) and blood (15 mL each) samples at screening and at day 8.
- Patients with other hematologic malignancies* (optional): If a tumor is easily accessible to tumor cell collection using non-invasive method (i.e., skin or superficial lymph node deposits), optional tumor core biopsy will be strongly encouraged, with patient's express additional consent, for intra tumor PK at baseline, and on D15 $\pm$ 7 days.

PD/safety correlation: The incidence and severity of AEs will be compared to the most pertinent biomarker(s), if any.

PK/PD correlation: Cmax, CL and AUC of OTX015/MK-8628 will be compared to the most pertinent biomarker(s), if any.

As far as possible the same cytology/tissue samples will be used for intratumor PK and PD

Predictive biomarkers

- Available archived tumor material (lymphoma) will be collected, as well as fresh tumor material at baseline (leukemic blasts or optional biopsy for other hematologic malignancies) for preliminary detection of predictive factors of OTX015/MK-8628 clinical antitumor activity. The availability of a paraffin-embedded block is a pre-requisite for inclusion of patients with lymphoma into the study if no fresh tumor cells/tissue are available.

Study endpoints

- Primary: the primary endpoint for the determination of the RD will be DLT
- Secondary: treatment-emergent adverse events (TEAEs), PK and PD parameters, laboratory results, tumor response assessment (according to most recently published standard criteria) (see details by disease in the core protocol), tumor-related symptoms, performance status (PS).
- Exploratory: tumor phenotype, karyotype, molecular biology, etc.

Safety parameters

Safety will be assessed on every patient having received the study treatment. It will be evaluated on:

- Vital signs (temperature, breath rate, blood pressure and heart rate), physical examination, within 1 week prior to the first study drug administration and then weekly for 3 weeks, and then every 21 days.
- In addition, vital signs will be collected immediately before, then, 1 and 2 hours (around the Tmax) after the first study drug administration on day 1
- ECG will be performed within one week prior to the first study drug administration, immediately before, then, 1 and 2 hours (around Tmax) after study drug administration at days 1.
- Echocardiography, with measurement of LVEF will be performed at baseline and at the end of treatment.
- AEs will be recorded and graded according to the NCI-CTC (v4.03).

Laboratory tests

- *Hematology:*
  Complete blood cell counts (CBC): platelets, WBC and differential and hemoglobin, INR, will be performed within 7 days prior to the first study drug administration, then at day 1, then weekly during the first 3 weeks and then every 3 weeks thereafter. In cases of grade >2 hematologic toxicity CBC will be performed twice a week until recovery to grade $\leq$ 2. In case of neutropenia/thrombocytopenia grade 4, CBC will be performed at least every other day until recovery to grade $\leq$ 3. In addition, in cases of thrombocytopenia grade 4 lasting > 3 days, a bone marrow aspiration is to be performed. In cases of fever $\geq$ 38°C, infection, purpura or bleeding, additional CBC should be done as clinically indicated.
- *Biochemistry:*
  LDL, HDL, β2-microglobulin (only for patients with myeloma), serum creatinine, glucose, ionogram (sodium, potassium, chloride, HCO_3^- (bicarbonate)), calcium, phosphorus, magnesium, total protein, albumin, AP, ASAT, ALAT, total bilirubin, LDH, CPK and CRP will be performed within 7 days prior to the first OTX015/MK-8628 intake, then at day 1, then weekly during the first 3 weeks, and then every 3 weeks thereafter. In addition, apolipoprotein A-1 (Apo A1) will be assessed within 7 days prior to first OTX015/MK-8628 intake and at day 22 only.
- *Urinalysis:*
  Dipsticks for protein, glucose and blood at day 1, 2, 8, 15, 22, then every 3 weeks.

Efficacy parameters

- Tumor response will be evaluated using standard criteria for lymphoma, acute leukemia and multiple myeloma.
- Any hints of anti-tumor activity will be quantified and recorded, even if they do not meet criteria for response
- Overall survival (OS)

Statistical considerations:

This is an exploratory Phase I study aimed to assess the pharmacological effects of OTX015/MK-8628 in humans with hematologic malignancies. The small subject sample size by cohort does not allow for statistical hypotheses. The decisions will be taken by a board of experts (SMC) and the recommended dose will be validated in further studies.

Study duration and dates	Enrolment: 24-26 months according to the number of DLs explored. First-patient in: January 2013 Last patient in: December 2015- January 2016 End of study follow-up: December 2016

4. ABBREVIATIONS

AE	Adverse Event
AL	Acute Leukemia
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
ALAT	Serum Alanine Aminotransferase
AP	Alkaline Phosphatase
Apo A1	Apolipoprotein A-1
ASAT	Serum Aspartate Aminotransferase
aSCT	Allogenic Stem Cell Transplant
ASCT	Autologous Stem Cell Transplant
BID	Twice Daily
BJ	Bence Jones Protein
BMI	Body Mass Index
BP	Blood Pressure
BRD	Bromodomain
BSA	Body Surface Area
CBC	Complete Blood Count
CHOP	Cyclophosphamide, Adriamycin, Vincristine, Prednisone
CI	Confidence Interval
CPK	Creatine PhosphoKinase
CR	Complete Response
CRi	CR With Incomplete Blast Clearance
CRF	Case Report Form
CRO	Contract Research Organisation
CRP	C-Reactive Protein
CSC	Clinically Significant Change
CYP	Cytochrome P
DIC	Disseminated Intravascular Coagulation
DL	Dose Level
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GCB	Germinal Center B-Cell-Like
GVHD	Graft Versus Host Disease
IMid	Immunomodulatory Drug
INR	International Normalized Ratio
ITT	Intent To Treat

LDH	Lactate Dehydrogenase
LFTs	Liver Function Tests
LVEF	Left Ventricle Ejection Fraction
MDRD	Modification Of Diet In Renal Disease
MLFS	Morphologic Leukemia-Free State
MM	Multiple Myeloma
MTD	Maximum Tolerated Dose
NA	Not Applicable
NCI-CTCAE	National Cancer Institute -Common Toxicity Criteria For Adverse Events
OHM	Other Hematologic Malignancies
PC	Predefined Change
PD	Progressive Disease
PP	Per Protocol
PK	Pharmacokinetics
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, M-Component, Skin Changes
PR	Partial Remission
PS	Performance Status
PT	Preferred Term
QD	Daily
RD	Recommended Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SMC	Safety Monitoring Committee
SCO	System Organ Class
TEAE	Treatment Emergent Adverse Event
Tmax	Time To Peak Concentration
UNL	Upper Normal Limit
UPN	Unique Patient Number
WHO	World Health Organization

5. STUDY CONDUCT

The study has been completed and the current SAP applies to all the patients included in the study (dose escalation and cohort expansion).

All statistical programs employed in the analysis, data reporting and statistical outputs will be validated by the statistician in charge of the study. In addition, primary criteria (DLT) will be validated by a second eXYSTAT statistician.

6. STATISTICAL METHODOLOGY

6.1 GENERAL CONSIDERATIONS

The statistical analysis will be performed by eXYSTAT, under the responsibility of the Sponsor OncoEthix GmbH and the study CRO, OTD, on the basis of the present document.

The statistical analysis will be performed using SAS® software, version 9.4 in a Windows XP operating system environment.

The baseline value is defined as the last available value prior to administration of the investigational product.

The study treatment phase is defined as the period between the date of first administration of investigational product and the date of last administration of investigational product + 30 days.

No replacement of missing values is planned, other than those noted in Section 6.2. Thus the number of patients included in the analyses may vary depending on availability of the parameter considered.

Descriptive statistics will be provided by dose level (DL1 to DL5 or DL6 then expansion cohort, depending on the disease cohort) and overall for each of the two patient cohorts (AL and OHM), and by time point when appropriate, according to the nature of the variable.

- For quantitative variables, descriptive statistics will include: number of missing values, number of observed values, minimum, maximum and median or mean and standard deviation.

- For qualitative variables, descriptive statistics will include: number and percentage of missing values, number of observed values, frequencies and percentages (only for the overall column) per modality.

Calculated statistics and percentages will be displayed with one decimal, unless otherwise specified.

No statistical tests will be performed due to the descriptive nature of this analysis.

In terms of terminology, the mention of "by dose level and overall" will always correspond to the following, according to the cohort:

Acute Leukemia Patients

DL1 (10mg QD) 14-21 (N=3)	DL2 (20mg QD) 14-21 (N=3)	DL3A (40mg QD) 14-21 (N=4)	DL3B (20mg BID) 21-21 (N=3)	DL4A (80mg QD) 14-21 (N=4)	DL4B (40mg BID) 14-21 (N=8)	DL5A (120mg QD) 14-21 (N=7)	DL5B (120mg QD) 21-21 (N=6)	DL6 (160mg QD) 14-21 (N=7)	Exp. (80mg QD) 14-21 – AML/de novo (N=19)	Exp. (80mg QD) 14-21 – AML/MDS (N=16)	Total (N=80)

Other Hematologic Malignancies Patients

DL1 (10mg QD) 21-21 (N=5)	DL2 (20mg QD) 21-21 (N=3)	DL3 (40mg QD) 21-21 (N=4)	DL4A (80mg QD) 21-21 (N=7)	DL4B (40mg BID) 21-21 (N=6)	DL5A (120mg QD) 21-21 (N=7)	DL5B (120mg QD) 14-21 (N=3)	DL5C (120mg QD) 5-7 (N=5)	DL5D (120mg QD) 7-21 (N=5)	Exp. (80mg QD) 14-21 - DLBCL (N=16)	Total (N=61)

All analyses will be repeated in the two populations, AL patients and OHM patients, unless otherwise specified.

6.2 HANDLING OF MISSING DATA

In the event of a missing date, replacement will be applied so as to be in the worst case scenario, as follows:

For <u>the concomitant medication start date</u>:

Completely missing dates will be estimated as the first treatment administration date.

If the day and the month are missing:
- If the year is the same as the year of the first treatment administration date, the date will be estimated as the first treatment administration date.
- If the year is different to the year of the first treatment administration date, the date will be estimated as the 1st January.

If only the day is missing:
- If the month/year are the same as the month/year of the first treatment administration date, the date will be estimated as the first treatment administration date.
- If the month/year are different from the month/year of the first treatment administration date, the date will be estimated as the first day of the month.

For <u>the concomitant medication end date</u> (if ongoing is not ticked at the end of the study):

Completely missing dates will be estimated by the End of Study date.

If the day and the month are missing:
- If the year is the same as the year of the End of Study date, the date will be estimated as the End of Study date.
- If the year is prior to the year of End of Study date, the date will be estimated as the 31 December.

If only the day is missing:
- If the month/year are the same as the month/year of End of Study date, the date will be estimated as the End of Study date.
- If the year or month is different to the year or month of End of Study date, the date will be estimated as the last day of the month.

If after imputation, the end date is before the estimation start date, the estimation start date will be replaced by the end date.

For <u>the start date of an adverse event</u>:

Completely missing dates will be estimated as the first treatment administration date.

7. NUMBER OF PATIENTS

A total number of 141 patients were enrolled according to the number of observed DLs and expansion groups selected.

8. POPULATIONS

Enrolled Population: all patients who signed an Informed Consent Form.

Treated/Safety Population: all included patients receiving at least one dose of the investigational drug.

Evaluable for Efficacy Population: All treated patients with at least one available tumor assessment (BM aspiration for AL patients or imaging for OHM patients) by the end of cycle 2 or later, OR with earlier evidence (i.e. cycle 1) of response or progression.

Evaluable for DLT Population: all treated patients receiving at least 85% of the intended OTX015/MK-8628 dose during the first cycle (i.e. ≥ 12 days at full dose for AL and ≥ 18 days at full dose for other hematologic malignancies)*, as well as patients not fulfilling these conditions, but who experienced DLT.

*e.g. for DL1 (10 mg/day), AL patients receiving ≥ 120 mg over the first 21 days (10 mg x 12), or other hematologic malignancy patients receiving ≥ 180 mg over the first 21 days (10 mg x 18).

8.1 DATA SETS ANALYZED

Statistical analyses will be carried out as described below. The number of patients per analysis set will be tabulated by DL and overall according to the population evaluated.

A listing will also be provided (for CSR appendices).

The following table describes use of the above-defined patients populations in the different analyses conducted.

Analyses Sets	Enrolled	Safety	Evaluable for efficacy population	Evaluable for DLT
Disposition	✓			
Population characteristics		✓		
Compliance and exposure		✓		
Efficacy assessments			✓	
DLT				✓
Safety assessment		✓		

9. PATIENT DISPOSITION AND PROTOCOL DEVIATIONS

9.1 PROTOCOL DISPOSITION

The number of patients per center will be tabulated for enrolled, treated, evaluable for DLT and evaluable for safety patients will be detailed by DL and overall.

Reasons for discontinuation will be tabulated by DL and overall, and detailed in a patient listing for the CSR appendices. Patients classified by the investigator as reason="Other" but with evidence of clinical or tumoral progression will be reclassified as progression in the table.

Overview of treated conditions will be tabulated by AL (AML/ALL) or OHM (lymphoma, multiple myeloma, other).

9.2 PROTOCOL DEVIATIONS

Totals of major/minor protocol deviations, the number of patients with at least one major/minor protocol deviation and type of major/minor deviation will be tabulated for the enrolled population.

A listing of patients with protocol deviations for relevant items will be presented in the CSR Appendices.

Protocol deviations will be examined prior to database lock relative to inclusion and exclusion criteria and to protocol compliance with regard to administration of treatment and prohibited medication.

Major protocol deviations are defined as deviations liable to prevent or change the interpretation of the results of the study.

10. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics recorded at the baseline visit (Day 0) before the first product administration will be described by DL and overall for the safety population.

10.1 DEMOGRAPHICS

- Age (years; by category) and gender.
- ECOG performance status at the screening visit by score (0, 1, 2, 3, 4)
- Height (cm), weight (kg), BMI (kg/m^2) = weight in kg/(height in m)² and BSA (m^2) = (W 0.425 x H 0.725) x 0.007184.
- Pregnancy test (positive, negative, NA)

10.2 DISEASE CHARACTERISTICS

- Acute leukemia: Disease duration (months; = [screening year - diagnosis year] *12 + [screening month - diagnosis month]), number of lines (in total=number of lines + number of NA in CRF page 17), number of lines prior therapy (from CRF page 17), type of systemic therapy (standard, AZA, aSCT, other: coded from CRF), leukemia WHO 2008 Classification, FAB classification, genetic group, bone marrow (from CRF page 401) (absolute value and 5-20%/>20%), presence peripheral blasts, hyperleukocytis (absolute value and $>15*10^9/l$, hydroxyurea requirement (coded from prior medication), type (de novo/secondary/therapy related/ALL), cellularity (poor, intermediate, rich), extramedullary disease, cytogenetics and molecular genetics (from CRF page 15).
- For lymphoma: disease duration (months), number of lines in total (=number of lines + number of NA in CRF page 17), number of lines prior therapy (from CRF page 17), prior therapy (systemic, surgery, radiotherapy), type of systemic therapy (CHOP/R-CHOP, ASCT, other; coded from CRF), lymphoma

WHO 2008 classification, number of tumor sites (from CRF page 21), number of nodal sites, number of extranodal sites, BM involved (CRF pages 19 and 301).

- Multiple myeloma: disease duration (months), M-component (IgG, IgA, Bence Jones, Other), Kappa or Lambda light chain (max of the two values from CRF page 201), bone lesions, extramedullary disease, bone marrow plasma cells, cellularity (poor, intermediate, rich), prior therapy (systemic, surgery, radiotherapy), type of systemic therapy (alkylating, steroid, bortezomib, IMiD, ASCT, other; coded from CRF), number of lines prior therapy (from CRF page 17)

Listings of disease characteristics and cancer treatments will be provided for the CSR Appendices.

10.3 SIGNS AND SYMPTOMS

Summary tables (number and % patients) grouped by System Organ Class (SOC) will be presented by DL and overall for Signs and Symptoms present at baseline (i.e., concomitant diseases "Ongoing" at the screening visit) and for Medical History (i.e., events "Not Ongoing" at the inclusion visit).

The totals of each Signs and Symptoms and the number of patients with at least one Sign and/or Symptom will be tabulated for the safety population for baseline Signs and Symptoms and for Medical History.

10.4 CONCOMITANT MEDICATIONS

Summary tables (number and % of patients) grouped by the first and the last level of ATC code will be presented by DL and overall. Concomitant medications are those ongoing at or started after the first treatment.

Presence at baseline of selected concomitant medications classes (e.g. cardiac antiarrhythmics, antihypertensive drugs, neurologic and/or psychiatric drugs) will be described by DL and overall.

10.5 MEASUREMENTS OF COMPLIANCE

Compliance to the study treatment will be derived only for patients with no missing data (collected in the CRF) using the following definition:

*Compliance (%) =[nb dose not equal to 0 in the CRF / ((nb completed lines in the CRF + 1)] * 100*

Compliance over the whole study treatment period (from first visit to last visit) and over cycle 1 only will be calculated.

11. EFFICACY ANALYSES

Response: tumor response will be assessed throughout the study according to standard criteria; acute leukemia patients will be assessed based on the recommendations from the European LeukemiaNet [*Döhner 2010*], lymphoma patients according to [*Cheson 2007*], and MM patients according to [*Durie 2006*].

Tumor response will be tabulated per DL and overall, according to disease indication (AL/lymphoma/MM) in evaluable patients.

Waterfall plots showing disease response according to DL will be prepared for lymphoma patients according to tumor dimensions, and for AL patients in terms of percent peripheral blood blasts decrease, percent BM blasts decrease and percent neutrophil increase (with different colors per dose level).

A listing of all responders will be provided including response, disease indication, duration of response.

Duration of response is defined as the time from the date of response to the date of documented progression or death. If progression or death is not observed during the study, data will be censored at the last date of documented response.

Event	Censoring decision	Event or censored date
PD during the study	Not censored	Date of last assessment
Lost to follow-up	Censored	Date of last assessment
Study ended without PD or death	Censored	Date of last assessment
Death during the study	Not censored	Date of death

Patients with any possible evidence of antitumor activity will be reported and described with narratives: standard responses (all patients), minor tumor shrinkages (lymphomas), neutrophil increase, platelets increase, transfusion requirement decrease, no further requirement of hydroxyurea, partial blasts clearance (AL patients), unexpected long stabilization (all patients).

12. SAFETY EVALUATION

12.1 SAFETY VARIABLES

Safety analyses will be performed in the Safety Population other than for DLT which will be presented in the evaluable for DLT population. All safety data from the study treatment phase will be presented.

Safety data are obtained from clinical and physical examinations, as well as vital signs evaluation.

TEAEs / signs and symptoms of disease observed by the investigator (preferably by the same physician for the same patient) or reported by patients to the study nurses will be recorded and graded according to NCI-CTCAE version 4.03.

Clinically significant laboratory results are those which have clinical consequences. The seriousness, the action taken regarding study medication and patient participation in the study, relation to study medication and the most likely cause, should then be recorded.

12.2 TREATMENT EXPOSURE

OTX015/MK-8628 treatment will be described by DL and overall.

The intended dose (mg, mg/kg, mg/m²), study duration (days), treatment duration (days), number cycles initiated, cumulative dose (mg), absolute dose intensity (mg/week), the relative dose intensity (%).

In addition, treatment modifications will be described including, the number (%) of patients having at least one dose reduction (compared to the initial DL), intra-cycle interruption (dose 0 between two non 0 doses),

delay (definition), or dose increase (compared to the initial DL). The number of modifications per patient and per modification type will be reported and listings will be provided.

- Intended dose (mg, mg/m^2, mg/kg) = nb of planned courses * planned dose by course
- Study duration =[(last cycle dose date - first cycle dose date)/7 + 1]
- N days treatment intake (observed) =
- Actual cumulative dose (mg) = sum of all doses received from first cycle 1 day 1 to actual last day of treatment during the last cycle
- Absolute dose intensity (mg/week) = Actual cumulative dose / Actual duration
- Relative dose intensity (%)=[Actual dose intensity / Planned dose intensity]*100
- Cumulative dose during the cycle 1 (mg/m^2)= sum of all doses received during cycle 1 with
- Planned period of administration = 21 days

12.3 PRIMARY CRITERION: DOSE LIMITING TOXICITY

DLTs are defined as any treatment-emergent adverse events (TEAEs) occurring during the first cycle (i.e., the first 21 days following study treatment initiation; note that hypocellular bone marrow and no marrow blasts in AL patients had to be confirmed at day 43), leading to treatment interruption or dose adjustment, or any unforeseen drug-related AE leading to study treatment interruption or discontinuation, unless a relationship to study medication can be definitively ruled out.

The number of patients evaluable for DLT/with DLT in cycle 1 will be tabulated per dose level and overall for safety population.

Type of DLT will be tabulated for patients evaluable for DLT by DL and overall.

Non-hematologic DLTs

- Any grade 3 or 4 non-hematologic event (regardless of duration), unless it was not optimally treated with supportive care (e.g. grade 3 vomiting not adequately treated according to antiemetic standard of care).
- Grade 3-4 asymptomatic laboratory abnormal values lasting > 7 days. This definition applies for patients with lab values grade < 1 at baseline. For patients with grade 2 values (liver function test (LFTs) or creatinine clearance) at baseline, only grade 4 lasting > 7 days will be accounted as DLT, unless the SMC considers the event clinically significant.
- Any other AE (such as prolonged and intolerable grade 2 event) resulting in study drug discontinuation or interruption with or without dose reduction

Hematologic DLTs

Acute leukemia

- Pancytopenia with a hypocellular bone marrow and no marrow blasts lasting for ≥ 6 weeks after the start of a cycle. DLT will be suspected in case of pancytopenia with a hypocellular bone marrow and no marrow blast on bone marrow aspiration on day 22, but confirmed on bone marrow aspiration on day 43. Decision of adding or not patients in the cohort will be based on day 22 findings.

Other hematologic malignancies

- Any grade 3 neutropenia, with fever or infection
- Any grade 3 thrombocytopenia with bleeding
- Any grade 4 neutropenia or thrombocytopenia, regardless of symptoms and lasting > 3 days.

12.4 ADVERSE EVENTS

Adverse events occurring or worsening after the treatment start date and before the last study treatment administration date +30 days were considered treatment-emergent adverse events (TEAEs).

Summary AEs (number and % of patients) will be tabulated by DL and overall for patients with:

- at least one treatment-emergent grade 1-5 adverse event (TEAE)
- at least one related treatment-emergent grade 1-5 adverse event (TEAE)
- at least one treatment-emergent grade 3-5 adverse event (TEAE)
- at least one related treatment-emergent grade 3-5 adverse event (TEAE)
- at least one serious TEAE
- at least one serious TEAE related to the study treatment
- a TEAE leading to treatment discontinuation
- a related TEAE leading to treatment discontinuation
- a TEAE leading to death

Tables of individual TEAEs (number and % of patients) grouped by primary System Organ Class (SOC) and Preferred Term (PT; for MedDRA) will be presented by DL and overall. Patients will be counted only once per primary SOC and PT.

These tables will be presented for all cycles as well as for cycle 1 only.

12.4.1 Listing of Adverse Events by Patient

AEs will be individually described per subject number, presenting: first/last application, treatment phase (Initial or Follow-up), emergence, description, SOC, preferred term, start and end date, duration, the toxicity grade, the relationship to study drug, the action taken and the seriousness.

12.5 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

All deaths and all SAEs experienced during the treatment period related to the study drug will be separately listed per subject number, presenting: first/last application, treatment phase (initial or follow-up), emergence, description, SOC, preferred term, start and end date, duration, the toxicity grade, the relationship to study drug, the action taken and the seriousness.

12.6 CLINICAL LABORATORY EVALUATION

All laboratory values recorded during the study (plus the calculated creatinine clearance) will be individually listed and flagged for values outside reference ranges.

12.6.1 Laboratory values over time

Each hematology and chemistry parameter will be described for each visit and by DL.

12.6.2 Individual patient changes

A listing of patients with worsening hematology or biochemistry parameters on study will be provided (baseline grade, worst grade, % decrease).

For thrombocytopenia, description of nadir (duration) and recovery (time to recovery) will be provided. A listing of patients experiencing thrombocytopenia during the study will be provided.

12.6.3 Individual clinically significant abnormalities

For each hematology and chemistry parameter, number and percentage of patients with at least one clinically significant value (according to the investigator) during the study as well as number and percentage of patients with at least one NCI-CTCAE worst grade of 3 to 5 during the study will be presented by DL.

12.7 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

12.7.1 Vital Signs

Raw values and changes from baseline of systolic/diastolic blood pressure (mmHg), Heart rate (beats/min) and respiratory rate (/min) will be described for each visit and for the last value during the study treatment phase by DL.

For weight (kg), systolic/diastolic blood pressure (mmHg) and heart rate (beats/min), number and percentage of patients with at least one predefined change (PC)/clinically significant change (CSC) during the study treatment phase will be presented by DL.

Predefined changes and clinically significant changes are defined below:

Parameter	**Predefined change (from baseline)**	**Clinically significant change**
Weight	Increase ≥ 5% Decrease ≥ 5%	
Systolic blood pressure	Increase ≥ 20 mmHg Decrease ≥ 20 mmHg	≥180 mmHg and PC Increase ≤ 90 mmHg and PC Decrease
Diastolic blood pressure	Increase ≥ 15 mmHg Decrease ≥ 15 mmHg	≥105 mmHg and PC Increase ≤ 50 mmHg and PC Decrease
Heart rate	Increase ≥ 15 bpm Decrease ≥ 15 bpm	≥120 bpm and PC Increase ≤ 50 bpm and PC Decrease

12.7.2 ECG and LVEF evaluations

Absolute and relative differences between max post dosing Day 1 and pre-dosing will be presented by DL and overall. Absolute and relative difference between end of study value and pre-dosing will be presented by DL and overall.

12.7.3 Physical examination

Physical examination will be individually listed.

13. PK ANALYSES

The PK analyses will performed by the Laboratoire de Pharmacology PPD Institut Curie (Hôpital René Huguenin), 35 rue Dailly, 92210 Saint Cloud, France.

A separate PK report will be provided.

14. CHANGES FROM PROTOCOL

The protocol allowed for analysis in a per protocol population (section 11.2). This analysis was not performed as it is not appropriate for a phase 1 study with small expansion cohorts.

Overall survival analysis planned in the protocol (section 7.2.2.7) were not performed.

The secondary objectives allowing for assessment of PK/safety, PD/safety and PK/PD relationships were not performed due to insufficient PD data, while PK analyses were not considered pertinent.

15. INDIVIDUAL LISTINGS

All relevant CRF data will be provided using individual data listings.

All listings will include center number, cohort, patient number, dose level.

16. APPENDIX

16.1 PROPOSED STATISTICAL OUTPUT TABLES

Templates of the planned tables and listings for the Clinical Study Report are provided as presented for two dry runs performed on 18 December 2016 & 11 February 2017 and validated by the Sponsor/Sponsor Representative.

Changes to the data presented or format may be made during the programing on the basis of the output results in agreement with the Sponsor Representative and the Statistician.

Each table will be presented for each of the two patient cohorts - the AL population and Other Hematologic Malignancies population - independently (a single table is shown per analysis with AL header); exceptions are noted when distinct tables are required for the two cohorts (disease characteristics, hematology examinations, efficacy). A representative table for each population is shown. For quantitative variables, % patients will only be reported in the total column, with N patients for individual dose levels.

Tables will be prepared according to the headers in Section 6.1

A) PATIENTS

i. PATIENT DISPOSITION

Table i-1 Patients enrolled by center and dose level, AL patients

Center	Center name
1	
2	
3	
…	
Total	

Data source: Statistical Output, Section

Table i-2 Patients enrolled by center and dose level, OHM patients

Center	Center name
1	
2	
3	
…..	
Total	

Data source: Statistical Output, Section

Listing i-1 Patient inclusion per site, AL / OHM enrolled patients

Dose level / schedule (initial)	Day 1, Cycle 1	Center Name	Cohort (AL/ OHM)	Patient #

Data source: Statistical Output, Section

Table i-3 Patient disposition, AL / OHM patients

Patients
Enrolled
Treated
Evaluable for DLT
Evaluable for safety

Data source: Statistical Output, Section

Listing i-2 Patients not evaluable or NA for DLT or safety evaluation, AL / OHM enrolled patients

Dose Level	Center name	Cohort	Patient ID	Treated	Evaluable for DLT	Evaluable for safety	Reason for non evaluability

Data source: Statistical Output, Section

Table i-4 Main r**eason for treatment discontinuation, AL / OHM enrolled patients**

Reason
Disease progression
Death, unrelated
Death, related
AE, related
AE, non-related
Non-compliance
Withdrawal of consent
Recurrence of toxicity*
Treatment delay >2 weeks for toxicity
Still on treatment
Other**

Data source: Statistical Output, Section

* Despite dose reduction; **Detail

Listing i-3 Discontinuation for progressive disease with date of death, AL / OHM enrolled patients

Center name	Patient ID	Dose Level	Disease Progression	Disease progression date	Patient status	Date of Death

Listing i-4 AEs leading to discontinuation, AL / OHM enrolled patients

Center name	Patient ID	Dose Level	Adverse Event	AE start date	AE stop date	Grade	Relation to study drug	SAE	Action taken for patient	Dose Adjustment	Dose modification: specify

ii. PROTOCOL DEVIATIONS

Inclusion/Exclusion criteria deviations

Table ii-1 Protocol deviations at inclusion, AL / OHM enrolled patients

Reason
N patients with ≥1 major deviation
Xxx (specify criterion)
Xxx
N patients with ≥1 minor deviation
xxx
xxx

Data source: Statistical Output, Section

iii. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Table iii-1 Patient characteristics at baseline, AL / OHM safety population

Characteristic
Gender, N
Male
Female
Age (years)
Median (range)
< 60 years, N
60 to < 70 years, N
70 to < 80 years, N
≥ 80 years, N
BMI (kg/m²), median (range)
BSA (m²), median (range)
ECOG PS, N
0
1
2
3

Data source: Statistical Output, Section

Table iii-2 Overview of treated conditions, AL / OHM safety population

AL, N
AML
ALL
MDS
OHM, N
Lymphoma
Multiple myeloma
Other*

Data source: Statistical Output, Section
*Detail: Provide listing with pt # and type

Table iii-3 Disease pathology, AL safety population

Bone marrow aspiration / Blasts (%)	
Median	
Range	
Bone marrow blasts category	
<5%	
[5-20%]	
>20%	
Bone marrow aspiration / Cellularity	
Poor	
Intermediate	
Rich	
Missing data	
Hyperleukocytosis > 15*10E9/L	
Yes	

Table iii-4 Disease characteristics (1), AML safety population

AML / Type (recoded)
De Novo
Therapy-related
Secondary to MDS
Secondary to MPD
AML / FAB Classification
M0
M1
M2
M5
M6
Missing data
AML / Cytogenetic-molecular genetic group
Favorable
Intermediate I
Intermediate II
Adverse
Missing data
Cytogenetics karyotype
Normal
Abnormal
Missing data
Molecular genetics
Normal
Abnormal
Missing data

Listing iii-1 Cytogenetics: abnormal karyotype, AML patients

Center name	Cohort	Patient ID	Cytogentics abnormalities

Listing iii-2 Molecular genetics: abnormal karyotype, AML patients

Center name	Cohort	Patient ID	Molecular genetics abnormalities

Table iii-5 Disease characteristics (2), AML safety population

Characteristic
Time since diagnosis (months)
Median (range)
Systemic therapy
Median (range)
N lines prior therapy (in total)*, N
Median (range)
1
2
3
≥4
N lines prior therapy current AML, N
Median (range)
1
2
3
≥4
Systemic therapy for AML, N
Standard intensive therapy (3+7)
Azacitidine
aSCT
Other**

Data source: Statistical Output, Section
aSCT: allogeneic stem cell transplantation
* Incudes therapies for previous conditions

Listing iii-3 Other systemic therapies, AML patients

Center name	Cohort	Patient ID	Molecular genetics abnormalities

Note that in light of the small patient numbers, a descriptive presentation of disease characteristics for the non-AML patients in the AL cohort will be provided from data listings.

Table iii-6 Disease characteristics (1), lymphoma safety population

Lymphoma / Classification
B-cell neoplasms
T-cell neoplasms
Hodgkin lymphoma
B-cell neoplasms
Diffuse large B-cell lymphoma (DLBCL)
Follicular lymphoma
Mantle cell lymphoma
Other
B-cell neoplasms/DLBCL
ABC
CGB
Missing data
Hodgkin Lymphoma
Classical Hodgkin lymphoma
Other
Nodal status
Nodal only
Extra nodal only
Extranodal and nodal
Missing data
BM involved, N

Data source: Statistical Output, Section
ABC, Activated B-Cell-Like; BM, bone marrow; GCB, Germinal Center B-Cell-Like

* Detail: Provide listing with pt # and type

Table iii-7 Disease characteristics (2), lymphoma safety population

Time since diagnosis (months)
Median (range)
Systemic therapy, N
N lines prior therapy (in total)*
Median (range)
1
2
3
≥4
N lines prior therapy for lymphoma, N
Median (range)
1
2
3
≥4
Prior therapy for lymphoma, N
Systemic
CHOP/R-CHOP
ASCT
Other*
Surgery
Radiotherapy

Data source: Statistical Output, Section
ASCT: autologous stem cell transplantation;
* Incudes therapies for previous conditions

Table iii-8 Disease characteristics (1), MM safety population

Multiple myeloma, N
M-component
IgG
IgA
Bence-Jones
Kappa light chain
Lambda light chain
Other*
Bone lesions, N
Extramedullary disease, N
Bone marrow plasma cells, N
Cellularity, N
Poor
Intermediate
Rich

Data source: Statistical Output, Section
* Detail: Provide listings with pt # and type

Table iii-9 Disease characteristics (2), MM safety population

Time since diagnosis (months)
Median (range)
N lines prior therapy, N
Median (range)
1
2
3
≥4
Systemic therapy, N
Systemic
Alkylating
Steroid
Proteosome inhibitor
IMiD
ASCT
Surgery
Radiotherapy

Data source: Statistical Output, Section
ASCT: autologous stem cell transplantation ; IMiD, immunomodulatory drug

Table iii-10 Signs and symptoms at baseline according to SOC and PT per patient, AL / OHM safety population

Overall
≥1 sign or symptom, N
xxx

Data source: Statistical Output, Section

Table iii-11 Medical history according to SOC and PT per patient, AL / OHM safety population

Overall
≥1 sign or symptom, N
xxx

Data source: Statistical Output, Section

Table iii-12 Abnormal biologic values at baseline (grade ≥1 NCI-CTCAE), AL / OHM safety population

Biochemistry, N
ASAT
ALAT
Alkaline phosphatase
LDH
CPK
Total bilirubin
Albumin
Creatinine
CRP
Calcium
Mg
Glucose
INR
Factor VII
β2-microglobulin*
Apo A1

Data source: Statistical Output, Section
* Patients with myeloma

Table iii-13 Abnormal hematologic values at baseline (grade ≥1 NCI-CTCAE), AL / OHM safety population

Hematology, N
Hemoglobin
Lymphocytes
Platelets
Neutrophils
Leucocytes

Data source: Statistical Output, Section

Table iii-14 Prior medications at baseline, by ATC classification, AL / OHM safety population

xx, N
xxx

Data source: Statistical Output, Section

Table iii-15 Concomitant medications at baseline, ATC classification, AL / OHM safety population

N patients
xx, N
xxx

Data source: Statistical Output, Section

B) SAFETY EVALUATION

i. EVALUATION OF DLT AND DETERMINATION OF RD

Table i-1 Determination of RD, AL / OHM safety population

N patients evaluable for DLT
N patients with DLT in cycle 1
N DLTs
Description of DLT
xxx

Data source: Statistical Output, Section
* including grade

Listing i-1 Patients with DLT during cycle 1, AL / OHM safety population

Cohort (AL/ OHM)	Dose level / schedule	Patient #	DLT (PT)	Date of Day 1 Cycle 1	Date of AE onset	Date of AE stop	Grade	Relation	SAE	Action/ Outcome	Comment

Data source: Statistical Output, Section

ii. EXPOSURE

Table ii-1 Extent of exposure, AL / OHM safety population

Intended dose*
Median (range) (mg/kg)
Median (range) (mg/m²)
Study duration (treatment start to last dose last cycle in days)
Median/patient (range)
Total
N days treatment intake (observed)
Median/patient (range)
Total
N cycles started
Median/patient (range)
1
2
3….
Cumulative dose (observed)
Median (range) (mg/kg)
Median (range) (mg/m²)
Absolute dose intensity (mg/week)
Median (range)
Relative dose intensity (%)
Median (range)

Data source: Statistical Output, Section
* From Day 1 until last treatment intake + 30 days ; Intended dose = nb of planned courses * planned dose by course

Table ii-2 Dose reductions, delays and interruptions, AL / OHM safety population

N patients with ≥1 dose reduction

N reductions/patient

1

2

N patients with ≥ 1 dose interruption

N interruptions/patient

1

2

N patients with ≥1 dose delay

N delay/patient

1

N patients with ≥1 dose increase

Data source: Statistical Output, Section

Listing ii-1 Reason for reduction/intracycle interruption/delay, AL / OHM enrolled patients

Cohort (AL/ OHM)	Patient #	Dose level / schedule (initial)	Reason for reduction	Other

Listing ii-2 Patients with dose reduction/delay for AE, AL / OHM enrolled patients

Patient ID	Dose Level	Visit	Adverse Event	AE start date	AE stop date	Grade	Relation to study drug	SAE	Action taken for patient	Dose Adjustment	Dose modification: specify

iii. ADVERSE EVENTS

Table iii-1 Summary of all AEs, AL / OHM safety population

N patients with ≥1 :
Grade 1-4 AE
Grade 3-4 AE
Related AE
Related grade 3-4 AE
DLT in cycle 1
SAE
Related SAE
AE leading to treatment discontinuation
Related AE leading to treatment discontinuation

Data source: Statistical Output, Section

AE TABLES FOR ALL CYCLES AND CYCLE 1 ONLY

Table iii-2 NCI-CTCAE grade 1-4 AEs regardless of relationship to treatment, worst grade per patient, AL / OHM/ ALL PATIENTS safety population

Adverse event
N patients with ≥1 AE / N AE
SOC
PT
PT

Data source: Statistical Output, Section

Table iii-3 NCI-CTCAE grade 1-4 related AEs, worst grade per patient, AL / OHM/ ALL PATIENTS safety population

Adverse event
N patients with ≥1 AE / N AE
SOC
PT
PT

Data source: Statistical Output, Section

Table iii-4 NCI-CTCAE grade 3-4 AEs regardless of relationship to treatment, worst grade per patient, AL / OHM/ ALL PATIENTS safety population

Adverse event
N patients with ≥1 AE / N AE
SOC
PT
PT

Data source: Statistical Output, Section

Table iii-5 NCI-CTCAE grade 3-4 related AEs, worst grade per patient, AL / OHM/ ALL PATIENTS safety population

Adverse event
N patients with ≥1 AE / N AE
SOC
PT
PT

Data source: Statistical Output, Section

iv. SAEs AND OTHER SIGNIFICANT AEs

Table iv-1 Summary of SAEs, related / non-related, AL / OHM safety population

Adverse event
N patients with ≥1 SAE / N AE
SOC
PT
Type SAE
Death (related)
Death (non-related)
Hospitalization
Other

Data source: Statistical Output, Section

Table iv-2 Summary of AEs resulting in discontinuation, related / non-related, AL / OHM safety population

Adverse event
N patients with ≥1 AE for discontinuation / N AE
SOC
PT

Listing iv-1 SAEs/ AEs resulting in treatment discontinuation, AL / OHM safety population

Center name	Patient ID	Dose Level	Visit	Adverse Event	AE start date	AE stop date	Grade	Relation to study drug	SAE	Action taken for patient	Dose Adjustment	Dose modification: specify

Data source: Statistical Output, Section

v. ECG AND LVEF EVALUATIONS

Table v-1 QT variations on study, AL / OHM safety population

QTc difference (msec)
QTc (msec)
Median (range)
<=450 msec
>450 to <=480 msec
>480 to <=500 msec
QTc (msec), absolute variation
Median (range)
<=30 msec
>30 to <=60 msec
QTc (msec), relative variation
Median (range)
QTc (msec) maximal post-dose value
Median (range)
<=450 msec
>450 to <=480 msec
>480 to <=500 msec
QTc (msec), maximal absolute variation
Median (range)
<=30 msec
30< to <=60 msec

Data source: Statistical Output, Section

Table v-2 QT variations on study, AL / OHM safety population

QTc difference (msec)
LVEF Baseline (%)
Median (range)
Normal
Notsignificant abnormalities
Clinically significant abnormalities
LVEF EOS (%)
Median (range)
Normal
No significant abnormalities
LVEF absolute change (%)
Median (range)
LVEF relative change (%)
Median (range)

Data source: Statistical Output, Section

Listing v-1 Patients QTc prolongation on study, AL / OHM safety population

Cohort (AL/ OHM)	Dose level / schedule	Patient #	Visit	Date	Time	CS	NCS	QTc (msec)

Data source: Statistical Output, Section

Listing v-2 Patients with LVEF decrease on study, AL / OHM safety population

Cohort (AL/ OHM)	Dose level / schedule	Patient #	Visit	Date	LVEF Value (%)	Normal/CS/NCS
			Baseline Visit….			

Data source: Statistical Output, Section

vi. CLINICAL LABORATORY EVALUATIONS

Table vi-1 Summary of hematologic abnormalities (NCI-CTCAE), worst grade per patient, AL / OHM safety population

Hemoglobin
Grade 1-4
Grade 3-4
Platelets
Grade 1-4
Grade 3-4
Neutrophils
Grade 1-4
Grade 3-4
Lymphocytes
Grade 1-4
Grade 3-4
Leukocytes
Grade 1-4
Grade 3-4

Data source: Statistical Output, Section

Table vi-2 Hematologic abnormalities (NCI-CTCAE) worst grade per patient, AL / OHM safety population

Hemoglobin	
Grade 1	
Grade 2	
Grade 3	
Grade 4	
Platelets etc…	

Listing vi-1 Patients with worsening hematology parameters, OHM safety population

Parameter	Dose level /schedule	Patient #	Baseline grade	Worst grade	Baseline absolute value	% decrease
Hemoglobin						
Neutrophils						
Platelets						
Lymphocytes						
Leukocytes						

Data source: Statistical Output, Section

Table vi-3 Nadir and recovery for patients with grade 3 or 4 thrombocytopenia, OHM safety population

Thrombocytopenia grade 3-4
Time to nadir, median (range)
Time to first G3 or 4, median (range)
Time to first G3, median (range)
Time to first G4, median (range)
Duration of G3 or G4

Data source: Statistical Output, Section

Listing vi-2 Patients with grade 3-4 thrombocytopenia, AL / OHM safety population

Dose Level	Pt ID	Start date	Stop date	Grade	Relation to study drug	SAE	Action taken for patient	Dose adjustment

Biochemistry

Table vi-4 Grade 1-4 biochemistry toxicity (NCI-CTCAE) worst grade per patient, AL / OHM safety population

NCI grade
ASAT
Grade 1-4
Grade 3-4
ALAT
Alkaline phosphatase
LDH
CPK
Total bilirubin
Albumin
Creatinine
CRP
Calcium
Mg
Glucose
INR
Factor VII
β2-microglobulin*
Apo A1

Data source: Statistical Output, Section

Table vi-5 Hematologic abnormalities (NCI-CTCAE) per patient, worst grade per patient, cycle 1 only AL / OHM safety population

ASAT	
Grade 1	
Grade 2	
Grade 3	
Grade 4	
ALAT etc…	

Listing vi-3 Patients with worsening biochemistry parameters, AL / OHM safety population

Parameter	Dose level /schedule	Patient #	Baseline grade	Worst grade	Absolute value at baseline	Absolute value at max change	% decrease
ASAT							
ALAT							
Alkaline phosphatase							
LDH							
CPK							
Total bilirubin							
Albumin							
Creatinine							
CRP							
Calcium							
Mg							
Glucose							
INR							
Factor VII							
β2-microglobulin*							
Apo A1							

Data source: Statistical Output, Section

Table vi-6 Change in hemato/bioch values on study, all patients combined, AL / OHM safety population

	Not done	Grade 0	Grade 1	Grade 2	Total
Worst grade post baseline - lowest value					
Grade 0					
Grade 1					
Grade 2					
Grade 3					
Grade 4					

C) PHARMACOKINETICS EVALUATION

REPORTED SEPARATELY AND WITH EXTENSION COHORT CLINICAL STUDY REPORT

D) PHARMACODYNAMICS EVALUATIONS

REPORTED SEPARATELY AND WITH EXTENSION COHORT CLINICAL STUDY REPORT

E) EFFICACY EVALUATIONS

Table vi-1 Tumor response, AL efficacy population

Best overall response
CR
CRi
MLFS
PR
CRc
CRm
RD
Death in aplasia
Death other
Overall response rate

Data source: Statistical Output, Section
CR, complete remission; Cri, CR with incomplete hematologic recovery; MLFS: Morphologic leukemia-free state; PR = Partial remission, CRc, cytogenetic CR, CRm, molecular CR, RD, resistant disease

Table vi-2 Tumor response, lymphoma efficacy population

Best overall response
CR
PR
SD
PD
Not evaluable
Overall response rate

Data source: Statistical Output, Section

Table vi-3 Tumor response, myeloma efficacy population

Best overall response
sCR
CR
VGPR
PR
SD
PD
Not evaluable
Overall response rate

Data source: Statistical Output, Section

Listing vi-1 Response, CR/CRi/PR, AL / OHM efficacy populations

Dose level /schedule	Patient #	Diagnosis	Response	Date of Response	Date of Progression/Last News	Duration of response

Data source: Statistical Output, Section

Figure: Waterfall plot of response, absolute maximal BM blasts value (10^9/L) relative to baseline per patient (AL patients)*
Figure: Waterfall plot of response, absolute minimal BM blasts value (10^9/L) relative to baseline per patient (AL patients)*
Figure: Waterfall plot of response, relative maximal BM blasts value (%) relative to baseline per patient (AL patients)*
Figure: Waterfall plot of response, relative minimal BM blasts value (%) relative to baseline per patient (AL patients)*
Figure: Waterfall plot of response, absolute maximal neutrophil value (10^9/L) relative to baseline per patient (AL patients)*
Figure: Waterfall plot of response, relative maximal BM blasts value (%) relative to baseline per patient (AL patients)*
Figure: Waterfall plot of response, absolute change in tumor dimension (mm²) (lymphoma patients)*
Figure: Waterfall plot of response, relative change in tumor dimension (%) (lymphoma patients)*

***** Different colors for different dose levels