Official Protocol Title:	A phase I, dose-finding study of the bromodomain (Brd) inhibitor OTX015/MK-8628 in haematological malignancies
NCT number:	NCT01713582
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CONFIDENTIAL

Sponsor : ONCOETHIX GmbH, a wholly owned subsidiary of Merck, Sharp & Dohme Corp

CLINICAL STUDY PROTOCOL

OTX015_104/MK-8628-001

EUDRACT number: 2012-003380-22

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

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Date of issue: 18 December, 2015 **Version N° : J** Amendment 9

CONFIDENTIAL

STUDY PROTOCOL AGREEMENT FORM

I, ----------, Principal Investigator, have examined this Oncoethix' Study Protocol OTX015_104/MK-8628-001 Version J, dated 18 December 2015, entitled:

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

I confirm that I have read the above protocol. The information it contains is consistent with the current risk-benefit evaluation of the investigational product.
I understand it, and I agree to conduct the study according to this protocol and to comply with its requirements, subject to scientific, ethical and safety considerations. More specifically, I will work according to the principles of GCP as described in CPMP/ICH/135/95 and 21 CFR parts 50, 54, 56, and 312 and according to applicable local requirements.

I understand that, I must keep confidential the information contained in the study documents that I have been or will be provided with.

I understand that, should the decision be made by the Sponsor to terminate prematurely or suspend the study at any time for whatever reason; such decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate immediately such decision in writing to the Sponsor.

Furthermore, by the present, I am committed to enrol the first patient in this Study within a month.

FOR THE SPONSOR	**INVESTIGATOR**
ONCOETHIX	
CRO Medical Project Leader	
Name: PPD	Name:
Date : __ __ d __ __ m __ __ y	__ __ d __ __ m __ __ y
Signature:	Signature:

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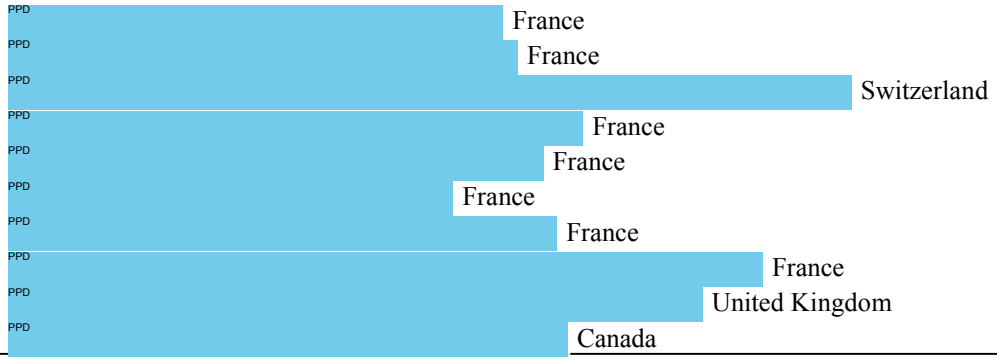
PROTOCOL SYNOPSIS

Title

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

Study code: OTX015_104/MK-8628-001

Investigator(s), study site(s)



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 hematological malignancies,

Secondary:

- To assess the safety profile of OTX015/MK-8628 as a single agent in patients with haematological malignancies
- To assess pharmacokinetics (PK) of OTX015/MK-8628 in patients with haematological malignancies and PK/safety relationship
- To assess pharmacodynamics (PD) of OTX015/MK-8628 in patients with haematological 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.

Dose escalation part:

- Two dose escalation subsets will be assessed independently in parallel: patients with acute leukemia (AL) and patients with other hematological malignancies.
- 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 will have 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 will have completed one cycle of study treatment (21 days following study treatment initiation, regardless of the treatment schedule).
- If one out 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 one patient out of 6 (or more than one 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 decision of the Safety Monitoring Committee (SMC). This decision could 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 hematological malignancies. Additional expansion cohorts may be decided by the SMC, based upon the data collected during the dose escalation phase.

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 hematological malignancy, or confirmed multiple myeloma using standard diagnosis criteria. For the dose finding part, any refractory/relapsing hematological malignancy will be accepted. For the expansion cohorts, only patients with selected hematological 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 $\geq$ 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 $\geq$ 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 $\geq$ 15 mm (long axis of lymph node) or $\geq$ 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 $\geq$ 1g/dL (IgG), or $\geq$ 0.5g/dL (IgA), or Bence-Jones (BJ) proteinuria $\geq$ 200mg/24h, or measurable plasmacytoma (not previously irradiated).
5. Patients $\geq$ 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-hematological toxic effects of prior treatment to grade $\leq$ 1, according to NCI-CTC classification, except alopecia.
10. Bone marrow function:
    - For patients with acute leukemia: No limitation
    - For patients with other hematological malignancies: Neutrophils $\geq 1.0 \times 10^9$/L, platelets $\geq 150 \times 10^9$/L (without transfusion), hemoglobin $\geq$8 g/dL (4 weeks without transfusion)
11. Calculated creatinine clearance $\geq$ 30 mL/min (Cockroft & Gault formula, or MDRD formula for patients aged $\geq$ 65 years).
12. Adequate LFTs: Total bilirubin $\leq$ institutional upper normal limit (UNL) (or $\leq$ 2 x UNL in cases of liver involvement); ALAT/ASAT $\leq$ 3 x UNL; if alkaline phosphatase (ALP) > 2.5 X ULN, then liver fraction should be $\leq$ 2.5 X ULN.
13. Serum albumin $\geq$ 28 g/L
14. International normalized ratio (INR) or prothrombin time (PT) and activated partial thromboplastin time (aPTT) $\leq$1.5 X ULN
15. 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 (see Appendix XI)
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:
    - patients with acute leukemia will initially take OTX015/MK-8628, over 14 consecutive days followed by a 7-day rest period. Upon SMC decision, patients with acute leukemia will take OTX015/MK-8628 continuously without planned rest period, like patients with other hematological malignancies.
    - patients with other malignancies will take OTX015/MK-8628 continuously without planned rest period
    - In all cases, one cycle = 21 days by convention.
- The initial daily schedule of administration will be once a day at the first DL. Based upon PK and PD results, this schedule could be modified (e.g. b.i.d.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 case of toxicity according to 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 definitely discontinued upon patient's request, or in case of disease progression, intolerable toxicity, treatment interruption > 2 weeks due to toxicity (except in case of suspicion of hematological DLT in acute leukemia, where treatment interruption for 3 weeks is allowed to confirm DLT), recurrence of the same toxicity despite dose reduction, specific liver toxicities (see Dose and Schedule Adaptation below), lack of compliance, or major protocol deviation.
- Dosing not performed at the same time ($\pm$ 2 hours) as the other days will be omitted.
- Omitted or vomited doses will not be replaced.

The recommended dose (RD) for expansion cohorts for both acute leukemia and other hematologic malignancies is 80 mg QD days 1 to 14 of 21-day cycles (2 weeks ON/one week OFF)

Dose & schedule adaptation

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

Non-hematological toxicities:

- any grade 3-4 non hematological toxicity despite adequate medication, regardless of duration;
- grade 3-4 asymptomatic non hematological laboratory abnormal values, deemed related to study medication, lasting > 7 days. This definition applies for patients with lab values grade $\leq$ 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. See below for liver function tests.
- Any prolonged grade 2 toxicity (lasting more than 2 weeks)**,** leading to treatment interruption and/or dose reduction.

Hematological toxicities:

-- *Patients with acute leukemia:*

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

- *Patients with other hematological malignancies:*

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

OTX015/MK-8628 dosing will be resumed when all toxic events have resolved to grade $\leq$ 1 (or to the baseline value) at a 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, recurrence of the same toxicity with the same severity despite one dose reduction, or specific liver toxicities* will lead to definitive study treatment discontinuation, unless the investigator thinks the patient's best interest is to pursue study treatment, with sponsor's agreement.

* Any of the following liver test abnormalities** (see Appendix 16.12)

- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN for > 2 weeks
- ALT or AST > 3 x ULN AND (total bilirubin > 2 x ULN OR INR > 1.5)

- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%), unless the investigator assesses the rash or fatigue to be related to OTX015 and not related to liver impairment with sponsor's agreement.

**Note: All patients with these liver test abnormalities should be monitored weekly until all abnormalities return to normal or to the baseline state. For patients with isolated total bilirubin increases >2 x ULN or 2 x baseline (if elevated at baseline), except if associated with direct bilirubin ≤ ULN, monitoring should be every 2 weeks until bilirubin returns to normal or to the baseline state. Drug induced liver injury (DILI) may develop or progress even after the causative drug has been stopped. Results should be recorded on the CRF and in the database. See guidelines on the handling of these events (potential Hy's law cases).

Premedication

No premedication is planned at the first cycle, in the first 3 patients. Decision of further systematic premedication should be taken 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 follows for each subset (AL and other hematological malignancies). 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 subsets when 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 Xmg 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 = 80mg → the first BID dose level explored = 40mg x 2/day). Then, further dose escalation with the BID schedule will proceed as described in the table above (e.g. if the first BID dose level explored= 40mg x 2/day, then the next dose level explored will be 80mg x 2/day if no DLT was observed at 40mg x 2/day, or 60mg x 2 if one DLT was observed).
  When the decision of delivering 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 will have been collected with the continuous schedule both in AL patients and in patients with other hematologic malignancies, the SMC may allow further cohorts of AL patients to receive continuous OTX015/MK-8628 treatment from cycle 1.
- 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, finally, 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 inevaluable 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 will be 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 (PI) of each participating center, the pharmacokinetics (PK) specialist, the medical and safety representatives of the Sponsor and one 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 (including liver function test abnormalities as reported in Dose and Schedule Adaptation) 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) are considered DLT, except the hematologic DLT for patients 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 acute leukemias/other hematological malignancies)

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

The total number of evaluable patients is estimated to be 125.

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 be performed preferably 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/other hematological malignancies) 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 (3mL) or one blood (7mL) sample of at day 8.
- Patients with other hematological 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 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 (3mL each) and blood (15mL each) samples at screening and at day 8.
- Patients with other hematological 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 ± 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 hematological malignancies) to preliminary detect 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, PS.
- Exploratory: tumor phenotype, Karyotype, molecular biology…

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 case of grade >2 hematologic toxicity CBC will be performed twice a week until recovery to grade ≤ 2. In case of neutropenia/thrombocytopenia grade 4, CBC will be performed at least every other day until recovery to grade ≤ 3. In addition, in case of thrombocytopenia grade 4 lasting ≥ 3 days, a bone marrow aspiration is to be performed. In case of fever ≥ 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 clue of anti-tumor activity will be quantified and recorded, even though it does 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 hematological 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 2014- January 2016 End of study follow-up: January – May 2016

STUDY SCHEDULE

Overall Study Flow Chart

PARAMETERS	BASELINE	DURING STUDY TREATMENT					END OF STUDY TREATMENT
	to be done within 7 days prior to first study drug administration (except tumor imaging, bone marrow biopsy and LVEF within 30 days and informed consent and blasts sampling within 14 days)	D1	D8	D15	D22	q3 wks from day 22 onward	
	V1	V2	V3	V4	V5 and higher	EOT	
Informed consent	x						
History incl. baseline concomitant illnesses; , Height	x						
Pregnancy test	x						
Availability of archived biopsy for lymphoma	x						
Physical examination (ECOG Performance Status (PS), Weight, clinical tumor measurement)	x	x	x	x	x	x	x
Vital Signs	x	x (1)	x	x	x	x	x
12-lead ECG	x	x (1)			x	x	x
Baseline symptoms / Adverse events	x	x	x	x	x	x	x

Prior / concomitant medications	x	x	x	x	x	x	x
Peripheral blood Hematology (*)	x	x	x	x	x	x	x
Bone marrow aspiration ([2])	x		(x)		(x)	(x)	
Biochemistry (**)	x	x	x	x	x	x	x
Imaging/Tumor assessment (***)	x					x[(3)]	x
Plasma M-component and/or BJ proteinuria (myeloma only)	x				x	x	x
Fresh tumor cells sampling [(4)] for baseline predictive biomarkers, PD biomarkers and intracellular PK	x			x[(5)]			
Bone marrow biopsy, (****)	x					x[(6)]	
Urinalysis°	x	x	x	x	x		x
Blood Pharmacokinetic (PK) sampling		x [(7)]	x [(8)]	x[(8)]	x[(8)]		
Echocardiography with LVEF measurement	x						x

(*) CBC with platelet counts, WBC differential and hemoglobin, INR. In case of fever NCI CTC grade > 2 or infection, additional CBC should be done.

(**) Biochemistry: LDL, HDL, β2-microglobulin (only for patients with myeloma), AP, LDH, ASAT, ALAT, total bilirubin, serum creatinine, ionogram (sodium, potassium, chloride, HCO_3- (bicarbonate)), calcium, phosphorus, magnesium, total protein, albumin, glucose, CPK and CRP. If a patient did not present ≥ grade 2 biochemistry toxicity in the first cycle, the tests will be performed at the end of each cycle, otherwise they will be performed every week until < grade 2 biochemistry toxicity. In case of extensive liver involvement, LFTs may change rapidly. In such circumstances, it is mandatory to repeat the liver tests the day before the study drug administration to confirm the eligibility of the patient. 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. **All patients with specific liver test abnormalities (see DLT definition) should be monitored weekly until all abnormalities return to normal or to the baseline state. For patients with isolated total bilirubin increases >2 x ULN or 2 x baseline (if elevated at baseline), except if associated with direct bilirubin ≤ ULN, monitoring should be every 2 weeks until bilirubin returns to normal or to the baseline state;**

(***) CT-scan or MRI in patients with evaluable tumor masses; PET-scan if deemed necessary for appropriate tumor assessment; bone X-ray or MRI in myeloma

(****) When necessary for the adequate assessment of disease spread

° Dipsticks for albumin, blood and glucose

(1) Before, then at 1 and 2 hours after study medication intake, around the T_{max}
(2) For AL patients: at screening, then on days 8, 22, 43. For MM patients: at screening, then only mandatory to validate CR. **In addition, in all patients with grade 4 thrombocytopenia lasting > 3 days, bone marrow aspiration will be performed**
(3) every 6-8 weeks for patients with lymphoma or any tumor necessitating imaging for the assessment of response. Every 6 months for bone lesions in responding MM patients
(4) In patients with other hematological malignancies, core biopsies without invasive procedure (e.g. superficial lymph node) are optional
(5) Day 15 ± 7 days:
(6) day 43 if positive at baseline,, then when deemed necessary by the investigator
(7) Complete PK sampling in only 3 patients per DL: T0 (just before drug intake), T1h, T 4h, T8h, T 12h, T24h, plus one sampling at either T10h OR T16h;
Limited PK sampling in other patients at the same DL: T0, T1h, T4h, T6h, T8h
(8) T0 in all patients at days 8, 15, 22

ABBREVIATIONS AND DEFINITIONS

ABC	Activated B-cell-like
AE	Adverse Event
AL	Acute leukemia
ALCL	Anaplastic Large Cell Lymphoma
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ALAT	Serum alanine aminotransferase
ALP	Alkaline Phosphatase
APO A1	Apolipoprotein A-1
aPTT	activated partial thromboplastin time
ASAT	Serum aspartate aminotransferase
AUC	Area under the plasma concentration vs time curves
BA	Bioavailability
BCC	Blood Cell Counts
BET	Bromodomain and Extra Terminal
BJ	Bence Jones protein
BP	Blood pressure
Brd	Bromo domains
BSA	Body surface area
CBC	Complete blood count
CFR	Code of Federal Regulations
CL	Total plasma clearance
Cmax	Peak concentration
Cmin	Residual/trough concentration
CPK	Creatine phospho kinase
CR	Complete Response
CRF	Case report form
CT-scan	Computerized tomography scan
CYP	Cytochrome P
DCF	Data Correction Form
DIC	Disseminated Intravascular coagulation
DILI	Drug Induced Liver Injury

DL	Dose level
DLT	Dose limiting toxicity
DLBCL	Diffuse large B-cell lymphoma
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GCB	Germinal Center B-cell-like
GI	Gastrointestinal
GVHD	Graft versus host disease
Hb	Hemoglobin
hERG	human Ether-a-go-go related gene
HNSTD	Highest Non-Severely Toxic Dose
HPMCAS-MG	Hypromellose Acetate Succinate
ICF	Informed Consent Form
Ig	Immunoglobulin
IMid	Immunomodulatory drug
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LFTs	Liver Function Tests
INR	International Normalized Ratio
LVEF	Left Ventricle Ejection Fraction
MCL	Mantle cell Lymphoma
MDRD	Modification of Diet in Renal Disease
MM	Multiple myeloma
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute -Common Toxicity Criteria for Adverse Events
NOAEL	No Observed Adverse Event Level
OS	Overall Survival
PD	Progressive Disease
PD	Pharmacodynamics
PI	Principal investigator
PIL	Patient Information Leaflet
PK	Pharmacokinetics
PO	*Per os*
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, M-component, Skin changes

PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
PVP	PolyVinyl Pyrolidone
RD	Recommended dose
SAE	Serious adverse event
SAERF	Serious adverse event Report Form
SAR	Suspected Adverse reaction
SD	Stable Disease
SMC	Safety Monitoring Committee
SMZL	Splenic Marginal Zone Lymphoma
SUSAR	Serious, unexpected suspect adverse reaction
$t_{1/2}$	Terminal half-life
TEAE	Treatment emergent adverse event
Tmax	Time to peak concentration
UNL	Upper Normal Limit
UPN	Unique Patient Number
UPLC-MS/MS	Ultra Performance Liquid Chromatography, with tandem Mass Spectrometry detection
US	Ultrasound
Vss	Volume of distribution at steady state
WHO	World Health Organization

1 INTRODUCTION AND STUDY RATIONALE

1.1 BACKGROUND INFORMATION (SEE INVESTIGATOR'S BROCHURE FOR DETAILS)

1.1.1 Name and description of the investigational product OTX015 (formerly known as Y-803)

OTX015 is a synthetic small molecule targeted to bromodomains (BRD) 2, 3 and 4 of the tandem-BRD-containing family of transcriptional regulators known as the BET (bromodomain and extraterminal) proteins. The structure is summarized below:

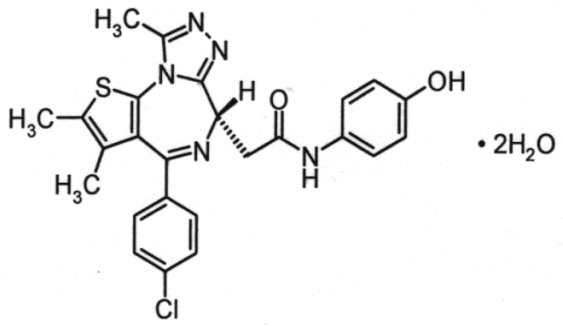
Chemical name: 2-[(6S)-4-(4-Chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo-[4,3-a][1,4]diazepin-6-yl]-N-(4-hydroxyphenyl)acetamide dihydrate

I.N.N.: Not yet issued

Molecular mass: 528.02

Molecular formula: $C_{25}H_{22}ClN_5O_2S \cdot 2H_2O$

Structural formula:



OTX015 is administered orally. It is provided size 3 gelatin capsules containing 10 mg,20 mg or 40 mg OTX015 (free base) as a solid molecular dispersion with HPMCAS-M, mixed with lactose monohydrate, microcrystalline cellulose, Ac-Di-Sol, colloidal silicon dioxide, and magnesium stearate 5712.

White opaque capsules are used for 10 mg and 40 mg strength and green opaque capsules are used for 20 mg strength.

Capsules are to be swallowed with little water, in a fasted state. They must not be open or chewed.

1.1.2 Summary of findings from nonclinical studies that potentially have clinical significance

1.1.2.1 Bromodomains (brd) of the Bromodomain and Extra Terminal (BET) proteins as Cancer Targets

The bromodomain (BRD) containing family of proteins [*Belkina 2012*] recognizes acetylated lysine residues within histone proteins and functions as a scaffold for the assembly of macromolecular complexes that alter chromatin accessibility to transcription factors and also allows the recruitment or activation of RNA polymerases. The tandem BRD-containing family of transcriptional regulators known as the BET (bromodomains and extraterminal) proteins, which comprise BRD2, BRD3, BRD4, and BRDt (also called BRD6) in humans, have emerged as major epigenetic regulators of proliferation, differentiation, and human cancer and also have been associated with predisposition to dyslipidemia or improper regulation of adipogenesis, elevated inflammatory profile, and increased susceptibility to autoimmune diseases *[Denis 2010]*. The four BET proteins exhibit similar gene arrangements, domain organizations, and some functional properties. With the exception of BRDt, which is expressed specifically in ovary and testis, BRDs 2, 3, and 4 are widely distributed.

Experimental evidence suggests a role for both BRD2 and BRD4 in oncogenesis. Both BRD2 *(Nakamura et al 2007)* and BRD4 *(Dey et al 2003)* bind acetylated histones and mobilize chromatin modification *(Wu & Chiang 2007)* to control cell cycle *(Denis et al 2000; Dey et al 2000)*. Additionally, both BRD2 *(Kanno et al 2004)* and BRD4 *(Dey et al 2009)* remain mitotically associated with chromatin.

BRD2 is a nuclear-localized serine-threonine kinase that has elevated activity in human leukemias *(Denis & Green 1996; Rachie et al 1993)*. BRD2 was shown to synergistically transactivate cell cycle regulatory genes including cyclin D1, cyclin A, cyclin E, and dihydrofolate reductase in combination with Ras or MEKK through E2Fs *(Denis et al 2000)*. Subsequently, it was shown that BRD2 associates with a transcription complex containing E2F1, E2F2, TBP, and chromatin remodeling *machines (Denis et al 2000, 2006)* and serves as a bridge between E2F1 and TBP *(Peng et al 2006)*. Taken together, these findings indicate that BRD2 can serve as a transcription regulator and a contributing element in oncogenesis.

BRD4 is a critical mediator of transcriptional elongation, functioning to recruit the positive transcription elongation factor complex (P-TEFb) *(Yang 2005; Yang et al 2005)*. Functional studies have suggested that BRD4 plays an important role in the regulation of growth-associated genes at the M/G1 boundary by retaining P-TEFb at the promoters of key regulatory genes throughout mitosis *(Dey et al 2009; Yang et al 2008)*. Additionally, BRD4 is a transcriptional coactivator of NF-κB via specific binding to acetylated RelA *(Huang et al 2011)*. Taken together, these findings indicate that BRD4 can serve as a transcription regulator and a contributing element in oncogenesis.

Recent studies showed that a small molecule inhibitor of the BET family elicited rapid and potent abrogation of MYC gene transcription in a range of leukemia and lymphoma cell lines, resulting in G1 arrest and extensive apoptosis *(Mertz et al 2011)*. While the BET inhibitor suppressed MYC transcription in the context of translocation, amplification, or with an unaltered, wild-type MYC

locus, cells exhibited a range of sensitivity to BET-inhibitor-dependent MYC suppression. Exogenous expression of MYC from an artificial promoter that is resistant to BET regulation significantly protected cells from cell cycle arrest and growth suppression by the BET inhibitor. MYC suppression was accompanied by deregulation of the MYC transcriptome, including potent reactivation of the p21 tumor suppressor *(Mertz et al 2011)*. Treatment with a small molecule BET inhibitor also resulted in significant antitumor activity in mouse models of Raji Burkitt's lymphoma and MV4-11 AML *(Mertz et al 2011)*. These findings were the first to demonstrate that pharmacologic inhibition of MYC is achievable by targeting BET bromodomains [*Delmore 2011*].

1.1.2.2 Interaction of OTX015 with BRD2/3/4

Binding of OTX015 to BRDs 2, 3, and 4 in Jurkat cells nuclear extract was demonstrated by a pull down assay using biotinylated OTX015 and streptavidin resin. CHO cells transfected with expression plasmids for Flag-tagged BRD 2, 3, or 4 or vector alone, europium-conjugated anti-Flag antibody, XL-665-conjugated streptavidin, and biotinylated OTX015 were incubated at room temperature for 0.5 to 2 hours and fluorescence was measured by time-resolved fluorescence energy transfer (TR-FRET). Results showed that OTX015 binds to similarly to all three BRDs, with EC_{50}s from 10 to 19 nM (Figure 1 and Table 1).

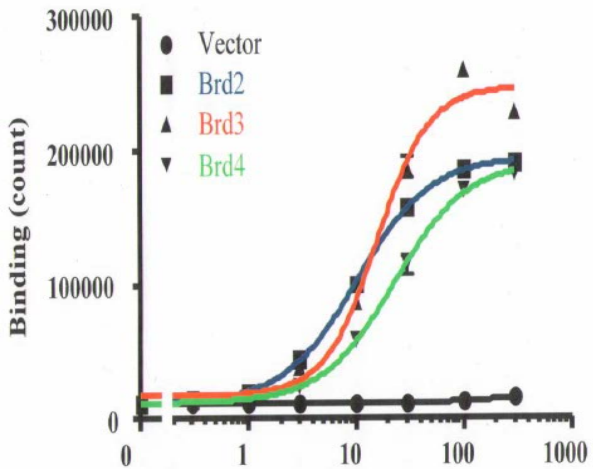


Figure 1. Binding of Biotinylated OTX015 to BRD2/3/4

Expression vector-transfected CHO cell lysate (4-fold dilution), FLAG-BRD2-transfected cell lysate (20-fold dilution), FLAG-BRD3-transfected cell lysate (22-fold dilution), and FLAG-BRD4-transfected cell lysate (4-fold dilution) were incubated with biotinylated OTX015, europium-conjugated anti-FLAG antibody, and XL-665 conjugated streptavidin for 30 minutes at room temperature. Binding was measured by TR-FRET.

Binding of biotinylated OTX015 to BRDs 2, 3, and 4 was inhibited by addition of OTX015 in a concentration-dependent manner, suggesting competitive inhibition.

The effect of OTX015 on binding of acetylated histone H4 (AcH4) to BRDs 2, 3, and 4 was measured using a similar system, by incubating biotin conjugated-AcH4, BRD-expressing CHO cell lysate, europium-conjugated anti-Flag antibody, and XL-665-conjugated streptavidin and then measuring fluorescence by TR-FRET. Percent binding was calculated by defining the value of the

sample without biotin conjugated AcH4 as 0% and the sample without OTX015 as 100% binding. Results showed that OTX015 inhibited BRD2, 3, 4 binding to AcH4 with similar effect, with IC_{50}s from 92 to 112 nM (Table 1 and Figure 2).

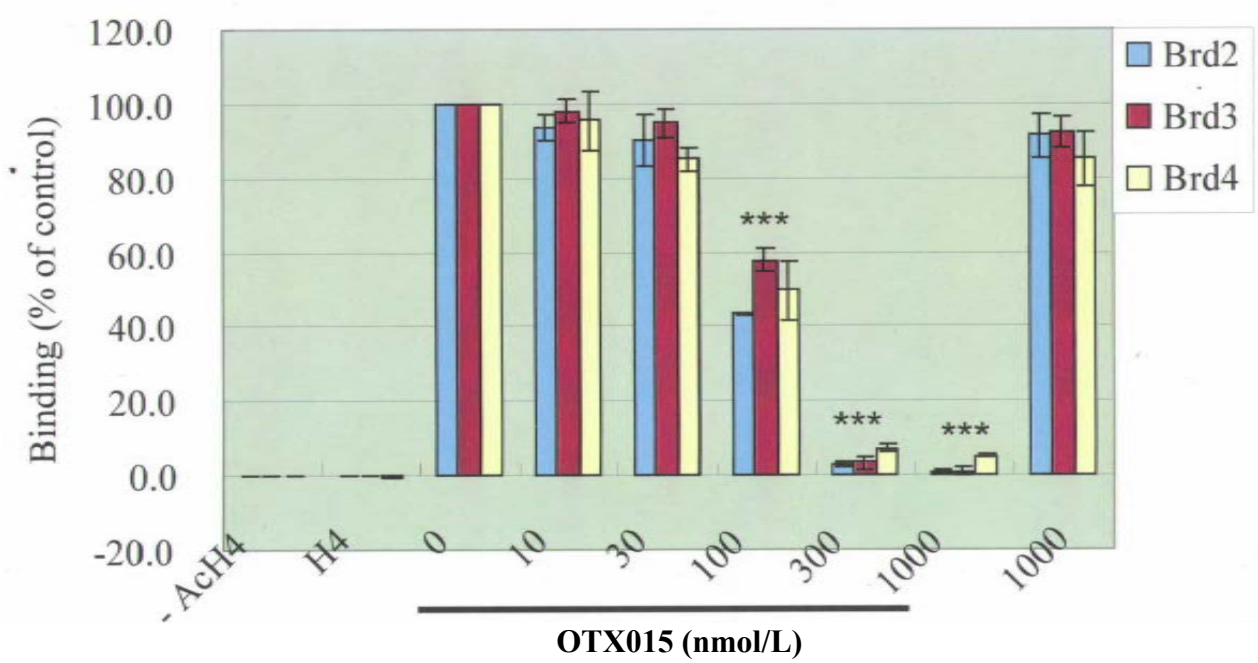


Figure 2. Inhibition of the BRD-AcH4 Binding by OTX015

Various concentrations of OTX015 were mixed with biotinylated AcH4 and then incubated with FLAG-BRD2- (8-fold dilution), FLAG-BRD3- (8-fold dilution), or FLAG-BRD4- (2.5-fold dilution)-transfected CHO cell lysate, europium conjugated anti-FLAG antibody, and XL-665-conjugated streptavidin for 2 hours at room temperature. Fluorescence was measured by TR-FRET Biotinylated H4 was used instead of AcH4 as a negative control. Percent of binding was calculated as 100 x [(count of sample minus count of sample without AcH4 sample) / (count without OTX015 sample minus count without AcH4 sample)] The columns represent mean ± SEM of three independent experiments. The mean value of the OTX015 treatment group and the control group was compared by Dunnett's multiple comparison test; NS: no significant difference, **: $p<0.01$.

Table 1: Interaction of OTX015 with BRDs 2/3/4

BRD	EC_{50} (nmol/L) for OTX015 binding (mean ± SEM)	IC_{50} (nmol/L) for OTX015 inhibition of BRD-AcH4 binding (mean, 95% CI)
2	9.95 ±0.90	91.8 (79.9 – 105.5)
3	13.37 ± 0.89	111.5 (100.9 – 123.3)
4	18.61 ± 2.56	95.5 (72.8 – 125.1)

1.1.2.3 Effects of OTX015 on Cell Cycle

It was reported that a BRD4 shRNA vector stably knocked down BRD4 protein expression by ~90% in NIH3T3 cells (Mochizuki *et al* 2008). BRD4 knockdown cells were growth impaired and grew more slowly than control cells. When synchronized by serum starvation and released, BRD4 knockdown cells were arrested at G1, via inhibition of cyclin D1 gene expression, whereas control cells progressed to S phase (Mochizuki *et al* 2008). In analogous experiments, cell cycle analysis showed that OTX015 treatment induced G1 arrest of NIH3T3 cells synchronized in the G0 phase by serum starvation. After serum stimulation for 10 hours, Western blot and RT-PCR analysis showed that OTX015 inhibited both protein and mRNA expression of cyclin D1.

1.1.2.4 Antitumor Effects of OTX015

Against a panel of human tumor cell lines, OTX015 showed antiproliferative effects against a variety of hematological malignancies, including leukemias (ALL, AML, CML), lymphomas (ALCL, DLBCL, MCL, SMZL), and multiple myeloma, with GI_{50}s ranging from 0.04 to 2.9 μM. OTX015 was also highly effective against the Ty82 midline carcinoma cell line with a BRD4-NUT fusion gene (GI_{50} of 0.04 μM). Most solid tumor cell lines did not respond to OTX015, though hepatocellular carcinoma, ovarian cancer, and some breast cancer cell lines were sensitive (GI_{50} s ranging from 0.25 to 0.94 μM).

More detailed examination of the effects on OTX015 on hematologic malignancies *in vitro* showed that OTX015 treatment induced G1 arrest and down-regulation of MYC mRNA and putative MYC target genes in most cell lines examined, including 4 of 4 AML lines, 3 of 3 ALL lines, 7 patient-derived primary AML cells, 9 of 11 diffuse large B-cell lymphoma lines, 5 of 8 anaplastic large T-cell lymphoma lines, 3 of 3 splenic marginal zone lymphoma lines, and 3 of 3 multiple myeloma lines. OTX015 treatment induced apoptosis in leukemia cell lines and patient blasts, but not in lymphoma and multiple myeloma cell lines. Induction of apoptosis in leukemia is not reversible after washout of OTX015 at 6 or 24 hours, while inhibition of proliferation in lymphoma cell lines is reversible after washout. There was no obvious correlation between sensitivity to OTX015 and BET expression in cell lines. In sensitive lines, MYC down-regulation was observed after as little as 30 minutes exposure, but reversed within 2 to 4 hours after wash-out in lymphoma cells,.

The *in vivo* efficacy of OTX015 was demonstrated in the Ty82 human BRD4-NUT t(15;19) midline carcinoma xenograft model in female BALC/c-nu/nu mice. Animals were inoculated in the right flank with exponentially growing Ty82 cells (1×10^7 cells/0.1 mL in serum-free RPMI-1640 medium with 10% Matrigel). When tumors reached a mean size of >100 mm^3 (usually at 7 days after implantation), mice were grouped (6/group) according to tumor size and body weight and treatment was initiated with 0 (placebo), 10 mg/kg qd, 30 mg/kg qd, 100 mg/kg qd, or 10 mg/kg bid OTX015 by gavage for 14 consecutive days. Body weights were measured at the time of grouping and prior to dosing each day and tumor size was measured by digital caliper on Days

1, 5, 9, 12, and 15. On Day 15 animals were euthanized by cervical dislocation and tumors, spleens, and livers were excised and weighed.

The mean relative tumor growth rates based on tumor volumes on Day 15 for mice treated with 0, 10, 30, 100 mg/kg and 10 mg/mg bid of OTX015 were 6.13 ± 0.51, 3.74 ± 0.30, 3.26 ± 0.58, 2.10 ± 0.28, and 3.00 ± 3.56, respectively (Figure 3). Compared with the placebo control, mice receiving 10, 30, 100 mg/kg and 10 mg/kg bid of OTX015 had tumor growth inhibition rates of 46.6%, 55.9%, 78.6%, and 61.1%, respectively. All treatment groups showed a significant reduction in tumor growth compared with vehicle control (Dunnett's test, $p<0.01$).

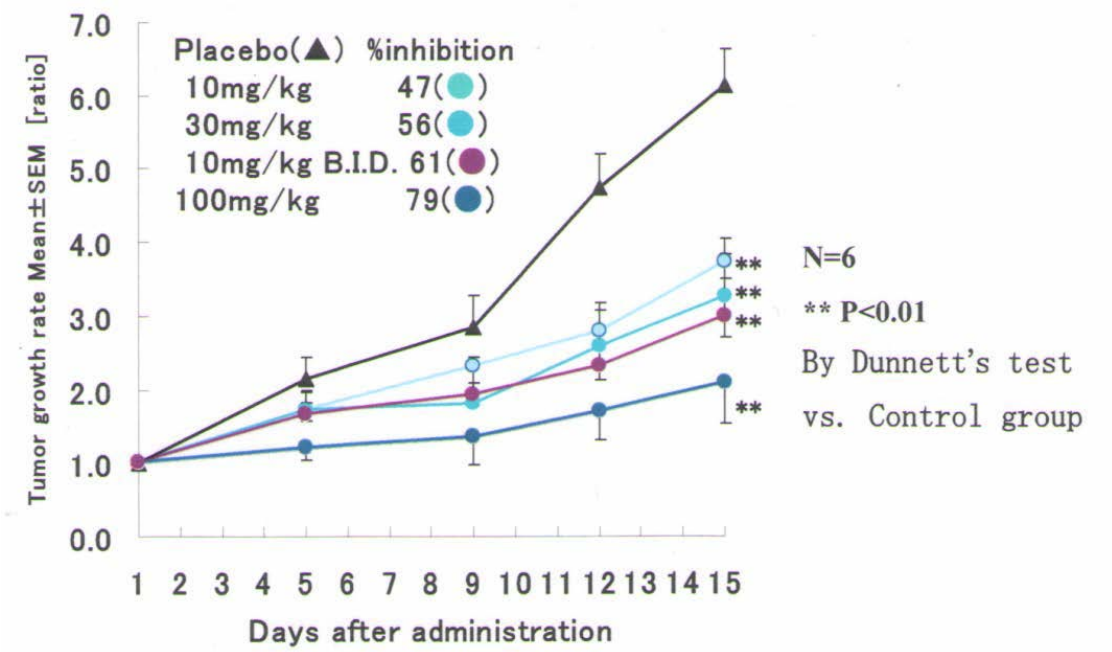


Figure 3. Effects of OTX015 on Growth of Ty82 Human BRD4-NUT/t(15;19) Midline Carcinoma Xenografts in BALBc/nu/nu Mice

The Ty82 model was repeated to assess the effects of OTX015 combined with docetaxel. Results showed that (1) docetaxel alone was not effective in this model; (2) OTX015 was effective, with BID dosing as effective as once daily dosing (i.e., 56% TGI at 50 mg/kg qd *vs*. 55% TGI at 25 mg/kg BID) and (3) combination treatment was more effective than either agent alone, with cures achieved using 50 mg/kg qd x 14 or 25 mg/kg BID x14 OTX015 combined with 10 mg/kg IV q7d x2 docetaxel.

1.1.2.5 Nonclinical Safety Evaluation of OTX015

The safety of OTX015 was evaluated in both safety pharmacology and toxicology studies, conducted in accordance with ICH Guidance S9: *Nonclinical Evaluation for Anticancer Pharmaceuticals*.

Safety pharmacology studies showed that OTX015 had no effects on general safety assessments at doses up to 10 mg/kg PO. OTX015 had no effect on hERG current at concentration up to 580 nM

and no effects on respiration rate, blood pressure, heart rate, and electrocardiogram in anesthetized dogs at doses up to 3 mg/kg IV.

The adverse effects of OTX015 were evaluated in 28-day repeated oral dose toxicity studies with 28-day recovery in both rats (12-18/sex/group dosed at 0, 3, 10, 30, and 60 mg/kg/day) and dogs (3-5/sex/group dosed at 0, 1, 3, 10, and 20 mg/kg/day) and in chronic 26-week studies in rats (14/sex/group dosed at 0, 3, 10, and 30 mg/kg/day) and 52-week studies in dogs (4/sex/group dosed at 0, 0.6, 2, and 6 mg/kg/day). Studies were conducted using a solid dispersion formulation of 10% or 25% OTX015:PVP, either suspended in water for administration to rats or combined with lactose, corn starch, crystalline cellulose, and calcium carmelose excipient and filled into gelatin capsules for administration to dogs.

The no-observed adverse effect levels (NOAELs) in rats were 10 mg/kg/day, corresponding with a mean Day 28 AUC0-24h of 1045 ng•h/mL, for 4-week dosing and 10 mg/kg/ day, corresponding with a mean Day 182 AUC0-24h of 1522 ng•h/mL, for 26-week dosing. The NOAELs in dogs

were 3 mg/kg/day, corresponding with a mean Day 28 AUC

0-24h of 922 ng•h/mL, for 4-week dosing; 3 mg/kg/day, corresponding with a mean Day 91 AUC0-24h of 938 ng•h/mL, for 13-week dosing; and 2 mg/kg/day, corresponding with a mean Day 365 AUC0-24h of 447 ng•h/mL, for 52-week dosing. Virtually identical AUCs were obtained in rats and dogs corresponding with the NOAELs for 28-day dosing (mean AUC0-24h of 1045 and 922 ng•h/mL for rats and dogs, respectively), while higher AUCS were obtained at the NOAELS for chronic dosing for rats compared to dogs (mean Day 182 AUC0-24h of 1522 ng•h/mL in rats and mean Day 365 AUC0-24h of 447 ng•h/mL in dogs).

From the 4-week repeated dose toxicity studies, the highest non-severely toxic dose (HNSTD) was 30 mg/kg/day in rats, corresponding with a mean Day 28 AUC0-24h of 6715 ng•h/mL, and 10 mg/kg/day in dogs, corresponding with a mean Day 28 AUC0-24h of 4377 ng•h/mL.

Considering results from the 28-day repeated dose and chronic toxicity studies, the main target organ toxicity was the digestive system, particularly liver. Other organs which should be monitored are lymphoid tissues, hematopoietic organs, lungs, and reproductive organs in males. Briefly:

• Digestive system: In both rats and dogs, clinical signs of loose stools and diarrhea were accompanied by histopathologic findings of mononuclear cell infiltration of the lamina propria mucosa and degeneration of the epithelium of the small and large intestine. In chronic toxicity studies, abnormal liver function tests were observed in both rats (decreased total protein and albumin) and dogs (increased SGOT and SGPT), accompanied by histological findings of pigment deposition in perilobular Kupffer cells in livers of both species and cholestasis and vacuolization of the centrilobular hepatocytes in livers of dogs. Prolonged APTT in both species was observed after 28-day dosing in rats and after both 28-day and chronic dosing in dogs.

• Hematopoietic system: Both rats and dogs showed decreased platelets and lymphocytes after 28-day dosing, accompanied by histopathologic findings of depletion of lymphocytes in the spleen and mesenteric and submandibular lymph nodes and myeloid hypoplasia in the bone marrow of femur and sternum. Rats showed decreased RBC after both 28-day and chronic dosing, accompanied by histopathologic findings of extramedullary hematopoiesis in spleen after chronic dosing.

• Lungs: In rats, histopatholoic exams showed intra-aveolar foamy macrophages in lungs and bronchus in both sexes after both 28-day and chronic dosing; these were resolved after one month recovery in the 28-day study.
• Reproductive organs in males: In male dogs, histopathologic exams showed tubular degeneration of testes after both 28-day and chronic dosing and bilateral decrease of sperm in the epididymides after chronic dosing.

OTX015 showed no genotoxic effects in the standard panel of *in vitro* and *in vivo* tests. From reproductive and developmental toxicity assessments in rats, the non-toxic dose for reproductive performance was considered to be 30 mg/kg/day for males and 10 mg/kg/day for females and the non-toxic dose for embryonic growth and development was 10 mg/kg/day. From reproductive and developmental toxicity assessments in rabbits, the non-toxic dose for reproductive function of dams and growth and development of embryos and fetuses was considered to be 3 mg/kg/day.

1.1.3 Phase 1 clinical Studies in healthy Volunteers

Three studies have been conducted in a total of 114 healthy volunteers:

- Study Y-803-E01 ("E01 Study") was a double-blind, randomized study to evaluate the safety, tolerability, and pharmacokinetics of single ascending oral doses of 2.5, 5, 10, 20, 40, 80, 120 and 180 mg OTX015 compared with placebo in healthy adults;
- Study Y-803-E02 ("E02 Study") was an open label, randomized, three-way crossover study to assess the bioavailabilty of a single oral dose of 20 mg OTX015 in healthy male subjects in the fasted state and before and after food, with at least a 10 day wash-out between doses; and
- Study Y-803-E04 ("E04 Study") was a double-blind, placebo-controlled repeat dose study to assess the safety, tolerability, and pharmacokinetics of OTX015 following a single oral dose on Day 1 and once daily oral doses of 10, 20, and 40 mg OTX015 for 10 days (Days 4-13) in healthy male subjects.

All three studies were performed using a capsule containing microcrystalline cellulose spheres coated with an ethanolic solution of OTX015, triethyl citrate, aminoalkyl methacrylate copolymer RS, and methacrylic acid copolymer, which was spray dried and mixed with excipients including talc, magnesium alunimometasilicate, and light anhydrous silicic acid.

Each study assessed safety, tolerability, and plasma and urinary pharmacokinetics of OTX015 and its two main metabolites, the glucuronide conjugate and an oxidation product termed M1. Additionally, the single dose studies assessed fecal excretion of OTX015 and the M1 metabolite.

The main findings for these studies are summarized in Table 2 and described briefly below.

<u>Pharmacokinetics</u>
Following administration of single oral doses of OTX015 to fasted subjects, plasma concentrations of OTX015 increased slowly, reaching C_{max} at a median of 4 to 6 hours. Thereafter, plasma levels declined slowly for all dose levels, maintaining levels about 50%-60% of C_{max} at 12 hours post-dose and 25%-30% of C_{max} at 24 hours post-dose. Semi-logarithmic plasma concentration-time curves gave an apparent monophasic decline, with mean t1/2 ranging from 12.0 to 16.3 hours for all dose levels. The mean $t_{1/2}$ and median tmax were statistically

constant. Exposure (C_{max}, $AUC0_{-24h}$, and $AUC_{0-\infty}$) increased in a dose proportional manner over the range from 2.5 to 80 mg. The MRT, Cl, Cl/F, Vz/F ranged from 17.8 to 21.4 h, from 0.11 to 0.20 L/h, from 28.2 to 54.0 L/h, and from 477.6 to 1159.6 L, respectively. The mean cumulative fecal excretion of OTX015 ranged from 54% to 88% of the administered dose for all dose levels, while the mean cumulative urinary excretion of OTX015 and its metabolites was less than 4.1% of the dose for all dose levels.

Overall, the pharmacokinetics of OTX015 appeared to be independent of dose and repeated dosing. Analysis of pre-dose plasma levels on Days 5 through 12 (for repeated dosing from Days 4 -13) showed steady-state to be achieved by Day 6, after 24 hours of dosing (i.e. the second consecutive day of repeated treatment), at each dose level. Geometric mean pre-dose (trough) plasma concentrations at steady state ranged from 3.9 to 4.9 ng/mL for the 10 mg dose, from 5.9 to 8.5 ng/mL for the 20 mg dose, and from. 13.6 to 22.4 ng/mL for the 40 mg dose; for each dose level the pre-dose plasma concentrations were constant. Statistical analysis of the first and last dose across all dose levels showed $t_{1/2}$, MRT, Cl/F, and Vz/F to be independent of dose, with no differences between the first and last dose.

Interestingly, the mean Cmax of 52-66 ng/mL achieved with 40mg repeated dosing, was equivalent to approximately 100nM, an active concentration against hematological malignancies in *in vitro* experiments.

Intake of a high-fat breakfast after and before administration decreased plasma OTZ015 concentration: Cmax by 45% and 47%, AUC0-24h by 35% and 38%, and AUC0-∞ by 20% and 27%, respectively, compared to the fasted state using geometric means. Cmax and AUCs in fed states were not bioequivalent to the fasted states (90% CI not within the range 80% to 125%). However, dosing after food was bioequivalent to dosing before food for Cmax and AUC0-24h and the deviation from bioequivalence criteria was small (90%CI 78.9% - 107.3%). The tmax of OTX015 was prolonged by food intake after and before administration, from 6h (fasted state) to 9h and 10h, respectively, while the MRT was constant for all dosing conditions. Urinary excretion also was reduced by food intake before and after administration: OTX015 by 10% and 9%, M1 metabolite by 22% and 24%, and OTX015 conjugate by 18% and 21%. Fecal excretion of OTX015 and its metabolites was only slightly lowered by food intake.

Mean plasma concentrations of the OTX015 glucuronide conjugate and M1 oxidized metabolite were parallel to OTX015 for all dosing conditions and dose levels. In Cmax and AUC, the OTX015 glucuronide conjugate ranged from 50%-73% and from 40%-64% of the OTX015 level, respectively, while the M1 metabolite ranged from 3% to 5% and from 3% to 6% of the OTX015 level, respectively.

Safety and Tolerability

A total of 92 healthy volunteers (86 males, 6 females) received at least one dose of OTX015 in the three Phase 1 studies, while 22 males received at least one dose of placebo. Overall, OTX015 was well tolerated. No severe or serious adverse events (AEs) were reported. The most frequent AEs, occurring in ≥3% of subjects receiving OTX015, were headache (17% of subjects), abdominal pain/discomfort (14%), diarrhea/loose stools (8%), rhinitis (5%), constipation (4%), myalgia (4%), back pain (3%), and paresthesia (3%). With the exception of one mild headache, all of these events were both mild and transient. These AEs occurred with similar frequency among subjects receiving placebo, i.e., headache (17% of subjects), diarrhea/loose stools (17%), and abdominal pain/discomfort (13%).

Table 2: Summary of previous clinical experience in humans (healthy volunteers)

Study design	Single-dose, dose escalation, double blind study vs placebo (study E01)	Repeated dose (10 consecutive days) , dose escalation, double-blind study vs placebo (study E04)	Open label, randomized, 3-way crossover, food-effect study (study E02)
N.subjects (M/F)	72 (64/8)	24 (24/0)	18 (18/0)
Dose levels tested (mg)	2.5, 5, 10, 20, 40, 80,120, 180 (placebo 2 subjects /DL); fasted	10, 20, 40 (placebo 2 subjects /DL); fasted	20
Safety data	Mild –moderate headaches and GI symptoms . A similar percentage of subjects had AES on placebo (33% [6/18]) and at 120 mg (33% [2/6]). No dose-related laboratory, ECG, or vital signs changes	Mild (98%) –moderate (2%) headaches and GI symptoms. A similar percentage of subjects had AEs on placebo (67% [4/6]) and 40 mg (100% [6/6]). No dose-related laboratory, ECG, or vital signs changes	Mild –moderate headaches and GI symptoms. The percentage of subjects with AEs was higher in the fasted state (44% [8/18]) than before food (17% [3/18]) and after food (39% [7/18]).
MTD	Not reached	Not reached	Not applicable
PK results	Exposure (C_{max}, AUC) increased in a dose proportional manner over the range from 2.5 to 80 mg. Mean C_{max} (ng/mL) ranged from 5.0 ± 1.4 (2,5 mg dose) to 210 ± 67 ng/mL (80 mg dose). Mean $AUC_{0-\infty}$ (ng•h/mL) ranged from 95 ± 30 (2.5 mg dose) to 3585 ± 1100 (180 mg dose). Following administration, plasma levels of OTX015 increased slowly, reaching C_{max} at a median of 4 to 6 hours. Thereafter, plasma levels declines slowly, maintaining levels abot 50%-60% of C_{max} at 12 hours post-dose and 25%-30% of C_{max} at 24 hours post-dose. The median t_{max} (4-6 hours) and mean $t_{1/2}$ (12.0 – 16.1 hours) were statistically constant. Mean MRT ranged from 18.3 to 20.5 h and mean Cl/F ranged from 28.2 to 54.0 L/h.	OTX015 OK appeared to be independent of dose and repeated dosing. Analysis of pre-dose plasma levels on Days 5 through 12 (for repeated dosing from Days 4 – 13) showed steady state to be achieved by approximately Day 6, after 24 hours of dosing, at each dose level. Geometric mean pre-dose (trough) plasma concentrations at steadt state ranged from 3.9 to 4.9 ng/mL for the 10 mg dose, from 5.9 to 8.5 ng/mL for the 20 mg dose, and from 13.6 to 22.4 ng/mL for the 40 mg. dose; for each dose level, the pre-dose plasma concentrations were statistically constant. Statistical analysis of the first and last dose across all dose levels showed $t_{1/2}$, MRT, Cl/F, and Vz/F to be independent of dose, with no differences between the first and last dose.	High fat breakfast taken before or after OTX015 intake decreased C_{max} by 45 and 47% and $AUC_{0-\infty}$ by 20 and 27%, respectively. Tmax was delayed from 6h (fasted state) to 9 and 10 h with breakfast before and after OTX015 intake, respectively

MTD: maximum tolerated dose PK: pharmacokinetic

1.1.4 Summary of the known and potential risks and benefits, if any, to human subjects

In three Phase 1 studies in healthy volunteers, no major toxicities were reported following administration of single oral doses up to 180 mg OTX015 and oral doses of 10 to 40 mg/day administered over 10 consecutive days. No severe AE, no SAE, and no AE leading to study treatment discontinuation were reported. The maximum tolerated dose (MTD) was not reached. The main toxicities were mild (about 90% of AEs) to moderate headaches and miscellaneous gastrointestinal (GI) events, mainly abdominal pain and loose stools. Based on these results, the expected toxicities at low doses are headache, abdominal pain, diarrhea, nausea, vomiting, constipation, dizziness, and myalgias.

Considering the results from 28-day repeated dose and chronic toxicity studies in rats and dogs, the main target organ toxicity is the digestive system, particularly liver. Other organs which should be monitored are lymphoid tissues, hematopoietic organs, lungs, and reproductive organs in males. Briefly:

• Digestive system: In both rats and dogs, clinical signs of loose stools and diarrhea were accompanied by histopathologic findings of mononuclear cell infiltration of the lamina propria mucosa and degeneration of the epithelium of the small and large intestine. In chronic toxicity studies, abnormal liver function tests were observed in both rats (decreased total protein and albumin) and dogs (increased SGOT and SGPT), accompanied by histological findings of pigment deposition in perilobular Kupffer cells in livers of both species and cholestasis and vacuolization of the centrilobular hepatocytes in livers of dogs. Prolonged APTT in both species was observed after 28-day dosing in rats and after both 28-day and chronic dosing in dogs.

• Hematopoietic system: Both rats and dogs showed decreased platelets and lymphocytes after 28-day dosing, accompanied by histopathologic findings of depletion of lymphocytes in the spleen and mesenteric and submandibular lymph nodes and myeloid hypoplasia in the bone marrow of femur and sternum. Rats showed decreased RBC after both 28-day and chronic dosing, accompanied by histopathologic findings of extramedullary hematopoiesis in spleen after chronic dosing.

• Lungs: In rats, histopatholoic exams showed intra-alveolar foamy macrophages in lungs and bronchus in both sexes after both 28-day and chronic dosing; these were resolved after one month recovery in the 28-day study.

• Reproductive organs in males: In male dogs, histopathologic exams showed tubular degeneration of testes after both 28-day and chronic dosing and bilateral decrease of sperm in the epididymides after chronic dosing. There is no evidence of reversibility of this effect. Male patients should therefore be informed of the risk of definite infertility.

No phototoxicity studies have been performed yet. However OTX015 absorbs light in the range of 290 and 400 nm with a molar extinction coefficient (MEC) of >1000 L mol-1 cm-1. Recommendation to avoid sun exposure should be made until results of phototoxicity studies are available.

The present study plans to continue dose escalation, possibly up to MTD, in order to achieve higher systemic exposures than those obtained in the healthy volunteer studies and thereby optimize antitumor activity. Accordingly, the target organ toxicities observed in nonclinical studies may be expected, with target organs including digestive tract, liver, lungs, lymphoid tissues, hematopoietic organs, and reproductive organs in males.

In addition, other unexpected toxicities may occur. Patients with advanced, multi-treated, life-threatening diseases will be treated, who might tolerate OTX015 differently than healthy volunteers.

1.2 JUSTIFICATION OF THE STUDY AND OF THE STUDY DESIGN

1.2.1 Justification of selecting patients with hematological malignancies

Hematological malignancies are heterogeneous diseases. There is increasing evidence in preclinical models that brd inhibition can lead to anti tumor activity against various illnesses from acute leukemia [*Redner 1999; Zuber 2011; Dawson 2011; Blobel 2011*] to lymphoma [*OTX015 Investigator's Brochure*]. and myeloma [*Delmore 2011*] [*OTX015 Investigator's Brochure*]. It is known that in many hematological malignancies, the oncogenesis is driven by the oncogene c-Myc [*Boxer 2001 ; Vita & Henriksson 2006; Mertz 2011; Delmore 2011 ; Cuccuini 2012*]. It has been shown that brd inhibition was frequently associated with c-Myc, and downstream targets downregulation [*Mertz 2011*].

Though a significant proportion of patients with acute leukemia and lymphoma can be cured or can benefit of prolonged overall survival with current therapies, the majority of patients with hematological malignancies will die from their disease. The level of unmet medical need is therefore very high and innovative new drugs are eagerly expected.

1.2.2 Justification of the new drug product formulation

The drug product formulation used in the healthy volunteer studies was designed to deliver the active agent to the lower intestine for treatment of inflammatory bowel disease. For treatment of cancer, it is desirable for have a formulation that achieves the highest possible systemic levels of active agent. A bioavailability study in dogs comparing the clinical formulation used for the healthy volunteer studies (Eudragit; microcrystalline cellulose spheres coated with an ethanolic solution of OTX015, triethyl citrate, aminoalky methacrylate copolymer RS, and methacrylic acid copolymer, spray dried and mixed with talc, magnesium aluminometasilicate, and light anhydrous silicic acid) and the formulation used for nonclinical safety studies (25% OTX015:PVP in ethanol, spray dried and mixed with lactose, corn starch, crystalline cellulose, and carmellose calcium) found 16%-17% bioavailability (mean C_{max} of 211 ng/mL and mean AUC_{0-24h} of 833 ng•h/mL at 3 mg/kg) for the clinical formulation compared with 30%-40% bioavailability (mean C_{max} of 414 ng/mL and mean AUC_{0-24h} of 1787 ng•h/mL at 3 mg/kg) for the nonclinical formulation. The 2-fold higher systemic exposure achieved with the solid dispersion OTX015:PVP formulation used

in nonclinical safety studies compared with the formulation used in the healthy volunteer studies was consistent with the design of the clinical formulation.

Although the solid dispersion OTX015:PVP formulation achieved adequate systemic exposure, polyvinyl pyrrolidone (PVP) is hygroscopic, so screening was performed to identify an alternative excipient for a solid dispersion formulation for clinical studies in cancer patients. A bioavailability study in dogs of the solid dispersion OTX015:PVP formulation used in nonclinical safety studies and the solid dispersion OTX015:HPMCAS-MG formulation to be used in the clinical studies in cancer patients found comparable (not statistically different) bioavailability for both the PVP solid dispersion (mean C_{max} of 487 ng/mL and mean AUC_{0-24h} of 1555 ng•h/mL at 3 mg/kg) and the HPCMAS solid dispersion (mean C_{max} of 371 ng/mL and mean AUC_{0-24h} of 1970 ng•h/mL at 3 mg/kg). Accelerated stability studies have confirmed that the solid dispersion PVP formulation absorbs some moisture, while the solid dispersion HPMCAS formulation does not.

1.2.3 Justification of the starting dose

Traditionally, for first-in-human oncology trials in patients with advanced and/or metastatic disease the starting dose is calculated based on the maximally tolerated dose (MTD) or highest non-severely toxic dose (HNSTD) in the most sensitive species in 28-day repeated dose toxicology studies *[CHMP/SWP/997/96; Senderowitz 2010]*. In the case where rodents are the most sensitive species, the starting dose in humans is one-tenth the rodent MTD or LD_{10}. In the case where dogs are the most sensitive species, the starting dose in humans is one-sixth the dog HNSTD or MTD. In 28-day repeated dose toxicity studies of OTX015, the MTD in rats was 30 mg/kg/day, corresponding to a mean Day 28 AUC_{0-24h} of 6715 ng•h/mL, and the HNSTD in dogs was 10 mg/kg/day, corresponding to a mean Day 28 AUC_{0-24h} of 4377 ng•h/mL. Based on the MTD in rats and using a conversion factor of 6 from mg/kg to mg/m^2 in rats and assuming a mean BSA of 1.5 m^2 for humans, the starting dose is calculated as 27 mg [i.e., (30 x 6 x 1.5)/10]. Based on the HNSTD in dogs and using a conversion factor of 20 from mg/kg to mg/m^2 in dogs and assuming a mean BSA of 1.5 m^2 for humans, the starting dose is calculated as 50 mg [i.e., (10 x 20 x 1.5)/6]. The most conservative estimate, based on the MTD in rats, gives a starting dose of 27 mg in humans. As noted above, the bioavailabilites in dogs found for the solid dispersion OTX015:PVP formulation used in nonclinical safety studies and the solid dispersion OTX015:HPMCAS formulation to be used in clinical studies in cancer patients were not statistically different, so a starting dose of 27 mg can be justified.

However, a starting dose of 10 mg will be used, based on the following considerations: (1) in the healthy volunteer studies, a dose of 40 mg/day over 10 consecutive days was well tolerated, with no severe AEs or dose-limiting toxicities; (2) patients with advanced hematologic malignancies may tolerate treatment less well than healthy volunteers, justifying a starting dose one level below the highest repeated dose administered to healthy volunteers, or 20 mg/day, and (3) the systemic bioavailability in dogs of the formulation to be used in studies in cancer patients is 2-fold higher than the formulation used in healthy volunteers, so a dose of 10 mg/day using the new formulation is expected to give a systemic exposure comparable to the dose of 20 mg/day using the formulation in the healthy volunteer study.

1.2.4 Justification of the schedule of administration and of various schedules according to the treated condition

In vitro experiments of OTX015 against lymphoma and leukemia cells have shown that c-Myc downregulation and anti-proliferative effect were reversible after washout [*OTX015 Investigator's Brochure*]. Thus, a continuous exposure is deemed appropriate for an optimal antitumor effect. An intermittent schedule (14 days ON/ 7 days OFF every 21 days) was initially deemed more appropriate for the assessment of toxic effects in acute leukemia patients, known to experience many disease-related AEs. After the assessment of 3 dose levels with both an intermittent and a continuous schedule, showing the tolerance and feasibility of a continuous schedule and accumulating evidence that a continuous exposure to adequate concentrations of OTX015 is required for an optimal antitumor activity, the same continuous schedule will be finally delivered to all patients.

1.2.5 Justification of two parallel dose escalation subsets

Patients with relapsed/refractory acute leukemia usually experience severe/life-threatening AEs associated to disease-related severe bone marrow failure (especially fever, sepsis and hemorrhages) sometimes associated with metabolic disorders (hyperuricemia, hyperkalemia, hypocalcemia, renal failure, metabolic acidosis…). Thus, it is difficult to assess the relationship of treatment emergent AEs to a new medication having yet an undefined safety profile. Especially, hematological toxicities in acute leukemia cannot be assessed according to the same guidelines as other hematological malignancies, such as lymphoma or myeloma, without or with only mild/moderate bone marrow failure. Because peripheral blood cell counts (BCC) are usually extremely low at study entry in patients with acute leukemia, bone marrow toxicity cannot be assessed based upon decrease of BCC on study treatment. Hence it is not possible to pool and assess together acute leukemia and other malignancies in very small patient cohorts of 3-6 patients to assess toxicities and establish a reliable recommended dose.

Therefore, dose escalations and the safety and pharmacokinetics of OTX015 will be evaluated separately in patients with acute leukemia on one hand, and in patients with other hematological malignancies on the other hand.

1.3 CONCLUSION

OTX015 is a new innovative compound acting through Brd inhibition and epigenetic modulation of gene expression with promising anti-tumor activities in various hematological malignancies. It has been already tested in human healthy volunteers and was well tolerated at doses which achieved plasma concentration in the range of active concentration against *in vitro* tumor models. The antitumor effect is often associated with c-Myc down-regulation.

This clinical study is aimed at assessing the recommended dose (RD), the safety profile, PK and PD of OTX015 in patients with refractory/relapsed hematological malignancies, and to detect clues of clinical anti-tumor activity.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

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 hematological malignancies.

2.2 SECONDARY OBJECTIVES

The secondary objectives of the study are:

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

2.3 EXPLORATORY

- To detect predictive factors (among patient or tumor characteristics) of clinical activity

3 STUDY DESIGN, DURATION AND DATES

3.1 STUDY DESIGN

This is a multicenter, multinational dose finding, open label, phase Ib study.

3.1.1 Dose escalation part

- Two dose escalation subsets will be assessed independently in parallel: patients with acute leukemia and patients with other hematological malignancies.
- Patients will be enrolled by successive cohorts of 3 patients in each dose escalation subset.
- 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 in section 5.2.4.1. In the absence of DLT observed at the completed 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 will have completed at least 2 weeks of treatment (i.e. 14 consecutive daily administrations). The first patient enrolled in a higher DL cohort will not start the study treatment before the last treated patient in the DL immediately below will have completed at least one cycle of study treatment (i.e. 21 days following study treatment initiation, regardless of the treatment schedule)..

- If one out of 3 patients of a cohort experiences a DLT during the first cycle (i.e. 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 section 5.2.4.1).

- If more than one patient out of 6 (or more than one out of 3) patients experiences a DLT, the DL will be considered exceeding the maximum tolerated dose (MTD) for this subset.

- Patients not evaluable for DLT are those having received less than 85% of the intended cumulative dose during the first 21 days (i.e. those receiving less than 18 days of treatment for the continuous, 21-day schedule or less than 12 days of treatment for the intermittent, 14 days ON/ 7 days OFF schedule) and who have not experienced a DLT, will be replaced.

- The dose escalation will be stopped independently in each subset upon decision of the Safety Monitoring Committee (SMC). This decision could 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 (one DL below the dose exceeding the MTD) in each subset. At least 6 evaluable patients will be enrolled at the supposed RD. 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 patients treated.

3.1.2 Expansion part

- Once the RD will be established with at least 3 patients having received at least 2 cycles of study treatment in 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 lymphoma and at least 12 patients with multiple myeloma will be treated at the RD established for patients with other hematological malignancies. Additional expansion cohorts may be decided by the SMC, based upon the data collected during the dose escalation phase.

3.2 DEFINITION OF DOSE LIMITING TOXICITIES (DLTS)

DLTs are defined as any of the following treatment-related adverse events occurring in the first cycle (during the first 21 days following study treatment initiation (except hematological toxicity in AL patients confirmed at day 43, see below), regardless of the administration schedule), leading to dose modifications, study treatment interruption or discontinuation, unless a relationship to study medication can be definitely ruled out.

DLTs will be reported immediately to the sponsor using Serious Adverse Events Report Forms (SAERF) with reason for seriousness: "other important medical event" if there is no other reason for seriousness.

3.2.1 Non-hematological DLTs

- Any grade 3 or 4 non-hematological 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 at baseline, only grade 4 lasting > 7 days will be considered DLT, unless the SMC considers the event clinically significant. See below for liver function tests*.
- Any prolonged grade 2 toxicity (lasting more than 2 weeks) leading to treatment interruption and/or dose reduction

* Any of the following liver test abnormalities** (see Appendix 16.12)

- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN for > 2 weeks
- ALT or AST > 3 x ULN AND (total bilirubin > 2 x ULN OR INR > 1.5)
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%), unless the investigator assesses the rash or fatigue to be related to OTX015 and not related to liver impairment with sponsor's agreement.

**Note: All patients with these liver test abnormalities should be monitored weekly until all abnormalities return to normal or to the baseline state. For patients with isolated total bilirubin increases >2 x ULN or 2 x baseline (if elevated at baseline), except if associated with direct bilirubin ≤ ULN, monitoring should be every 2 weeks until bilirubin returns to normal or to the baseline state. Drug induced liver injury (DILI) may develop or progress even after the causative

drug has been stopped. Results should be recorded on the CRF and in the database. See guidelines on the handling of these events (potential Hy's law cases).

Investigators must be warned about qualifying fatigue/asthenia as a DLT. Grade 3 fatigue/asthenia deemed to be related to the study medication is a DLT as per protocol. However, multiple causal events, often intricate, may result in severe fatigue/asthenia in cancer patients participating to a phase I clinical trial, including disease progression, concomitant medications, concomitant medical conditions, anxiety, depression, transportation, etc.

3.2.2 Hematological DLTs

3.2.2.1 In patients with 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.

3.2.2.2 In patients with other hematological 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.

3.3 INDEPENDENT SAFETY MONITORING COMMITTEE (SMC)

The SMC will be composed of the principal investigators (PI) of each participating center, the pharmacokinetics (PK) specialist, the medical and safety representatives of the Sponsor and one independent expert in oncology/hematology phase I development (see Appendix VIII, section 16.8). All decisions taken by the SMC and their rationale will be recorded in meeting minutes that will be integrated as appendix in the final Clinical Study Report.

The SMC will be responsible for the following decisions:

- Proceeding to the next higher DL or stop dose escalation
- Definitely ruling out a relationship of an adverse event (AE) to study medication
- Adding patients at a given DL, if appropriate
- Modifying the treatment schedule of administration (e.g. BID) or shifting from an intermittent schedule to a continuous schedule
- Determining the RD

- Starting enrollment into expansion cohorts and determining the number of cohorts
- Closing patient enrollment
- Taking any decision aimed at improving participating patients' safety.

In addition, according to the nature, suspected relationship to study drug, or other clinical considerations, the SMC will make *ad-hoc* decisions, such as replacing inevaluable 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 and, if possible, PD results will be forwarded to the SMC and will be taken into account for the determination of the RD, especially if no DLT occurs.

3.4 STUDY DURATION AND DATES

The duration of this study will depend upon the number of DLTs encountered and the number of dose levels explored.

It is anticipated to be 40 months, with subject enrolment starting in January 2013 and ending January 2016 and a minimum follow-up over 1 month after the last patient entered (end of study May 2016).

The study will be closed after the last visit of the last patient still on study.

4 SELECTION OF SUBJECTS

4.1 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 acute leukemias/other hematological malignancies).

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

The total number of evaluable patients is estimated to be approximately 125.

4.2 INCLUSION CRITERIA

Subjects meeting all of the following criteria will be considered for enrollment into the study:

1. Signed informed consent must be obtained for all subjects at enrollment into the study (see section 12.3), i.e. prior to beginning protocol specific procedures. Patients registered for this trial must be treated and followed at the participating center.
2. Histologically or cytologically proven hematological malignancy or confirmed multiple myeloma according to standard diagnosis criteria [*Durie, 2006*]. For the dose escalation part, any refractory/relapsing hematological malignancy (having failed all standard therapies) will be accepted. For the expansion cohorts, only patients with selected hematological malignancies will be enrolled: At least 4 diseases are foreseen, but additional medical conditions may be decided by the SMC: acute myelocytic leukemia (AML), acute lymphocytic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL), multiple myeloma (MM). **Acute leukemia** (AL) is defined according to the WHO 2008 classification [*Vardiman, 2009*]. Acute myeloblastic leukemia (AML) and B-cell or T-cell acute lymphoblastic leukemia (ALL), *de novo,* as well as secondary AL (i.e. transformation of a pre-existing myelodysplastic syndrome, chronic myelogenous leukemia or other myeloproliferative neoplasms) may be enrolled. For lymphoma, an archived formaldehyde-fixed paraffin-embedded block must be available.
3. Patient with resistant/refractory disease, having failed all standard therapies or for whom standard treatments are contra-indicated.

DEFINITION OF RESISTANT/REFRACTORY DISEASE

- **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.

- **Lymphomas:** Patients having failed 2 standard lines of therapy, or for whom such treatment is contra-indicated. B-cell lymphoma patients must have received at least one anti-CD20 monoclonal antibody-based regimen.
- **Multiple myeloma**: Patients adequately exposed to at least one alkylating agent, one corticosteroid, one immunomodulatory drug (IMiD) and bortezomib, or for whom one or more of such treatments are contra-indicated.

4. Patients with evaluable disease:
   - AL patients must have $\geq$ 5% bone marrow blasts at study entry, without alternative causality (e.g. marrow regeneration), or reappearance of blasts in peripheral blood, or evaluable extramedullary disease *[Döhner, 2010]*. In case of low marrow blast count (5-10%), relapse should be confirmed by a second myelogram.
   - Lymphoma patients must have at least one non-irradiated tumor mass $\geq$ 15 mm (long axis of lymph node) or $\geq$ 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 $\geq$ 1g/dL (IgG), or $\geq$ 0.5g/dL (IgA), or Bence-Jones (BJ) proteinuria $\geq$ 200mg/24h, or measurable plasmacytoma (not previously irradiated).
5. Patients $\geq$ 18 years old.
6. Life expectancy of at least 3 months
7. ECOG performance status (PS) of 0 to 2
8. Off previous anti-tumor 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-hematological toxic effects of prior treatment to grade $\leq$ 1, according to NCI-CTC classification, except alopecia.
10. Bone marrow function
    - For patients with AL: no limitation
    - For patients with other hematological malignancies: Absolute neutrophil count (ANC) $\geq$ 1.0 x 10^9/L, platelets $\geq$ 150 x 10^9/L, hemoglobin $\geq$8 g/dL (4 weeks without transfusion)
11. Calculated creatinine clearance $\geq$ 30 mL/min (Cockroft & Gault formula, or MDRD formula for patients aged $\geq$ 65 years).

12. Adequate LFTs: Total bilirubin ≤ institutional upper normal limit (UNL) (or ≤ 2 x UNL in cases of liver involvement); ALAT/ASAT ≤ 3 x UNL (or ≤ 5 x UNL in case of liver involvement).
13. Serum albumin ≥ 28 g/L
14. International normalized ratio (INR) or prothrombin time (PT) and activated partial thromboplastin time (aPTT) ≤1.5 X ULN.
15. Complete baseline disease assessment workup (including bone marrow examination and tumor imaging for lymphomas; bone marrow aspiration for AL, measurement of serum M-component and/or BJ proteinuria, imaging of bone lesions and bone marrow aspiration or biopsy for MM) prior to first study treatment administration.

4.3 EXCLUSION CRITERIA

Subjects presenting with any of the following will not be included in the study:

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. Uncontrolled disease-related metabolic disorder (e.g. hypercalcemia)
9. 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..)
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 30 days prior to first study treatment administration, or 5 half-lives of previously administered drugs, whichever is longer.
13. Concurrent treatment with any other anticancer therapy, except hydroxyurea to reduced hyperleukocytosis.
14. Concomitant treatment with corticosteroids except chronic treatment with ≤ 30 mg of methylprednisolone daily or equivalent dose of other corticosteroids.
15. Patients taking concomitant strong CYP3A4 interacting drugs (see appendix XI)
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.

Any waiver of these inclusion and exclusion criteria should be exceptional and justified and must be approved by the investigator and the sponsor on a case-by-case basis prior to enrolling the subject. This must be documented by both the sponsor and the investigator.

No subject will be allowed to be enrolled in this study more than once.

No subjects who have previously been treated with OTX015/MK-8628 will be enrolled in this study.

4.4 SUBJECTS OF REPRODUCTIVE POTENTIAL

Female patients must not be pregnant or breast-feeding at inclusion in the study (mentioned as exclusion criteria in Section 4.3). Absence of pregnancy must be demonstrated by serum or urine testing unless there is a proven menopause (age ≥ 50 years and last menarche ≥ 3 years, or documented menopausal sex hormone profile, or surgical castration) prior to exposure to the investigational product or any study procedure with potential risk to the fetus.

The patient must not become pregnant during the study.

Female patients of childbearing potential (i.e. without proven menopause, see above), as well as male patients with a sexual partner of childbearing potential, must use a medically effective contraception during study and within 6 months after the last study medication intake.

5 STUDY TREATMENT

5.1 DETAILS OF STUDY TREATMENT

Drug code :	**OTX015/MK-8628 (investigational agent)**
INN:	Not yet issued
Formulation:	OTX015/MK-8628 is provided as size 3 (10 mg and 20 mg strengths) or size 0 (40 mg strength) gelatin capsules, each containing a solid molecular dispersion of: For 10 mg capsules: 10 mg OTX015/MK-8628 with 10 mg HPMCAS, mixed with lactose monohydrate (85 mg), microcrystalline cellulose (70 mg), Ac-Di-Sol (10 mg), colloidal silicon dioxide (2.5 mg), and magnesium stearate (2.5 mg). For 20 mg capsules: 20 mg OTX015/MK-8628 with 20 mg HPMCAS, mixed with lactose monohydrate (74 mg), microcrystalline cellulose (61 mg), Ac-Di-Sol (10 mg), colloidal silicon dioxide (2.5 mg), and magnesium stearate (2.5 mg). For 40 mg capsules: 40 mg OTX015/MK-8628 with 40 mg HPMCAS, mixed with lactose monohydrate (196 mg), microcrystalline cellulose (162 mg), Ac-Di-Sol (25 mg), colloidal silicon dioxide (6 mg), and magnesium stearate (6 mg).
Storage:	Capsules should be stored at 2-8°C (refrigerated).

5.2 DOSAGE SCHEDULE

5.2.1 Prophylactic medication regimen

No systematic premedication will be given at least at the first cycle, in the first 3 patients of each subset. Decision of further systematic premedication would be taken by the SMC, if appropriate.

5.2.2 Body surface area/weight adjustment

Flat doses will be used for the investigational agent OTX015/MK-8628. No adjustment on BSA, or weight will be made.

5.2.3 Schedule

Details of the exact dose and time of administration of medication (day/month/year, h: min) will be documented in a specific patient's diary (Appendix VII; section 16.7) and reported in the case report form.

- Study medication: OTX015/MK-8628. All patients enrolled should receive first study treatment intake within 7 days after registration.
- The study treatment may be delivered to hospitalized patients or outpatients, depending of their need of supportive care according to investigator's judgment. However, for the once-a-day schedule, 3 patients by dose level (among a minimum number of patients of 6 by DL: 3

with AL and 3 with other malignancies) will be hospitalized at least 24 hours for complete PK sampling (see section 7.3.3.1) All other patients enrolled in the same DL will have limited PK sampling and will stay at least 8 hours at the hospital on day 1. For the BID schedule, all patients will be hospitalized for 24 hours for PK sampling.

- Route: Oral capsules will be swallowed with water in a fasted state before lunch, at least 3 hours after breakfast end), except the first dose (C1D1) that will be taken at the hospital before breakfast.
- Capsules must not be open or chewed.
- Schedule: The schedule of administration will initially depend on the indication:
  - patients with acute leukemia will initially take OTX015/MK-8628, over 14 consecutive days followed by a 7-day rest period. Upon SMC decision, patients with acute leukemia will take OTX015/MK-8628 continuously without planned rest period, like patients with other haematological malignancies.
  - patients with other malignancies will take OTX015/MK-8628 continuously without planned rest period
  - In all cases, one cycle = 21 days by convention and day 22= day 1 of next cycle.

ACUTE LEUKEMIA (initial schedule before amendment # 4)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	**22**	etc..

OTHER HEMATOLOGICAL MALIGNANCIES and ACUTE LEUKEMIA after amendment # 4

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	**22**	etc..

- Interruptions are planned in case of toxicity according to specific guide lines (see section 0). If study medication interruptions due to toxicity are regularly observed, the SMC may decide to modify the schedule and to assess new cohorts of patients with this modified schedule.
- Based upon human PK in the healthy volunteers study with repeated dose and especially long plasma half-life ($t_{1/2}$), the first patients entered will take study medication once a day, According to PK data observed in these patients, and/or PD data the schedule of administration could be modified in further patients, upon SMC decision (e.g. b.i.). For the BID schedule, patients will take their medication in a fasted state around 8 a.m. ($\pm$ 2 hours) and 8 p.m ($\pm$ 2 hours).
- Omitted doses will not be replaced. Dosing not performed at the same time ($\pm$ 2 hours) as the other days will be omitted
- Vomited doses will not be replaced.

5.2.4 Dose

5.2.4.1 Dose escalation

- Starting dose: the starting dose will be 10 mg/day (once a day, flat dose, without adaptation for body weight or surface area), See justification in section 0.
- DLTs will be collected during the first cycle (the first 21 days after study treatment initiation).
- The dose escalation scheme is provided on Table 3. Dose escalation will proceed independently for each subset (acute leukemias and other hematological malignancies). The magnitude of dose escalation between two consecutive dose levels will depend upon the occurrence or not of DLT at the current DL: In the absence of any DLT (see definition section 3.2), the dose will be doubled between two successive DLs. In case of at least one DLT, dose escalation will proceed according to a modified Fibonacci model.
- If and when the decision of exploring a BID schedule is taken by the SMC after the assessment of dose level Xmg 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 = 80mg → the first BID dose level explored = 40mg x 2/day). Then, further dose escalation with the BID schedule will proceed as described in the table (e.g. if the first BID dose level explored= 40mg x 2/day, then the next dose level explored will be 80mg x 2/day if no DLT was observed at 40mg x 2/day, or 60mg x 2 if one DLT was observed).

- When the decision of delivering 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 will have been collected with the continuous schedule both in AL patients and in patients with other haematological malignancies, the SMC may allow further cohorts of AL patients to receive continuous OTX015/MK-8628 treatment from cycle 1.
- 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).

Table 3 : Dose escalation scheme

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 guidelines are detailed in section 3.1.1. The dose escalation will proceed following the same rule in two separate subsets of patients (i.e. AL or other hematological malignancies)
- Enrolled patients will take OTX015/MK-8628 at the DL they were assigned at study entry throughout the study, or at reduced dose according to toxicity encountered (see 0).
- **Intrapatient dose escalation**: In exceptional circumstances, intra-patient dose escalation could be allowed, provided all the following conditions are met: 1) The patient did not experienced 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 the patient could benefit from dose increment and 5) the SMC agrees.

The recommended dose (RD) for expansion cohorts for both acute leukemia and other hematologic malignancies is 80mg QD days 1 to 14 of 21-day cycles (2 weeks ON/one week OFF).

5.2.4.2 Dose adaptation

Study product dosing (OTX015/MK-8628) will be interrupted in the event of AEs corresponding to the definition of a DLT (see section 3.2), but regardless of the cycle in which they occur:

Non hematological toxicity

- Any grade 3 or 4 non-hematological 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 at baseline, only grade 4 lasting > 7 days will be considered DLT, unless the SMC considers the event clinically significant. See below for liver function tests*.

- Any prolonged grade 2 toxicity (lasting more than 2 weeks) leading to treatment interruption and/or dose reduction.

* Any of the following liver test abnormalities** (see Appendix 16.12)

  - ALT or AST > 8 x ULN
  - ALT or AST > 5 x ULN for > 2 weeks
  - ALT or AST > 3 x ULN AND (total bilirubin > 2 x ULN OR INR > 1.5)
  - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%), unless the investigator assesses the rash or fatigue to be related to OTX015 and not related to liver impairment with sponsor's agreement.

**Note: All patients with these liver test abnormalities should be monitored weekly until all abnormalities return to normal or to the baseline state. For patients with isolated total bilirubin increases >2 x ULN or 2 x baseline (if elevated at baseline), except if associated with direct bilirubin ≤ ULN, monitoring should be every 2 weeks until bilirubin returns to normal or to the baseline state. Drug induced liver injury (DILI) may develop or progress even after the causative drug has been stopped. Results should be recorded on the CRF and in the database. See guidelines on the handling of these events (potential Hy's law cases).

Hematological toxicity

Patients with AL

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

Patients with other hematological 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.

OTX015/MK-8628 dosing will be resumed when all toxic events have resolved to grade < 2 (or baseline value).

- At reduced dose :
  - During the dose escalation, at the DL immediately below.
  - During expansion cohorts, patients treated at 80mg QD (2 weeks ON/ 1 week OFF) will have their dose first reduced to 60mg QD (2 weeks ON/ 1 week OFF), then to 40mg QD (2 weeks ON/ 1 week OFF), should the same toxicity recurs.

- Dosing interruption for > 2 weeks due to toxicity will lead to definitive study treatment discontinuation, unless the investigator thinks the patient's best interest is to pursue study treatment.

- If the same DLT is observed again after dose reduction, the study treatment should be definitely discontinued, unless the investigator thinks the patient's best interest is to pursue study treatment with further dose reduction, with sponsor's agreement.

5.2.5 Supportive care guidelines in case of study treatment toxicity

Toxicity will be managed by the investigators according to local standard of care.

Supportive treatment of toxicities should be reported in the concomitant medication section of the case report form (CRF).

Handling of hepatotoxicity for potential DILI will be managed according to the treatment guidelines outlined in Appendix 16.12.

5.3 TREATMENT DURATION

Treatment will be continued until:

- Disease progression
- Intolerable toxicity
- Treatment interruption for > 2 weeks due to toxicity (except in case of suspicion hematological DLT in acute leukemia, where treatment interruption for 3 weeks is allowed to confirm DLT)
- Recurrence of DLT despite dose reduction.
- Any of the following liver test abnormalities (see Appendix 16.12)
  - ALT or AST > 8 x ULN
  - ALT or AST > 5 x ULN for > 2 weeks
  - ALT or AST > 3 x ULN and (total bilirubin > 2 x ULN OR INR > 1.5)
  - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%), unless the investigator assesses the rash or fatigue to be related to OTX015 and not related to liver impairment with sponsor's agreement
- Patient's request (consent withdrawal).

5.4 TREATMENT ASSIGNMENT

The investigational product will be administered only to subjects included in this study following the screening procedures set out in the clinical study protocol.

All patients must be registered prior to the start of treatment. A patient, who has not been registered before the first treatment administration, will not be accepted for the study at a later date.

After verifying that the patient meets eligibility criteria and has signed the Informed Consent Form, the investigator will request the patients' registration number by faxing/e-mailing the Patient's Registration Form to:

PPD

Study project leader, Oncology Therapeutic Development (OTD)

Fax : PPD

Mobile : PPD

E-mail : PPD

The Patient's Registration Form will (see Appendix III, section 16.3) contain the following information necessary to determine eligibility:

1. Institution name,
2. Sender's name,
3. Principal investigator's name,
4. Patient's identification (first letter of first, middle and last name),
5. Patient's age and gender
6. Performance status,
7. Planned date of treatment,
8. Date when informed consent obtained.
9. Verification of selected inclusion and exclusion criteria with values of the hematological, and biochemical results and dates of all the examinations performed,
10. Prior anticancer therapies and dates of last therapies
11. Co-morbidities
12. Tumor-related symptoms present at screening.
13. In- or outpatient

After validation and signature by the Sponsor's Medical Monitor, the registration form will be returned to the investigators, with or without inclusion agreement. Any inclusion refusal will be motivated on the inclusion form. In case of inclusion, a unique patient number (UPN) will be assigned to the patient and reported on the inclusion form.

The UPN will consist of 3 to 5 digits (1 or 2 for the center and 2 or 3 for the patient, by increasing order of inclusion) and will be recorded in the case report form (CRF).

The dose level allocated, and the schedule of administration will be specified on the form.

A patient should be included and therefore will receive a UPN only when the patient is about to start the treatment. Anyway, the treatment must begin within 7 days after registration.

Subjects withdrawn from the study retain their UPN. New subjects must always be allotted a new UPN.

5.5 PACKAGING AND LABELING

The investigational product is supplied as size 3 gelatin capsules containing 10 mg or 20 mg of OTX015/MK-8628 or size 0 gelatin capsules containing 40 mg of OTX015/MK-8628.

OTX015/MK-8628 will be supplied in bottles of 21 capsules. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

5.6 CAPSULE STRENGTHS

OTX015/MK-8628 will be provided as capsules with strengths of 10 mg, 20 mg and 40 mg of active compound.

5.7 SUPPLIES AND ACCOUNTABILITY

The pharmacist of the investigational center will inventory and acknowledge receipt of all shipments of the investigational medicinal product. The investigational product must be kept in a locked area with restricted access. The investigational product must be stored and handled in accordance with the manufacturer's instructions. Traceability of the temperature will be required. The pharmacist will also keep accurate records of the quantities of the investigational product dispensed, used, and returned by each subject. The study monitor will periodically check the supplies of investigational product held by the pharmacist to verify accountability of all investigational product used. The sponsor will verify that a final report of drug accountability to the unit dose level is prepared and maintained in the Pharmacy study file. At the conclusion of the study, all unused investigational product will be destroyed by the pharmacist or returned to the Sponsor after final accountability by the study monitor and agreement of the Sponsor. A certificate of destruction will be provided by the pharmacist to the Sponsor.

At each study visit, the hospital pharmacist will provide the patients with the adequate number of capsules to ensure continuous study treatment until the next visit.

5.8 COMPLIANCE

Administration of the investigational product will be supervised by the investigator. Any delegation of this responsibility must follow *Section* 12.2.

In practice, during study visit days, study nurses will supervise the intake of the appropriate dose of OTX015/MK-8628, explaining to patients the exact number of capsules. They will document the administration, the dose, the time of administration, as well as immediate reaction, if any.

For non-visit days, OTX015/MK-8628 will be taken at home. The patient will notice the number of taken capsules, the time of administration, as well as reaction, if any, including occurrence and time of vomiting, on a specific patient's diary (see Appendix VII; section 16.7).

When a patient will attend a study visit, he/she will bring back to the pharmacist the unused capsules and their diary. According to the center procedures, the diary could be used to fill in the CRF treatment administration part, either directly as Source Document, or as a help for filing in nurse's notes, which will be used as Source Document.

6 PRIOR AND CONCOMITANT ILLNESSES AND TREATMENTS

6.2 PRIOR AND CONCOMITANT MEDICAL CONDITIONS

Additional illnesses, independent of the treated condition, present at the time informed consent is given or within 30 days prior to first study treatment administration must be documented in the section "prior and concomitant conditions" of the CRF. Relevant past illnesses (including other cancers) must also be documented in this section.

Medical conditions first occurring or detected during the study, or worsening of a concomitant illness during the study, are to be regarded as treatment emergent adverse events (TEAEs) and must be documented as such in the section "Adverse Events" of the CRF (see *Section 8.1* of the protocol).

6.3 PRIOR AND CONCOMITANT MEDICATIONS

All treatments being taken by the subjects at study entry, or within 30 days prior to first study treatment administration, or at any time during the study in addition to the investigational product are regarded as concomitant medications and must be documented on the appropriate pages of the CRF.

6.3.1 Forbidden concomitant medications / treatments

- Concurrent treatment (or within 30 days, or 5 half-lives, whichever is longer) with other investigational drugs.
- Concurrent treatment (or within 21 days) with any anticancer therapy including chemotherapy, immunotherapy, hormone therapy, or biological therapies, other than those specified in the protocol. The only exception is hydroxyurea given to control hyperleukocytosis that can be continued until 48 hours before OTX015/MK-8628 treatment initiation, but must be stopped at that time; Furthermore, should rapidly increasing white blood cell count occur during the first cycle of OTX015/MK-8628, hydroxyurea could be given not earlier than day 3 and not beyond day 43 for the shortest period as clinically indicated to control hyperleukocytosis and keep the patient on study. At day 43 the decision to start OTX015/MK-8628 cycle 3 will be taken by the investigator according to patient's anticipated benefit but without hydroxyurea. If, nonetheless, hydroxyurea has to be resumed during cycle 3, this would be considered as OTX015/MK-8628 treatment failure and the patient would be withdrawn from the study.
- Prophylactic anti-emetic drugs or other drugs given with a prophylactic intent at the first cycle, unless the SMC decides to deliver systematic premedication.
- Corticosteroid, except chronic treatment with $\leq$ 30 mg/day of methymprednisolone or equivalent.
- Concurrent treatment with drugs with potential interaction: No drug interaction study has been undertaken with OTX015/MK-8628 so far. However, OTX015/MK-8628 has been shown to inhibit CYP3A4 and CYP2A6. Thus, patients using concomitant drugs or other substances

interfering with these CYP450 species (see Appendix XI, section 16.11) should be followed-up carefully for possible potentialization/inhibition of effects of OTX015/MK-8628 and/or concomitant substance. In addition, concomitant treatment with strong (see Appendix XI, section 16.11) CYP3A4 interacting drugs is prohibited. Note that as these lists are not comprehensive, the investigator should use his/her medical judgment when a patient presents with a medication not on the list or call the Sponsor Medical Expert for clarification.

6.3.2 Allowed concomitant medications / treatments

- Supportive treatment of symptoms/adverse events or standard treatment of concomitant conditions, especially transfusion support and antibiotics, bisphosphonates will be given as medically indicated and reported in the CRF.

7 Patients on anticoagulant or antiaggregant (including low-dose aspirin) therapy at screening for concomitant medical conditions should be evaluated in coordination with their cardiologist for the benefit/risk ratio of continuing their anticoagulant or antiaggregant therapy during study due to the potential increased risk of bleeding in case of occurrence of severe thrombocytopenia. Blood cell count should be more frequently performed in such patients, at least weekly during the whole study, and more in case of grade 2 to 3 thrombocytopenia. Study procedures and schedule.

7.2 DESCRIPTION OF STUDY DAYS

7.2.1 Pre-study screening

Each potential subject will be examined before the start of the study to determine their eligibility for participation. These tests are to be conducted within 7 days prior to the first study treatment administration, except tumor imaging, bone marrow biopsy and LVEF measurement that can be performed within 30 days and informed consent, and fresh tumor cell sampling that should be obtain within 14 days prior to the first study treatment administration.

The following investigations will be performed:

PARAMETERS	INVESTIGATIONS	TIMING
1.Informed consent	Obtain written subject informed consent prior to any specific study procedure	Within **14 days*** prior to registration
2. Medical history	Diagnosis of hematological malignancy; prior anticancer therapies; Non cancer medical history; Concurrent illness; concomitant medications.	Any time before registration
3. Pregnancy test	Blood or urine tests unless menopause is proven (age > 50 and last menarches > 3 years, or menopausal hormone levels, or surgical castration)	Within **7 days** * prior to first administration
4. Clinical Examination	Height and weight, vital signs, ECOG PS, clinical tumor measurement, and Physical examination.	Within **7 days** * prior to first administration
5. Cardiac function	ECG Echocardiography (LVEF measurement)	Within **7 days** * Within **30 days** * prior to first administration
6. Existing signs and symptoms	Baseline evaluation (to document residual toxicity from previous therapy, and baseline symptoms) graded according to NCI-CTCAE.	Within **7 days** * prior to first administration
7. Hematology (peripheral blood)	CBC with platelets counts, WBC differential and hemoglobin, INR.	Within **7 days** * prior to first administration (including day 1)
8. Hematology (bone marrow aspiration)	for patients with AL** and MM	Within **7 days** * prior to first administration
9. Biochemistry	LDL, HDL, β2-microglobulin (for patients with myeloma), Alkaline phosphatases (AP), LDH, CPK, CRP, ASAT, ALAT, total bilirubin, serum creatinine, ionogram (sodium, potassium, chloride, HCO3-), calcium, phosphorus, magnesium, total protein, albumin, glucose, Apo A1.	Within **7 days** * prior to first administration
10. Urinalysis	Dipstick for blood, glucose and albumin	Within **7 days** * prior to first administration
9. Tumor assessment/imaging	CT-scan or MRI (baseline) if evaluable tumor masses; PET-scan if deemed necessary for proper response assessment; skeletal X-ray/MRI in multiple myeloma Bone marrow biopsy if necessary for tumor assessment Serum M-component or BJ proteinuria (for patients with MM)	Within **30 days**** prior to first administration
10. Fresh tumor cell collection for biomarkers and intracellular PK	Fresh tumor biopsy of superficial lymph nodes, or blood/bone marrow for leukemia	Within **14 days** * prior to first administration
11. Other Investigations	Others as clinically or biologically indicated.	Within **7 days** * prior to first administration

**In case of delay in the planned first study treatment administration, the tests should be repeated, or the ICF re-signed.*

***Routine imaging and bone marrow biopsy performed outside of the scope of this study will be acceptable for baseline data, if performed ≤ 30 days prior to study entry*

****Screening bone marrow aspiration for patients with AL will include cytology, cytogenetics and 3mL to be kept for cellular PK/PD and predictive factors.*

7.2.2 Evaluation during each study visit during study treatment

Days 1, 8, 15 and 22 of the first 21 days (first cycle), then every 3 weeks

PARAMETERS	INVESTIGATIONS	TIMING
1. Clinical Examination	Weight, vital signs, ECOG PS, clinical tumor measurement, and physical examination. Concurrent illness; concomitant medications,	Before study treatment administration. In addition, on days 1, vital signs will be recorded, 1 and 2 hours after administration, in order to capture possible peak effects
2. ECG	ECG	**Only on days 1 and 22**: Before study treatment administration, then on day 1 only at 1 and 2 hours after administration **,** in order to capture possible peak effects
3. Adverse Events*	**Adverse events** **Serious adverse events** have to be declared up to 30 days after last OTX015/MK-8628 intake regardless of relationship with study drugs and beyond if drug related.	Before study treatment administration **Within 24 working hours**
4. Hematology**	CBC with platelets counts, WBC differential and hemoglobin, INR. Bone marrow aspiration for patients with leukemia and myeloma Bone marrow aspiration in all patients	Before study treatment administration **Only on day 1** (if not done at screening) **then on days 8[§], 22 and 43** (for AL). For myeloma, mandatory only to confirm CR), **then at the investigator's discretion** In case of grade 4 thrombocytopenia lasting > 3 days
5. Biochemistry***	LDL, HDL, β2-microglobulin (for patients with myeloma), AP, LDH, CPK, CRP, ASAT, ALAT, total bilirubin, serum creatinine, ionogram (sodium, potassium, chloride, HCO3-), calcium, phosphorus, magnesium, total protein, albumin, glucose. Apo A1	Before study treatment administration **Only at day 22 for Apo A1**
6. Urinalysis	Dipsticks for albumin, blood and glucose	Before study treatment administration
7. Pharmacokinetics	Plasma sampling. Please, refer to the sampling schedule (section 7.3.3.1).	**Only on Days 1,-2** (complete PK) **or 1** (limited sampling)- , then **days 8, 15 and 22** (all patients)
8. Optional fresh tumor cell sampling for biomarkers and intracellular PK for patients with other hematological malignancies	Biopsy of superficial lesion	**Day 1 (or within 14 days prior to first study drug administration) and Day 15 ± 7**
9. Tumor measurement	CT-scan or MRI in patients with evaluable tumor masses; PET-scan if deemed necessary for proper response assessment	**Every 6 -8 weeks**
8. Plasma M-component and/or BJ proteinuria	In patients with multiple myeloma	**Only on day 1, 22, then every 3 weeks.**

9. Bone marrow biopsy	If deemed necessary for the assessment of disease response	**Only at day 43** (if positive at baseline), **then at the investigator's discretion**
10. Bone imaging in MM patients	Skeletal X-ray / MRI	**Every 6 months in case of response**
10. Other Investigations	As clinically or biologically indicated.	**-**

**Additional collection of TEAEs during telephone calls by study nurses at days 4-5 and 11-12. Recording of TEAEs by the investigator will be performed using patient's interrogatory during study visits and consultation of study nurse notes reporting telephone calls between the visits.*

*** Additional in case of any NCI-CTCAE grade 4, or fever/infection, or bleeding, as clinically indicated but at least twice weekly until recovery of NCI-CTC grade ≤ 1.*

**** Additional in case of NCI-CTC grade ≥ 3 as clinically indicated but at least twice a week until recovery of NCI-CTC grade ≤ 1. All patients with specific liver test abnormalities (see Section 5.2.4) should be monitored weekly until all abnormalities return to normal or to the baseline state. For patients with isolated total bilirubin increases >2 x ULN or 2 x baseline (if elevated at baseline), except if associated with direct bilirubin ≤ ULN, monitoring should be every 2 weeks until bilirubin returns to normal or to the baseline state. DILI may develop or progress even after the causative drug has been stopped.*

[§]Day 8 bone marrow aspiration for patients with AL: 2 tubes of 3mL to be kept for cellular PK/PD.

7.2.3 End of therapy

PARAMETERS	INVESTIGATIONS	TIMING
1. Clinical Examination	Weight, vital signs, ECOG PS, clinical tumor measurement, and physical examination. Concurrent illness; concomitant medications,	35 ± 5 days from last study treatment administration
2. Cardiac function	ECG Echocardiography (LVEF measurement)	35 ± 5 days from last study treatment administration
3. Adverse Events	**Adverse events occurring on study must be followed up until resolution to NCI-CTC grade ≤ 1 or sequella** **Serious adverse events** have to be declared up to 30 days after last OTX015/MK-8628 intake regardless of relationship with study drugs and beyond if drug related.	35 ± 5 days from last study treatment administration
4. Hematology	CBC with platelets counts, WBC differential, hemoglobin and INR.	35 ± 5 days from last study treatment administration
5. Biochemistry	LDL, HDL, β2-microglobulin (for patients with myeloma), AP, LDH, CPK, CRP, ASAT, ALAT, total bilirubin, serum creatinine, ionogram (sodium, potassium, chloride, HCO3-), calcium, phosphorus, magnesium, total protein, albumin, glucose.	35 ± 5 days from last study treatment administration
6. Urinalysis	Dipsticks for albumin, blood and glucose	35 ± 5 days from last study treatment administration
6. Tumor assessment	CT-scan or MRI (baseline) if evaluable tumor massesBone marrow biopsy if necessary for tumor assessment	35 ± 5 days from last study treatment administration
7. Plasma M-component and/or BJ proteinuria	In patients with multiple myeloma	35 ± 5 days from last study treatment administration

8. Other Investigations	As clinically or biologically indicated.	**-**

7.2.4 Follow-up

After the end of therapy visit, subjects will be followed until resolution of TEAEs possibly related to the study treatment or the return to baseline value, if abnormal, or the categorization into sequella.

All deaths occurring within 30 days after the last dose of study treatment (regardless of relationship to study treatment), or considered related to study drug treatment (regardless of their date of occurrence) will be reported as serious adverse events (SAEs). Deaths occurring more than 30 days after the last study medication administration and not related to drug treatment will not be considered as SAEs.

7.3 METHODS

7.3.1 Efficacy data

7.3.1.1 Tumor assessment methods

- *Patients with evaluable tumor masses (e.g. lymphomas)*

To ensure comparability, the baseline and subsequent tumor measurements to assess response should be performed using identical imaging techniques (i.e., CT-scan or MRI, or PET-scan, preferably the same machine, identical contrast agent and standard volume of contrast agent…).

Superficial skin lesions or visible adenomegaly will be photographed.

- *Bone marrow biopsy*

Bone marrow biopsy will performed each time it is necessary to assess appropriately tumor response (e.g. lymphoma or other disease if bone marrow aspiration is technically impossible). Bone marrow biopsy at day 43 may be omitted if normal at baseline.

- *Bone marrow aspiration*

Will be used to assess response in acute leukemia and multiple myeloma

- *Plasma M-component (protein electrophoresis) and/or Bence-Jones proteinuria*

Will be used to assess response in multiple myeloma.

7.3.1.2 Tumor assessment criteria

The lesions will be assessed throughout the study according to standard criteria, for lymphomas [*Cheson 2007*], and multiple myeloma [*Durie 2006*]. Patients with acute leukemia will be assessed based on the recommendations from the European LeukemiaNet [*Döhner 2010*]
For details, see section 16.10; Appendix X.
Nonetheless, in the context of a phase I study, any tumor shrinkage will be quantified and recorded, even though it does not meet admitted criteria for response, as clue of clinical activity.

7.3.1.3 Overall survival (OS)

Survival is defined as the duration between the date of first OTX015/MK-8628 intake and the date of death whatever the cause, or censored at the date of last contact if there is no documentation of death before the cut-off date.

7.3.2 Safety data

All the tests and laboratory measurements that will be performed prior and/or on specific days during and following therapy are described in section 7.2.

7.3.2.1 Clinical Safety

Clinical and physical examinations, as well as vital signs evaluation, will be performed. Patient data will be analyzed for evidence of cumulative toxicity with repeated cycles of therapy.

TEAEs / signs and symptoms of disease observed by the investigator (preferably by the same physician for a same subject) or reported by the subjects to the study nurses will be recorded and graded according to NCI-CTCAE version 4.02, accessible via internet [http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf]. It is crucial that all events, even if not related to the study drug are reported in the CRF.

7.3.2.2 Laboratory measurements

All clinically significant laboratory values require to be reported as TEAEs in the CRF. Clinically significant laboratory results are those, which have clinical consequences (i.e. need for treatment or corrective measures, study drug dose reduction or interruption or discontinuation, hospitalization, prolongation of hospitalization, death, or are life-threatening, or are reported as SAE whatever the reason). 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.

Other laboratory changes, even severe in intensity (i.e. NCI-CTCAE grade 3-4), but without the aforementioned clinical consequences, are not clinically significant. They will be only reported in the laboratory results part of the CRF and should not be reported in the TEAE part of the CRF.

7.3.3 Pharmacokinetics (PK)

7.3.3.1 PK sampling schedule

7.3.3.1.1 Blood collection schedule

1. *Once-a-day schedule*

- At each dose level (DL) 3 patients will have complete PK sampling. Other patients will have limited PK sampling. All patients enrolled at the same DL across both subsets (AL/other hematological malignancies) will be considered for the selection of the 3 patients with complete PK sampling. Patients hospitalized due to medical reasons will be first considered for complete PK sampling.

- Patients with complete PK sampling:

Seven blood samples will be collected for PK analysis on days 1-2: T0,(before dosing), then T1h, T4h, T8h, T12h, T24h + either T10h or T16h (one of these points mandatory) (Table 4).

- Patients with limited PK sampling

Five blood samples will be collected on day 1: T0,(before dosing), then T1h, T4h, T6h, T8h.

2. *Twice-a-day (BID) schedule*

- All patients will have complete PK sampling during a 24-hour inpatient hospitalization. Height blood samples will be collected on days 1-2: T0 (before dosing), then T20min±5min, T1h±10min, T2h15min±15min, T3h15min±15min, T9h±1h, T12h±15min (just before the second intake), T24h (before drug dosing)

In all patients residual plasma concentration (C_{min}) will be assessed just before drug intake, at days 8, 15 and 22

- Three mL of blood will be collected in a peripheral vein for each sample, corresponding to a total of 21 mL of blood drawn on day 1-2 for patients with complete PK sampling and 15 mL of blood drawn on day 1 for patients with limited PK sampling. In addition, a total of 9 mL of blood will be collected on days 8, 15 and 22. In total, 30 mL of blood will collected for PK for patients with complete PK sampling and 24 mL for patients with limited PK sampling.
- Collected blood samples will be centrifuged immediately. Late samples (T10-16h) can be left vertically into refrigerator and centrifuged early in the morning the day after. Plasma will be harvested, then stored at -20°C until centralized collection. See Appendix IV, section 16.4 for sample centrifugation, storage and shipment

Table 4: Blood sampling schedules for OTX015/MK-8628 pharmacokinetics

	Sampling Time for OTX015/MK-8628 concentration									
	T0 (just before OTX015/MK-8628 administration)	**T1h**		**T4h**	**T6h**	**T8h**	**T10h**	**T12h**	**T16h**	**T24h**
PATIENTS WITH COMPLETE PK SAMPLING (once-a-day)										
Day 1-2	**X**	**X**		**X**	**-**	**X**	**X***	**X**	**X***	**X** (just before OTX015/MK-8628 administration)
PATIENTS WITH LIMITED PK SAMPLING (once-a-day)										
Day 1	**X**	**X**		**X**	**X**	**X**	-	-	-	-

PATIENTS WITH COMPLETE PK SAMPLING (twice-a-day)								
	T0 (just before OTX015/MK-8628 administration)	**T20min**	**T1h**	**T2h15**	**T3h15**	**T9h**	**T12h** (just before OTX015/MK-8628 administration)	**T24h** (just before OTX015/MK-8628administration)
Day 1-2	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

ALL PATIENTS										
Day 8, 15, 22	**X**	-		-	-	-	-	-	-	-

*only one of these (10h or 16h)

7.3.3.1.2 Fresh tumor cells

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

- Fresh leukemic cells will be collected either from peripheral blood or bone marrow (depending on the number of blasts available) on day 8.
- For patients with other malignancies, optional fresh tumor biopsy will be obtained after specific consent at baseline (between day -14 and day 1) and at day 15 $\pm$ 7 from superficial lymph nodes, or any other easily accessible tumor without invasive procedure. See Appendix IV, section 16.4 for sample centrifugation, storage and shipment

Of note, fresh cells collected on day 8 (AL) or 15 $\pm$ 7 (other hematological malignancies) will be also used for assessment of pharmacodynamic biomarkers (see section 7.3.3.1.2).The total blood or marrow volume for PKwill be 7 and 3 mL respectively.

7.3.3.2 Assay method*:*

Plasma and tumor concentrations of OTX015/MK-8628 will be measured using Ultra Performance Liquid Chromatography with tandem Mass Spectrometry detection (UPLC-MS/MS).

The following parameters will be determined: Trough (Cmin) and peak (Cmax) concentrations, Tmax, AUC [0-∞], Vdss, t1/2, steady state, total Clearance (CL).

7.2.4.7 Pharmacokinetic analysis:

Pharmacokinetic analysis will be carried out using the nonlinear mixed effect modelling software program Monolix version 412. (http://wfn.software.monolix.org).

7.3.4 Pharmacodynamic assessment

PD biomarkers in tumor cells will be explored in tumor cells. Based on current knowledge, c-MYC and BRD2, 3 and 4 expression will be measured. Other biomarkers could be explored according to increasing scientific knowledge.

7.3.4.1 Fresh tumor cells

Fresh leukemic cells will be collected from peripheral blood and bone marrow at baseline (between day -7 and day 1) and on day 8. *The total blood and marrow volume for PD will be 15 and 3 mL, respectively, each day.*

For patients with other malignancies, fresh tumor cells may be optionally obtained in selected patients at baseline (between day -14 and day +1) and at day 15 $\pm$ 7 days from superficial lymph nodes core biopsy, or any other easily accessible tumor without invasive procedure.
Of note, fresh cells collected on day 8-22 will be also used for assessment of intracellular PK (see section 7.3.3.1.2) and that collected at baseline will be assessed for predictive biomarkers (see section 7.3.6.1).
See Appendix V, section 16.5 for sampling technique, storage and shipment.

7.3.5 Pharmacokinetic / pharmacodynamic relationship

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

PD/safety correlations: The incidence and severity of AEs will be compared to the most pertinent biomarkers, if any.

PK/PD correlations: Cmax, CL and AUC of OTX015/MK-8628 will be compared to the most pertinent biomarkers, if any.

7.3.6 Tumor phenotype/Predictive factors of clinical activity

7.3.6.1 Archived tumor material

Available archived tumor material will be collected. The availability of a paraffin-embedded block is a pre-requisite for inclusion of patients with lymphoma into the study if no fresh tumor tissue is available.
At least one H&E colored slide and 6 to 7 blank slides will be requested from the most recent biopsy.

Albeit not mandatory, archived bone marrow biopsy, if available, will also be requested in patients with multiple myeloma for analysis of predictive biomarkers.

7.3.6.2 Fresh tumor cells

Fresh leukemic cells will be collected from peripheral blood and bone marrow at baseline (day -14 to day +1).

For patients with other malignancies, mainly lymphoma, fresh tumor cells may be obtained in selected patients (optional and under specific consent) at screening from superficial lymph nodes core biopsy, or any other easily accessible tumor without invasive procedure.

Of note, fresh cells collected at baseline will be also used for assessment of PD biomarkers (see section 7.3.4.1).

8 ASSESSMENT OF SAFETY

Patients will be monitored for signs and symptoms of adverse events (AEs) throughout the study by a qualified oncologist/hematologist, with experience in clinical research. All AEs will be reported in the case report form (CRF), including seriousness, NCI-CTCAE grade severity, causal relationship to the study medication, and action taken. If AEs occur, the first concern will be the safety of the study participant.

8.1 ADVERSE EVENT DEFINITIONS (21 CFR§312.32)

- **Adverse event (AE)** means any untoward medical occurrence associated with use of a drug in humans, whether or not considered drug related. (The term **treatment emergent adverse event** [TEAE] covers any unfavorable and unintended sign, symptom, syndrome, or illness that develops or worsens during the period of observation in the clinical study). Surgical or other procedures themselves are not TEAEs. The condition for which the surgery/other procedure is required is a TEAE, if it occurs or is detected during the study period. Planned surgical or other procedures planned/permitted by the study protocol and the condition(s) leading to these measures are not TEAEs, if the condition(s) was (were) known before the start of study treatment. In the latter case the condition should be reported as medical history.

- **Suspected adverse reaction (SAR)** means any AE for which there is a reasonable possibility that the drug caused the AE. A "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
  - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
  - One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
  - An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those

events occur more frequently in the drug treatment group than in a concurrent or historical control group.

SAR implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

- **Adverse reaction (AR)** means an AE caused by the drug.
- **Serious adverse event (SAE)** or **serious suspected adverse reaction (SSAR)** is an event that, in the view of either the investigator or sponsor, results in any of the following outcomes:
  - Death occurring within 4 weeks after the last administration study drug, irrespective of cause, or within any interval if related to the study drug
    [Although death may occur as a result of the basic disease process, all deaths occurring within 30 days of the last administration of study drug must be managed as SAEs and reported as such. Additionally, all deaths that may be considered as related to the study drug, regardless of the interval, must be treated as SAEs and reported as such.];
  - A life-threatening adverse event;
  - Inpatient hospitalization or prolongation of existing hospitalization;
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
  - A congenital anomaly/birth defect.

In addition, medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include overdose even not complicated, or AE requiring intensive treatment without hospitalization. A diagnosis of a new cancer type during the course of a treatment should be considered as medically important. In addition, any pregnancy diagnosed in a female subject on treatment with the investigational product or in the partner of a male subject on treatment with the investigational product must be reported to the sponsor immediately. The List of Critical Terms (1998 adaptation of WHO Adverse Reaction Terminology Critical Terms List, provided in the "Instructions for completing the 'Serious Adverse Event/Expedited Report from a Clinical Trial' form") should be used as guidance for adverse events that may be considered serious because they are medically important.

Finally, for the purpose of this phase I study, any suspected DLT will be considered as medically important and reported as SAE, even if it does not meet other criteria for seriousness. In the latter case, the reason for seriousness will be "other important medical event". The specific SAE report form for this study includes a box "DLT: Yes/No"

- **Life-threatening adverse event** or **life-threatening suspected adverse reaction** is an AE that, in the view of either the investigator or sponsor, places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- **Unexpected adverse event or unexpected suspected adverse reaction** is an AE or suspected adverse reaction that is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected", as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.2 DOCUMENTATION OF ADVERSE EVENTS

Each and every TEAE occurring during the course of the study, whether or not considered related to the study drug or to underlying disease, must be individually recorded in the CRF, including the nature of the event, date and time of onset (where appropriate), duration of effect, action taken, seriousness, severity, and relationship to study medication. Any consequent change to the dosage schedule or any corrective therapy should be recorded.

Every attempt should be made to describe the TEAE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

All subjects who experience a TEAE, regardless of the relationship to study treatment, must be monitored to determine the outcome. The clinical course of the adverse event will be followed up even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up. Should the adverse event result in death, post-mortem examination should be considered as far as possible.

After last study treatment administration, patient will be observed during **at least 30 days** to document any late side effect and until resolution in case of AE thought to be related to study treatment, and every month and a half for the first three months, then every three months until death.

AEs already recorded and designated as "continuing" should be reviewed at each subsequent assessment. If resolved, details are to be recorded in the CRF. If an AE changes for the worse, in frequency of attacks/symptoms or in severity, a new record of the event must be started (i.e., distinct AE reports are required for differing frequencies and/or severity of the same event to enable comprehensive safety reports and later analysis).

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, must be reported under "concomitant procedures" in the CRF and not as an AE. The medical condition for which the procedure was performed must be reported.

A clinical laboratory abnormality should be reported as an AE only if the abnormality is "clinically significant", i.e. the abnormality is serious, OR requires active management (e.g., specific treatment, change or delay of dose, discontinuation of study drug, more frequent follow-ups, and diagnostic investigation) OR is considered as a toxicity of the study treatment.

8.2.1 AE Grade

All AEs, whether or not they are considered related to the study drug, must be graded using the NCI Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.02 [http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf]. The worst grade for that particular event is to be documented.
AE grades usually reflect their severity, with grade 1 meaning "mild", grade 2 meaning "moderate", grade 3 meaning "severe", grade 4 meaning "life-threatening" and grade 5 meaning "fatal".

8.2.2 AE Severity

The term "severity" is used to describe the **intensity** of an adverse event; the event itself, however, may be of relatively minor clinical significance (e.g., 'severe' headache). This is **not** the same as "serious". Seriousness of AEs is based on the outcome/action of an AE and usually is associated with events that pose a threat to a patient's life or functioning.

Intensity of the adverse event will be evaluated using the following criteria:

- **Mild**: The patient is aware of the sign or symptom, but finds it easily tolerated. The event is of little concern to the patient and of little clinical significance. The event is not expected to have any effects on the patient's overall health or well-being.
- **Moderate**: The patient has discomfort enough to cause interference with or change in usual activities. The event is of some concern to the patient's health or well-being and may require medical intervention and/or close follow-up.
- **Severe**: The adverse event interferes considerably with the patient's usual activities. The event is of definite concern to the patient and/or poses substantial risk to the patient's health or well-being. The event is likely to require medical intervention and/or close follow-up and may be incapacitating or life-threatening. Hospitalization and treatment may be required.

8.2.3 Adverse event relationship to study treatment or procedure

All TEAEs occurring during treatment with an investigational agent may be related to the investigational agent. All TEAEs, regardless of the supposed relationship to study treatment, must therefore be collected. However, the investigator often has arguments to think that a TEAE is or is not related to the study treatment. Albeit subjective, and susceptible to be challenged, the assessment of relationship to study treatment is an important role of the investigator. Thus, the investigators should decide, based on their knowledge and medical expertise, whether, in their opinion, an AE is "reasonably related" or "unlikely related" to the study treatment (or to study specific procedures).

8.3 EVENTS OF CLINICAL INTEREST

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until patient registration, any ECI, or follow up to an ECI, that occurs to any patient must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

For the time period beginning at patient registration through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the data entry guidelines.

1. An elevated AST or ALT lab value that is ≥3X ULN and an elevated total bilirubin lab value that is ≥2X ULN and, at the same time, an alkaline phosphatase lab value that is < 2X ULN, as determined by protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in Appendix 5 and the Investigator Brochure section on discussion and guidance for investigator.

2. An elevated total bilirubin lab value that is > 2X ULN.

3. Any of the following liver test abnormalities are observed (see also Appendix 3):
   - ALT or AST > 8X ULN
   - ALT or AST > 5X ULN for more than 2 weeks
   - ALT or AST > 3X ULN AND (total bilirubin > 2X ULN OR INR > 1.5)
   - ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%), unless the investigator assesses the rash or fatigue to be related to OTX015 and not related to liver impairment with sponsor's agreement.

**All patients with these liver test abnormalities should be followed weekly until all abnormalities return to normal or to the baseline state. DILI may develop or progress even after the causative drug has been stopped. Results should be recorded on the case report form and in the database. See Appendix 16.12 for guidelines on the handling of events of ALT or AST >3 x ULN AND total bilirubin >2 x ULN or INR>1.5 (potential Hy's law cases).

8.4 IMMEDIATE REPORTING BY INVESTIGATOR TO SPONSOR

SAEs and other events that fulfill a reason for expedited reporting to Pharmacovigilance (overdose and pregnancy and DLT for the present study) must be documented on a "Serious Adverse Event Report Form" (SAERF) at the time the SAE is detected. This form must be completed and sent within 24 hours, or at the latest on the following working day to the sponsor's Pharmacovigilance representative:

Oncology Therapeutic Development (OTD)

Tel : PPD
Fax : PPD
E-mail: PPD

The SAERF and the guidelines for filling it in are provided in the investigator's study file.

The sponsor will ensure that all legal reporting requirements are met.

The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s).

Information not available at the time of the initial report (e.g., an end date for the AE or laboratory values received after the report) must be documented on a follow-up SAERF.

8.5 PERIOD OF OBSERVATION

For the purposes of this study, the period of observation for collection of AEs extends from the start of treatment with investigational product until the end of study treatment (i.e. 30 days after the last study drug administration), except for adverse events related to study drug, which must be reported during follow-up period until resolution or change of causality from related to non-related or initiation of further antitumor therapy.

If the investigator detects a SAE in a study subject after the end of the period of observation, and considers the event possibly related to prior study treatment, he or she should contact the sponsor to determine how the adverse event should be documented and reported.

9 STUDY TREATMENT DISCONTINUATION

Study treatment will be definitely discontinued for the following reasons:

- Patient's request (consent withdrawal) at any time without need for any justification
- If, in the investigator's opinion, the benefit/risk ratio is no longer favorable and continuation in the study could be detrimental to the subject. This includes:

1. Progressive disease
2. Intolerable toxicity
3. Treatment interruption > 2 weeks due to TEAEs (except in cases of suspicion of hematologic DLT in acute leukemia, where treatment interruption for 3 weeks is allowed to confirm DLT) related to the study medication, unless the investigator thinks resuming study treatment is the best patient's interest
4. Recurrence of the same toxicity, with the same severity after one dose reduction, unless the investigator thinks pursuing study treatment at lower dose is the best patient's interest, with sponsor's agreement
5. Lack of patient compliance
6. Major protocol deviation
7. Any of the following liver test abnormalities (see Appendix 5)
    - ALT or AST > 8 x ULN
    - ALT or AST > 5 x ULN for > 2 weeks
    - ALT or AST > 3 x ULN and (total bilirubin > 2 x ULN OR INR > 1.5)
    - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%), unless the investigator assesses the rash or fatigue to be related to OTX015 and not related to liver impairment with sponsor's agreement.

- Upon specific request of the sponsor

In all cases, the reason for and date of study treatment discontinuation must be recorded in the CRF at the "End of Study Treatment" page and source documented in the patient's medical records. As far as possible, there should be only one reason for study treatment discontinuation. If there are several reasons (e.g.; concomitant progressive disease and toxicity), efforts will be made to select the most important one (i.e. the reason that would have been sufficient, should it occur alone). The subject must be followed up to establish whether the reason was a TEAE, and, if so, this must be reported as such (see Section 8.2*)*.

As far as possible, all examinations scheduled for the final study day must be performed on all subjects who receive the investigational product but do not complete the study according to protocol.

The investigator must make every effort to contact subjects lost to follow-up. Especially, when a patient is treated in another, non-study, center, the investigator is responsible for collecting follow-up data from this center.

Subjects early withdrawn from study (i.e. those receiving less than 18 days of treatment for the continuous, 21-day schedule or less than 12 days of treatment for the intermittent, 14 days ON/ 7 days OFF schedule), or those having received < 85% of the intended cumulative dose during the first 21 days and who do not experience a DLT; (i.e. patients not evaluable for DLT, the primary study endpoint) will be replaced.

After study withdrawal, patients' care will be managed in their best interest, by the investigator and/or the referring physician

10 EMERGENCY PROCEDURES

10.1 EMERGENCY SPONSOR CONTACT

In emergency situations, the investigator should immediately contact a sponsor representative at the telephone number or email address given on the title page of the protocol.

10.2 EMERGENCY IDENTIFICATION OF INVESTIGATIONAL PRODUCTS

This section is not applicable as this is an open-label study.

11 STATISTICAL PROCEDURES

11.1 ANALYSIS VARIABLES/ STUDY ENDPOINTS

Primary: DLT is the endpoint for the determination of the RD in each subset.

Secondary: treatment-emergent adverse events (TEAEs), vital signs, laboratory results, ECG and LVEF changes, PK and PD parameters, disease specific tumor response assessment, quantitative tumor shrinkage, tumor-related symptoms, PS.

Exploratory: Predictive factors of clinical activity: clinical features / tumor phenotype/ cytogenetics / molecular biology markers / gene expression profile,

11.2 ANALYSIS POPULATIONS

- **Intent-to-treat population**: all enrolled patients
- **Per protocol population**.: all enrolled patients with no violation of inclusion/exclusion criteria
- **Evaluable for safety population**: all patients having received at least one dose of OTX015
- **Evaluable for DLT population**: all treated patients having received at least 85% of the intended dose during the first cycle (i.e. $\geq$ 12 days at full dose for AL and $\geq$ 18 days at full dose for other hematological malignancies)* of OTX015/MK-8628 treatment, as well as patients not fulfilling these conditions, but having experienced a DLT.

***e.g.** for DL1 (10 mg/day), patients with AL having received $\geq$ 120 mg over the first 21 days (10 mg x 12), or patients with other hematological malignancies having received $\geq$ 180 mg over the first 21 days (10 mg x 18).

11.3 STATISTICAL METHODS

This is an exploratory Phase Ib study aimed to assess the pharmacological effects of OTX015/MK-8628 in patients with hematological malignancies. The small subject sample size by cohorts does not allow for statistical hypotheses. The decisions will be taken by the SMC, composed of experts. The recommended dose will be validated in further phase II studies.

11.4 INTERIM ANALYSIS

No interim analysis is planned. Regular assessment by the SMC of the data of the last cohort of 3 evaluable patients will be performed.

11.5 SAMPLE SIZE JUSTIFICATION

There is no justification of the sample size.

Approximately 50 to 75 evaluable patients, depending on the number of DL in the dose escalation part and number of patients at each DL, are planned.

12 ETHICAL AND LEGAL ASPECTS

12.1 GOOD CLINICAL PRACTICE

This Phase 1 trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), as defined in ICH Guidance E6: *Good Clinical Practice: Consolidated Guidance*, in agreement with the Declaration of Helsinki and applicable federal and local regulatory requirements

12.2 DELEGATION OF INVESTIGATOR DUTIES

The investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The investigator should maintain a list of subinvestigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

12.3 SUBJECT INFORMATION AND INFORMED CONSENT

Before being enrolled in the clinical study, subjects must give a written informed consent to participate into the study.

A Patient Information Leaflet (PIL), including an Informed Consent Form (ICF) (see Appendix VI; section 16.6) will be given to each patient screened in the study. This document contains all the information required by the ICH E6 Guideline for Good Clinical Practice and any additional elements required by local regulations. The master document in Appendix VI is also translated into the national language(s) and in terms that are understandable to any subject. In addition to the document, the investigator should provide oral information and answer to patient's questions. Patients should have a minimal time for thought and for asking questions and should not sign the ICF while first given to them.

The patient's consent must be confirmed by their dated signature and by the name and dated signature of the principal investigator or subinvestigator conducting the informed consent discussions.

A copy of the signed consent document must be given to the subject. The original signed consent document will be retained in the investigator study file.

The investigator will not undertake any measure specifically required for the clinical study until valid consent has been obtained.

12.4 CONFIDENTIALITY

Subject names will not be supplied to the sponsor. Only the unique patient number and subject initials will be recorded in the case report form, and if the subject name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor, independent ethics committee (IEC)/ institutional review board (IRB), or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The investigator will maintain a patients' identification list (subject numbers with the corresponding subject names) to enable records to be identified.

12.5 APPROVAL OF THE CLINICAL STUDY PROTOCOL AND AMENDMENTS

Before the start of the study, the clinical study protocol, PIL/ICF, and any other appropriate documents will be submitted to the IEC/IRB and to the national Health Authorities, in accordance with local legal requirements.

Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IEC/IRB and the authorities must be informed of all administrative changes and any important finding that could modify the risk of exposed patients. They also must be informed or their authorization obtained for all subsequent protocol, in accordance with local legal requirements.

The investigator must keep a record of all communication with the IEC/IRB and the Health Authorities.

12.6 ONGOING INFORMATION FOR INDEPENDENT ETHICS COMMITTEE/ INSTITUTIONAL REVIEW BOARD AND HEALTH AUTHORITIES

The sponsor must submit to all investigators of OTX015/MK-8628 studies, the IEC/IRB and health Authorities:

- Information on serious or unexpected adverse events from the investigator's site, as soon as possible
- Expedited safety reports according to regulations
- Periodic reports on the progress of the study

12.7 CLOSURE OF THE STUDY

The study must be closed at the site on completion. Furthermore, the sponsor or the investigator has the right to close this study site at any time.

Study materials must be returned, disposed of or retained as directed by the sponsor.

12.8 RECORD RETENTION

Study documents should be retained by the investigator for at least 15 years. Beyond this period, the investigator still must obtain approval in writing from the sponsor before destruction of any records.

The documents to be retained include:

- Original signed ICFs for all subjects
- Subject identification code list*, screening log and enrollment log
- Record of all communications between the investigator and the IEC/IRB
- Composition of the IEC/IRB
- Record of all communications between the investigator and sponsor (or CRO)
- List of subinvestigators and other appropriately qualified persons to whom the investigator has delegated significant trial-related duties, together with their roles in the study and their signatures
- Copies of CRFs and of documentation of corrections (DCF) for all subjects
- Investigational product accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (subject medical records, hospital records, laboratory records, etc.)
- All other documents as listed in section 8 of the ICH E6 Guideline for Good Clinical Practice (Essential Documents for the Conduct of a Clinical Trial)

12.9 LIABILITY AND INSURANCE

Liability and insurance provisions for this study are given in separate agreements. Patient's travel expenses made within the scope of the study will be reimbursed by the Sponsor to the patient, upon presentation of justification.

The Sponsor has subscribed an insurance covering their civil responsibility.

The Sponsor, OncoEthix, is a company established outside the European Union. As such, they have empowered the following Contract Research Organization (CRO) for representing them in the European Union:

OTD (Oncology Therapeutic Development) SARL,

100 rue Martre

92110 Clichy,

France.

12.10 FINANCIAL DISCLOSURE

Before the start of the study, the investigator will disclose to the sponsor any proprietary or financial interests he or she might hold in the investigational products or the sponsor company as outlined in the financial disclosure form provided by the sponsor. The investigator agrees to update this information in case of significant changes during the study or within one year of its completion. The investigator also agrees that, where required by law or regulation, the sponsor may submit this financial information to domestic or foreign regulatory authorities in applications for marketing authorizations.

Similar information will be provided by each subinvestigator to whom the investigator delegates significant study related responsibilities.

13 STUDY MONITORING AND AUDITING

Monitoring and auditing procedures developed or endorsed by the sponsor will be followed, in order to comply with GCP guidelines. Direct access to the on-site study documentation and medical records must be ensured.

13.1 STUDY MONITORING AND SOURCE DATA VERIFICATION

Monitoring will be done by personal visits from representatives of the sponsor (study clinical research assistant and medical monitor) who will check the CRFs for completeness and clarity, and crosscheck them with source documents. In addition to the monitoring visits, frequent communications (letter, telephone, e-mail and fax), by the study monitors will ensure that the investigation is conducted according to protocol design and regulatory requirements.

Study close-out will be performed by the study monitor upon closure of the study.

13.2 ON-SITE AUDITS/INSPECTIONS

An external auditor, appointed by the study sponsor, or the EC/IRBs, as well as inspectors, appointed by domestic and foreign regulatory authorities, may request access to all source documents, case report forms, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that subject names are obliterated on the copies to ensure confidentiality.

14 DOCUMENTATION AND USE OF STUDY FINDINGS

14.1 DOCUMENTATION OF STUDY FINDINGS

A case report form (CRF) will be provided for each subject.

All protocol-required information collected during the study must be entered by the investigator, or designated representative, in the CRF. Details of CRF completion and correction will be explained to the investigator. If the investigator authorizes other persons to make entries in the CRFs, the names, positions, signatures, and initials of these persons must be supplied to the sponsor.

The investigator, or designated representative, should complete the CRF pages as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure and at the latest before the next monitoring visit. An explanation should be given for all missing data.

A source data location list will be prepared prior to study start. This list will be filed in both the trial master file and the investigator study file and updated as necessary.

The completed CRFs must be reviewed and signed by the investigator named in the clinical study protocol or by a designated co-investigator.

All errors detected after the monitoring visit will be queried using data correction forms (DCFs). The Sponsor will answer the question and/or correct errors in the DCF duly signed and dated. Original DCFs will be taken by the sponsor's study monitor, while a copy will be kept by the investigator and recorded in the investigator study file with the corresponding CRFs.

The sponsor will retain the originals of all CRFs and DCFs. The investigator will retain a copy of all completed CRF pages and DCFs.

14.2 CONFIDENTIALITY/USE OF STUDY FINDINGS

All information concerning the product as well as any matter concerning the operation of the sponsor, such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the sponsor and are unpublished, are confidential and must remain the sole property of the sponsor. The investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the sponsor is obtained.

The sponsor has full ownership of the original CRFs completed as part of the study.

By signing the clinical study protocol, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

The sponsor will ensure that a final report on the study is prepared.

All materials, documents and information supplied by the sponsor to the investigator, and all materials, documents and information prepared or developed in the course of the study to be performed under this protocol, shall be the sole and exclusive property of the sponsor. Subject to obligations of confidentiality, the investigator reserves the right to publish only the results of the work performed pursuant to this protocol, provided, however, that the investigator provides an authorized representative of the sponsor with a copy of any proposed publication for review and comment at least 60 days in advance of its submission for publication. In addition, if requested, the investigator will withhold publication an additional 90 days to allow for filing a patent application or taking such other measures as sponsor deems appropriate to establish and preserve its proprietary rights.

It is agreed that, consistent with scientific standards, publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the protocol.

15 REFERENCES

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16 APPENDICES

16.1 APPENDIX I: ECOG PERFORMANCE STATUS

PERFORMANCE STATUS:

ECOG	Characteristics
0	Normal Activity
1	Symptoms of disease, but ambulatory and able to carry out activities of daily living
2	Out of bed more than 50% of the time, occasionally needs assistance
3	In bed more than 50% of the time, needs nursing care
4	Bed ridden, may need hospitalization

16.2 APPENDIX II: CALCULATION OF THE RENAL CLEARANCE

- In patients aged < 65 years: **Cockroft &Gault** formula

Male = 1.25 x **weight (kg)** x (140-**age**) / serum **creatinine (µmol/L)**

Female = 1.04 x **weight (kg)** x (140-**age**) / serum **creatinine (µmol/L)**

- In patients aged ≥ 65 years: **MDRD** (Modification of Diet in Renal Disease) formula

Male = 186 x (serum **creatinine (µmol/L)** x 0,0113)$^{-1,154}$ x **age**$^{-0,203}$

x 1,21 in subjects with black skin

x 0.742 in female

Automatic calculation on the web, e.g. http://filfola.fr/medecine/cockroft_MDRD.html, or http://mdrd.com/

16.3 APPENDIX III: PATIENT REGISTRATION FORM

The patient registration form is provided as a separate document

16.4 APPENDIX IV: PHARMACOKINETICS : SAMPLING SCHEDULE, SAMPLING METHOD, STORAGE AND SHIPMENT GUIDELINES

OTX015/MK-8628 concentrations will be measured in blood and, optionally, in tumor tissue, using UPLC-MS/MS.

BLOOD COLLECTION

- Blood samples of 3 mL each will be collected in EDTA tubes throughout the first cycle of study treatment.

The schedule of blood sampling is summarized in the table below:

	Sampling Time for OTX015/MK-8628 concentration									
	T0 (just before OTX015/MK-8628 administration)	**T1h**		**T4h**	**T6h**	**T8h**	**T10h**	**T12h**	**T16h**	**T24h**
PATIENTS WITH COMPLETE PK SAMPLING (once-a-day)										
Day 1-2	**X**	**X**		**X**	**-**	**X**	**X***	**X**	**X***	**X** (just before OTX015/ MK-8628 administration)
PATIENTS WITH LIMITED PK SAMPLING (once-a-day)										
Day 1	**X**	**X**		**X**	**X**	**X**	-	-	-	-

PATIENTS WITH COMPLETE PK SAMPLING (twice-a-day)								
	T0 (just before OTX015/MK-8628 administration)	**T20min**	**T1h**	**T2h15**	**T3h15**	**T9h**	**T12h** (just before OTX015/MK-8628 administration)	**T24h** (just before OTX015/MK-8628 administration)
Day 1-2	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

ALL PATIENTS										
Day 8, 15, 22	**X**	-		-	-	-	-	-	-	-

*only one of these (10h or 16h)

- Upon collection, the samples will be inverted a few times to mix the anticoagulant and then processed as soon as possible (within 15 min).
- Samples will be centrifuged at 1500 g (4000 rpm for a 14-15 cm centrifuge) at +4°C for 10 minutes and the plasma will be immediately aliquoted and stored in airtight stoppered polypropylene tubes at -20°C.

- IMPORTANT: All PK points described in Table above are mandatory to explore PK of OTX015/MK-8628. For samples to be collected late in the evening or early in the morning (i.e, T10h, T12h, T16h), in the absence of research nurse or technician, the tubes of blood mixed with anticoagulant can be left in vertical position into the refrigerator and be centrifuged/aliquoted ASAP during research nurses'/technicians' working hours.

- All samples will be labeled with Sponsor and ***study identification, Unique patient number and initials, sample number, and actual date and time*** the sample was collected.

TUMOR SAMPLE COLLECTION

OTX015/MK-8628 concentration will be measured in tumor cells, as far as possible,

- For AL patients: Approximately 7 mL of blood or 3 mL of bone marrow (whichever is more appropriate for blasts concentration) will be collected on specific Ficoll ready to use tubes (BD Vacutainer® CPT™), on day 8. Upon collection, the samples will be centrifuged at room temperature in a horizontal rotor (swing-out head) for a minimum of 20 minutes at 1500 to 1800 RCF; After centrigugation, the ring of mononuclear cells at the interface of plasma and density gradient fluid will then be resuspended into the plasma by inverting the unopened BD Vacutainer® CPT™ tube gently 5 to 10 times. The unopened will be labelled (date, time, patient number and initials) then sent to the pharmacology department at ambient temperature immediately after. Complete guidelines for sample processing and shipment will be provided in a separate document.

ATTENTION: PD procedure is different and is detailed in Appendix .5

- For patients with other hematological malignancies: If a patient has easily accessible tumor without invasive procedure (e.g. superficial lymph nodes or skin), an optional fresh core biopsy could be performed, conditional to a specific express informed consent) for intra-tumor OTX015/MK-8628 concentration measurement on day 15 ± 7 days. A tumor sample of 30mg* approximately should be divided in two aliquots immediately put into liquid nitrogen containing isopentane, then stored at -70 to -80°C until shipment. Complete guidelines for sample processing and shipment will be provided in a separate document.

*Warning: *a tumor sample should be kept from the same biopsy for PD analysis, so the ideal total tissue sample amount should be around 60mg.*

SHIPMENT

Blood samples on days 1-2 from a given patient must be sent as soon as possible to the laboratory below, to allow for results availability at the SMC meeting. If two patients in the same center are treated at the same time or a few days apart, the samples of the two patients should be sent together.

Day 22 sampling and optionally, tumor specimens should be stored until further shipments with samples from other patients

Blood samples shipment should be performed at -20°C and tumor samples at -70 to -80°C.

The central pharmacokinetics laboratory will be:

Laboratoire de Pharmacology PPD

Institut Curie (Hôpital René Huguenin)
35, rue Dailly

92210 Saint-Cloud

PPD tel: PPD e-mail: PPD
PPD tel: PPD e-mail: PPD

fax : PPD

TRANSPORTER CONTACTS

World Courier France

e-mail: PPD ;

Tel : PPD

fax : PPD

Adresse : Rue Montgolfier – 38090 Villefontaine

16.5 APPENDIX V: ARCHIVED TUMOR TISSUE AND COLLECTION OF FRESH TUMOR BIOPSY/CELLS FOR PHARMACODYNAMIC BIOMARKERS, PREDICTIVE BIOMARKER AND INTRACELLULAR PHARMACOKINETICS.

Archived tumor tissue

The availability of archived material should be checked at screening prior to inclusion procedures. This availability is mandatory for lymphoma patients only.

Bone marrow biopsy will be requested, if available for MM patients.

Archived paraffin-embedded block (formaldehyde-fixed) of histological material from lymphoma will be packed in plastic/carton boxes. At least one hematoxyn/eosin (H&E) colored slide and 6 to 7 blank slides from the most recent biopsy will be required.

Samples will be forwarded from the laboratory where they are stored to:

ANATOMIA PATOLOGICA GENERALE E ONCOGENETICA MOLECOLARE - U

Ospedale Molinette:

C.so Bramante, 88/90

10126 Torino

ITALY

1.1.1 To : PPD

e-mail : PPD

Phone: PPD

Fax PPD

Fresh leukemic cells (peripheral blood or bone marrow aspiration)

- For AL patients: Approximately 3 tubes of 5 mL of blood and 3 mL of bone marrow will be collected on K2 EDTA tubes (lavender top), at baseline (day -14 to day +1) during the same bone marrow aspiration/blood collection as for diagnosis procedures, then on day 8. Upon collection, the samples will be inverted a few times to mix the anticoagulant and then processed within 24 hours. The tubes should arrive to the central laboratory the day after early in the morning. Mononuclear cells will then be separated using Ficoll gradient at their arrival at the central laboratory (no manipulation in the clinical department). Complete guidelines for sample processing and shipment will be provided in a separate document.

Laboratoire d'hématologie A, Analyse spécialisée Biologie moléculaire

PPD

Centre de biologie pathologie Pierre-Marie Degand,

CHRU de Lille

bd du professeur Leclercq

59037 Lille cedex

France

Email : PPD

Phone : PPD

Fax : PPD

Warning: Day 8 mononuclear cells will also be used for Tumor PK. Attention : the procedure for PK sampling is different (see Appendix IV)

Fresh tumor biopsies (lymphoma)

- For patients with other hematological malignancies: If a patient has easily accessible tumor without invasive procedure (e.g. superficial lymph nodes or skin), an optional fresh core biopsy could be performed, conditional to a specific express informed consent) for Pharmacodynamic and predictive factors exploration at baseline (day -14 to day +1) and on day 15 ± 7 days. A tumor sample of 30mg* approximately should be divided in two aliquots immediately put into liquid nitrogen containing isopentane, then stored at -70 to -80°C until shipment to: .

IOR Institute of Oncology Research

Fondazione per la Ricerca e la Cura dei Linfomi nel Ticino,

via Vela 6, CH-6500 Bellinzona

SWITZERLAND

TO: PPD
e-mail/ichat: PPD
Phone: PPD (lab);
Fax: PPD

**Warning: a tumor sample should be kept from the same biopsy for PK analysis, so the ideal total tissue sample amount should be around 60mg*

Alternatively, a few micrograms of extracted RNA and one microgram of extracted DNA will be sent directly to the same laboratory. In this case, no intratumor PK will be performed

All tumor tissue/cell material (archived and fresh) will be identified by the pathology or hematology lab department of the investigational center, by study code, patient UPN and initials, origin of tumor tissue and date of biopsy. Complete guidelines for sample processing and shipment will be provided in a separate document.

TRANSPORTER COORDINATES

World Courier France

e-mail: PPD ;

Tel : PPD

fax : PPD

Adresse : Rue Montgolfier – 38090 Villefontaine

16.6 APPENDIX VI: PATIENT INFORMATION LEAFLET (PIL) AND INFORMED CONSENT FORM (ICF)

The Patient Information Leaflet/ Informed Consent Form is provided as a separate document in English (Master document) and in legally required local languages (French and Italian)

16.7 APPENDIX VII: PATIENT'S DIARY

The Patient's Diary is provided as a separate document.

16.8 APPENDIX VIII: SAFETY MONITORING COMMITTEE COMPOSITION AND CHART

The study will be driven by a Safety Monitoring Committee (SMC), composed of the principal clinical investigators (PIs) (or subinvestigator delegated by the PI), the PK investigator, two Sponsor representatives and one independent medical expert in oncology/hematology drug development (Table below)

Name	Institution/company	Position	Sponsor Representative
PPD	PPD	Principal Investigator	NO
		Principal Investigator	NO
		Principal Investigator	NO
		Principal Investigator	NO
		Principal Investigator	NO
		Principal Investigator	NO
		Principal Investigator	NO
		Principal Investigator	NO
		Principal Investigator	NO
		Principal Investigator	NO
		Principal Investigator	NO
		Pharmacokineticist	NO
	OTD, Clichy, France	Medical Monitor	YES
	Merck, USA	Medical Monitor	YES
	Merck, USA	Drug Safety	YES
	PPD	Independent Expert	NO

Curriculum Vitae provided in Appendix X

Safety Monitoring Committee Chart

- The SMC will meet on a regular basis (physically or through teleconference), every 6 to 8 weeks, as soon as possible after the full clinical data sets of a cohort of 3 patients independently in each subset (AL or other haematological malignancies) over their first cycle (i.e. 21 days following study treatment initiation) have been collected. PK data from at least day 1 of these 3 patients will be available for the meeting

- After examination of the clinical and PK data and discussion, the SMC will take any decision to ensure/improve patients' safety, and particularly the followings:

1. Validate dose limiting toxicities (DLTs)
2. Proceed to the dose level (DL) immediately above
3. Add patients at the same DL
4. Stop dose escalation and expand a DL
5. Modify treatment schedule according to new safety, pharmacokinetic and/or pharmacodynamic data
6. Add intermediate unplanned DLs
7. Recommend systematic premedications/supportive care for common toxicities
8. Establish the recommended dose (RD)
9. Discuss the relevance of the RD for further studies, based on PK and PD results.
10. Recommend initiation of expansion cohorts

- The minutes of the meetings will be written by the designed secretary (the sponsor's safety officer by default) within a week, approved and signed by all attendees. The minutes of all meetings will be archived in the Trial Master File and put as appendices in the Clinical Study Report.

- In addition, the SMC could be met in case of exceptional circumstance, justifying immediate decision to ensure patients' safety. If it is not possible to hold a meeting or teleconference of the whole SMC, at least the Independent Expert will met with the Sponsor's representatives.

- In addition, the Independent Expert will review all CIOMs forms released by the Safety Officer before they are sent to the Health Authorities, EC/IRB and investigators.

16.9 APPENDIX IX: CURICULUM VITAE OF INVESTIGATORS AND SAFETY MONITORING COMMITTEE MEMBERS

CVs are provided as separate documents

16.10 APPENDIX X: SUMMARY OF STANDARD RESPONSE CRITERIA FOR ACUTE LEUKEMIA, MALIGNANT LYMPHOMA, AND MULTIPLE MYELOMA

1) Acute Leukemia (after *Döhner, 2010*)

Response criteria in AML

Category	Definition
Complete remission (CR)*	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0 × 10^9/L (1000/µL); platelet count > 100 × 10^9/L (100 000/µL); independence of red cell transfusions
CR with incomplete recovery (CRi)‡	All CR criteria except for residual neutropenia (< 1.0 × 10^9/L [1000/µL]) or thrombocytopenia (< 100 × 10^9/L [100 000/µL])
Morphologic leukemia-free state‡	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	Relevant in the setting of phase 1 and 2 clinical trials only; all hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Cytogenetic CR (CRc)§	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Molecular CR (CRm)‖	No standard definition; depends on molecular target
Treatment failure	
Resistant disease (RD)	Failure to achieve CR or CRi (general practice; phase 2/3 trials), or failure to achieve CR, CRi, or PR (phase 1 trials); only includes patients surviving ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
Relapse¶	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease

* All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

↵† The criterion of CRi is of value in protocols using intensified induction or double induction strategies, in which hematologic recovery is not awaited, but intensive therapy will be continued. In such protocols, CR may even not be achieved in the course of the entire treatment plan. In these instances, the overall remission rate should include CR and CRi patients. Some patients may not achieve complete hematologic recovery upon longer observation times.

↵‡ This category may be useful in the clinical development of novel agents within phase 1 clinical trials, in which a transient morphologic leukemia-free state may be achieved at the time of early response assessment.

↵¶ In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML.

2) Revised Response Criteria for Malignant Lymphoma (after *Cheson, 2007*)

Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

3) Uniform Response Criteria forMultiple Myeloma (after *Durie, 2006*)

Response subcategory	***Response criteria***[a]
CR	Negative immunofixation on the serum and urine and
	Disappearance of any soft tissue plasmacytomas and
	≤5% plasma cells in bone marrow[b]
sCR	CR as defined above plus
	Normal FLC ratio and
	Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
VGPR	Serum and urine M-component detectable by immunofixation but not on electrophoresis or
	90 or greater reduction in serum M-component plus urine M-component <100 mg per 24 h
PR	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h
	If the serum and urine M-protein are unmeasurable,[d] a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria[2, 3]
	If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30%
	In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

[a] All response categories require two consecutive assessments made at anytime before the institution of any new therapy; complete and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

[b] Confirmation with repeat bone marrow biopsy not needed.

[c] Presence/absence of clonal cells is based upon thek/λ ratio. An abnormalk/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone isk/λ of >4:1 or <1;2. Alternatively, the absence of clonal plasma cells can be defined based on the investigation of phenotypically aberrant PC. The sensitivity level is 10^{-3}(less than one phenotypically aberrant PC within a total of 1000 Pc). Examples of aberrant phenotypes include (1) $CD38^{+dim}$ and $CD56^{+\ strong}$ and $CD19^{-}$ and $CD45^{-}$; (2) $CD38^{+dim}$ and $CD138^{+}$and $CD56^{++}$ and $CD28^{+}$; (3) $CD138^{+}$, $CD19^{-}$ $CD56^{++}$, $CD117^{+}$.

Relapse subcategory	***Relapse criteria***
	Laboratory or Biochemical Relapse or Progressive Disease: requires any one or more of the following:
	Increase of ≥25% from baseline in Serum M-component and/or (the absolute increase must be ≥0.5 g/dl)[b]
	Urine M-component and/or (the absolute increase must be ≥200 mg/24 h
Progressive disease[a]To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)	Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dl.
	Bone marrow plasma cell percentage: the absolute % must be ≥10%[c]
	Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
	Development of hypercalcemia (corrected serum calcium> 11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse (i.e., progressive disease requiring re-treatment or alternate treatment)[a]	Clinical relapse or progressive disease requires one or more of:
	Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)[b] It is not used in calculation of time to progression or progression-free

Relapse subcategory	*Relapse criteria*
	survival but is listed here as something that can be reported optionally or for use in clinical practice
	1. Development of new soft tissue plasmacytomas or bone lesions
	2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
	3. Hypercalcemia (>11.5 mg/dl) [2.65 mmol/l]
	4. Decrease in hemoglobin of $\geq$2 g/dl [1.25 mmol/l] (see Table 3 for further details)
	5. Rise in serum creatinine by 2 mg/dl or more [177 μmol/l or more]
Relapse from CR[a](To be used only if the end point studied is DFS)[d]	Any one or more of the following:
	Reappearance of serum or urine M-protein by immunofixation or electrophoresis
	Development of $\geq$5% plasma cells in the bone marrow[c]
	Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see below)

Abbreviations: CR, complete response; DFS, disease-free survival.

[a] All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.

[b] For progressive disease, serum M-component increases of $\geq$1 gm/dl are sufficient to define relapse if starting M-component is $\geq$5 g/dl.

[c] Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

[d] For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

16.11 APPENDIX XI: LIST (NON EXHAUSTIVE) OF DRUGS AND OTHER SUBSTANCES INTERFERING WITH CYTOCHROME P450 3A4 AND 2A6 (CYP3A4 AND CYP2A6)

Strong CYP3A4 interfering agents are prohibited (in bold and underlined). A strong inhibitor increases the AUC of a substrate for a given CYP by ≥5-fold or > 80% decrease in clearance. A **strong inducer** decreases the AUC of a substrate for a given CYP by ≥ 80%.

CYP3A4 inducers	**CYP3A4 inhibitors**	
avasimibe	**boceprevir**	atazanavir
carbamazepine	**clarithromycin**	amiodarone
phenytoin	**conivaptan**	amprenavir
rifampicin	**grapefruit juice**[1]	aprepitant
St John's wort[1]	**indinavir**	cimetidine
amobarbital	**itraconazole**	cyclosporine
dexamethasone	**ketoconazole**	darunavir
efavirenz	**lopinavir**	delavirdine
felbamate	**mibefradil**	diltiazem
nevirapine	**nefazodone**	erythromycin
omeprazole	**nelfinavir**	fluconazole
phenobarbital	**posaconazole**	fosamprenavir
pioglitazone	**ritonavir**	imatinib
primidone	**saquinavir**	miconazole
rifabutin	**telaprevir**	suboxone
tamoxifen	**telithromycin**	verapamil
troglitazone	**tipranavir**	
	voriconazole	

CYP2A6 inducers	**CYP2A6 inhibitors**	**Other CYP2A6 substrates**
phenobarbital	grapefruit juice	coumarin
rifampicin	ketoconazole	halothane
	methoxsalen	losigamone
	pilocarpine	methoxyflurane
	tranylcypromine	nicotine
		quinoline
		SM-12502
		valproic acid

1. Preparation-dependent

16.12 APPENDIX XII: GUIDANCE FOR POTENTIAL DRUG-INDUCED LIVER INJURY (DILI)I

1.1.1 Purpose

The purpose of this document is to provide guidance to enable the investigator/study coordinator to provide clinical follow-up and systematically gather and report data on potential DILI. The data collected will be used by the Sponsor to create narratives for regulatory agency reporting.

1.1.2 Introduction

Hepatotoxicity is injury or damage to the liver that may be associated with impaired liver function (Navarro and Senior 2006). Drug-induced hepatotoxicity is one of the most common causes of termination of drug development, a major reason for refusal of market authorization and for restricted use, and the single most important cause of the withdrawal of market authorization for products (Björnsson and Olsson 2005). Thus, drug-induced hepatotoxicity is a major concern during the discovery, development to post-authorization phases of the product life cycle (excerpted from Draft Guidance Document, Hepatotoxicity of Health Products, Ministry of Public Health, Canada, December 2010).

As stated in the United States Food and Drug Administration (FDA) “Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation”; hepatocellular injury (usually detected by serum aminotransferase elevations [AT]) can be caused by drugs that rarely, if ever, cause severe DILI (e.g., aspirin, tacrine, statins, and heparin), as well as by drugs that do cause such injury. The frequency of serum AT elevations also is not a good indicator of a potential for severe DILI because drugs such as tacrine (not a cause of severe DILI) can cause AT elevations in as many as 50 percent of patients. Very high levels of observed ATs may be a somewhat better indicator of potential for severe DILI, but the most specific indicator is evidence of altered liver function accompanying or promptly following evidence of hepatocellular injury.

The single clearest (most specific) predictor found to date of a drug’s potential for severe hepatotoxicity, is the occurrence of hepatocellular injury (AT elevation) accompanied by increased serum total bilirubin (TBL) not explained by any other cause, such as viral hepatitis or exposure to other hepatotoxins, and without evidence of cholestasis, together with an increased incidence of AT elevations in the overall trial population compared to control. Increased plasma prothrombin time, or its international normalized ratio (INR), a consequence of reduced hepatic production of Vitamin K-dependent clotting factors, is another potentially useful measure of liver function that might suggest the potential for severe liver injury.

Recognition of the importance of altered liver function, in addition to liver injury, began with Hyman Zimmerman’s observation that drug-induced hepatocellular injury (i.e., AT elevation) accompanied by jaundice (i.e., TBL elevation) had a poor prognosis, with a 10 to 50 percent mortality from acute liver failure (in pretransplantation days) (Zimmerman 1978, 1999). This became known as "Hy's Law". This document describes the recommended process for monitoring and evaluation of patients meeting the laboratory criteria for potential DILI defined as:

- an elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and

- an elevated TBL lab value that is greater than or equal to two times (2X) ULN and
- at the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,

as a result of within-protocol-specific testing or unscheduled testing.

The protocol identifies these laboratory criteria for potential DILI as ECIs. ECIs are selected adverse experiences that must be reported to the Sponsor within 24 hours. The Principal Investigator should record these ECIs on the Adverse Experience CRFs and complete pertinent adverse experience fields as outlined in the Data Entry Guidelines (DEGs).

1.1.3 Close Observation Recommendations

The following steps should be taken when a patient is observed to have an elevated AST or ALT lab value that is greater than or equal to 3X ULN and an elevated TBL lab value that is greater than or equal to 2X ULN and, at the same time, an ALP lab value that is less than 2X ULN, as a result of within-protocol-specific testing or unscheduled testing. In addition, close monitoring of isolated bilirubin increases greater than 2X ULN will be required.

Initiate **close observation**, defined below, and continue performing **follow-up to resolution**.

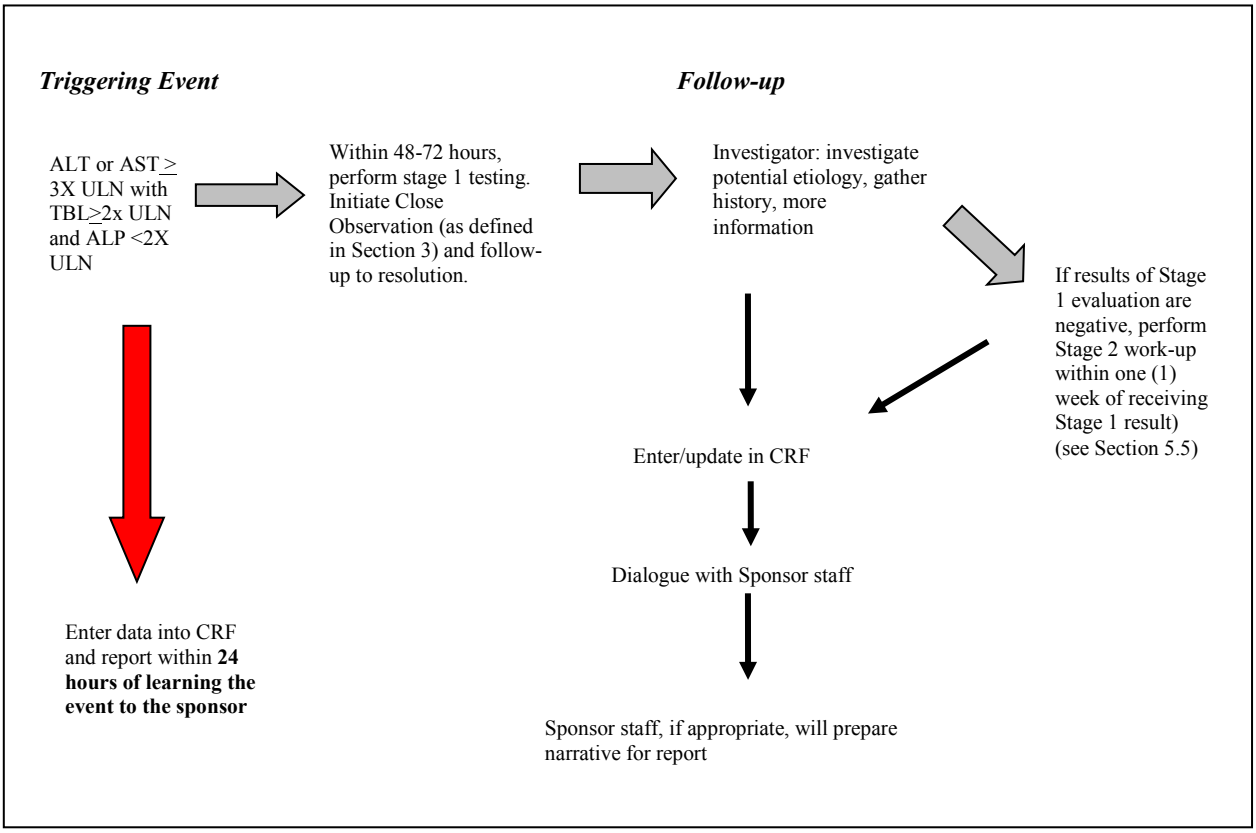
Close observation is defined as follows:

- Repeat liver enzyme and serum bilirubin tests two (2) or three (3) times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and the patient is asymptomatic.
    - For patients with *isolated* bilirubin elevations greater than 2X ULN, repeat serum bilirubin tests every 2 weeks until the bilirubin returns to normal or baseline.
- Obtain a more detailed history of symptoms and prior or concurrent diseases. (See Section 16.5).
- Obtain a history of concomitant medication use (including prescription and nonprescription medications, herbal and other dietary supplements), alcohol use, recreational drug use and special diets. (See Section 16.5 for details.)
- Obtain a history of exposure to chemical agents or other environmental toxins.
- Obtain additional history and complete Stage 1 work-up to attempt to rule out other potential causes of the transaminase elevation, including but not limited to the following: acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease. (See Section 16.5.5 for details.)
- Consider gastroenterology or hepatology consultation.

In general, treatment with study therapy should be stopped if the laboratory criteria for potential DILI are met. Please refer to the specific discontinuation criteria in the protocol as appropriate.

1.1.4 Hepatic Assessment Flow Chart

Hepatic Assessment Flow Chart



1.1.5 Factors to Consider in Assessing Potential DILI

When there is a potential DILI, it is important to thoroughly assess the patient's history, hepatic risk factors, clinical condition and hepatic function until resolution (normal or baseline levels).

Answers to the following questions should be recorded in source documents and in appropriate CRFs as outlined in the DEGs.

1.1.5.1 Study Medication

Considerations should include the following: What was the time interval between administration of study medication and the laboratory abnormality(ies)? What is the status of study medication use: Continuing? Interrupted? Discontinued? Was the patient re-challenged with study medication?

1.1.5.2 Treatment

Record any concomitant treatments.

1.1.5.3 Signs and Symptoms (associated with the potential DILI event)

Does the patient have a concomitant illness? Does the patient currently exhibit signs or symptoms of hepatitis/DILI? What are the patient's signs and symptoms (see examples below)? What are the pertinent findings from medical history, physical/laboratory examination (e.g., fatigue, nausea, vomiting, right upper

quadrant pain or tenderness, fever, rash, and/or eosinophilia > 5%, hepatomegaly, splenomegaly, etc.) that could suggest DILI?

Category	Examples of Signs and Symptoms
Blood/lymphatic	Eosinophilia, coagulopathy, susceptibility to bleeding/bruising
Circulatory	Varicose veins, edema
Constitutional	Fever, fatigue, malaise, weight gain, other (identify).
Digestive/hepatic	Anorexia, diarrhea, bloody or black stool, light-colored stools, nausea, vomiting, hematemesis, upper quadrant abdominal pain, upper quadrant tenderness, hepatomegaly, jaundice, splenomegaly, ascites, cholestasis
Endocrine/reproductive	Loss of libido
Integumentary	Rash, pruritus
Muscular	Myalgia
Nervous	Changes in mental status or level of consciousness
Urinary	Dark urine

1.1.5.4 Confounding Variables

What are the relevant medical history and findings? What is the differential diagnosis? What risk factors does the patient have for hepatic injury? (See examples below.) Provide onset of risk factor and duration.

Category	Examples of Confounding Variables
Subject medical history	Autoimmune disorder, cancer, Gilbert's syndrome, obesity, Wilson's disease
Substance use/abuse	Alcohol, illegal drugs, illegal intravenous (IV) drugs
Prior & Concomitant Medications: Review all non-study medications and therapies, including: over-the-counter (OTC), as well as prescription. Ask the patient to bring products/packaging to site and review contents.	History of recent concomitant acetaminophen (APAP)/paracetamol use, excessive nonsteroidal anti-inflammatory drug (NSAID) intake, use of non-study drug or therapy that can cause liver damage or idiosyncratic adverse drug reactions
Herbal and nutritional supplements	Herbal, complementary therapies, and nutritional supplements
Adulteration of products	History of previous exposure to the product or a similar product, and information on potential contamination or adulteration of products
Chemical exposure	Occupational or in other situations
Potential exposure to infectious agents	Infectious hepatitis, transfusion, travel, tattoos, sexually transmitted diseases, new sexual partner, shared needles
Special Diet	Special diet started since randomization
Other	Recent physical trauma, excessive exercise, or other prolonged physical exertion
Family history	Autoimmune disorder, cancer, Gilbert's syndrome, Wilson's disease

1.1.5.5 Evaluation algorithm for potential DILI if there are no other clinical reasons

Note: If clear etiology for the laboratory abnormalities has been confirmed, Stage 1 and 2 testing may not be required. In this case, consultation with the Sponsor is recommended.

Stage 1 work-up should be performed within 48-72 hours:

- ALT
- AST
- Bilirubin: total, direct, indirect
- Alkaline phosphatase (ALP)
- Prothrombin Time (PT)/international normalized ratio (INR)
- Creatine phosphokinase (CPK)
- Manual eosinophil count (if automated count was elevated)
- Toxicology screen for drugs of abuse (including ethanol) and for acetaminophen/paracetamol level should also be sent. Investigators may order additional toxicology tests as clinically indicated.
- Evaluate patient for the following signs and symptoms: fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, rash.
- Obtain the following additional history and assessment for associated risk/confounding factors:
  - More detailed history of symptoms and prior or concurrent illness
  - Aminotransferase values obtained prior to the study or administration of study medication
  - Alcohol consumption (recent and historical)
  - Acetaminophen (APAP)/paracetamol use
  - New prescription, concomitant, or non-prescription (including herbal and other dietary supplements) medications
  - Unusual foods (e.g. mushrooms) or special diets. Consumption of seasonal foods.
  - Recreational drug use
  - Prior history of liver injury or disease, including but not limited to Gilbert's syndrome, autoimmune disorders, cancer, Wilson's disease, NASH, alcoholic or infectious hepatitis, biliary tract disease, hypoxic/ischemic hepatopathy
  - Obesity/abdominal adiposity (record weight, height, and waist circumference)
  - Occupational history and history of exposure to chemical agents or other environmental toxins
  - Recent travel (last three [3] years)
  - Transfusion history

- Perform the following required laboratory tests**:**
  - Albumin
  - Eosinophils (percentage and absolute; obtain manual count if automated count is elevated)
  - Viral hepatitis serologies (obtain appropriate consent prior to testing, if required locally)
    - A (IgG, IgM)
    - B (HepBs Ag, Hep Bs Ab, Hep Bc Ab, Hep Be Ag)
    - C (RNA)
    - D (requires concomitant hepatitis B infection)

- Human Immunodeficiency Virus (HIV) testing (obtain appropriate consent prior to testing, if required locally)
- Evaluation for autoimmune hepatitis:
  - Serum gamma globulin levels/ serum protein electrophoresis
  - Antinuclear antibody (ANA)
  - Anti-mitochondrial antibody (if ALP or TBL >ULN)
- If AST/ALT ratio is greater than one (1) with suspicions of increased alcohol intake, perform the following:
  - Gamma-glutamyl transferase (GGT)

- Obtain a right upper quadrant ultrasound

Stage 2 work-up tests should be drawn within one (1) week of receiving the Stage 1 work-up results and the results of Stage 1 evaluation are negative.

Note: A specific test may be performed earlier if the investigator determines that the clinical presentation leads to a certain diagnosis.

Stage 2 work-up:

- Perform the following laboratory tests:
  - Genetic test for Gilbert's disease if there is a suspicious history. Ensure appropriate patient consent is obtained for this test.
  - Viral hepatitis E (IgG and IgM, obtain appropriate consent prior to testing, if required locally)
  - Anti-smooth muscle antibody
  - Anti-liver-kidney microsomal antibody
  - Anti-soluble liver antigen
  - Serologies for the following:
    - Cytomegalovirus (CMV) (IgG, IgM)
    - Epstein-Barr Virus (EBV) (IgG, IgM)
    - Herpes simplex
    - Toxoplasmosis
    - Varicella
    - Parvovirus
  - Ceruloplasmin
  - Serum alpha-1 anti-trypsin
  - Genetic test for hemochromatosis. Ensure appropriate patient consent is obtained for this test
  - Iron Studies:
    - serum ferritin,
    - serum iron,
    - total iron binding capacity
- Consider referral to hepatologist/gastroenterologist
- Consider screen for celiac disease and cystic fibrosis if clinically indicated

- If laboratory tests or ultrasound evidence of biliary tract obstruction, consider obtaining Endoscopic Retrograde Cholangiopancreatography (ERCP) or Magnetic Resonance Cholangiopancreatography (MRCP)

If applicable, request copies of hospital discharge summaries, consultation reports, pathology reports, special studies (e.g. imaging or biopsy), etc.

1.1.5.6 Potential diagnosis

What diagnosis do the history, clinical course, and laboratory tests suggest?

1.1.5.7 Overall clinical impression

What are the investigator's overall clinical impressions (e.g., differential diagnosis, potential alternative causes)?

1.1.5.8 Treatment plan

What is the plan for treatment and follow-up?

1.1.6 Contacts

If you have any questions, please refer to your Sponsor contact list for the following personnel:

- PPD (OTD)
- PPD (Merck)

1.1.7 References

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