PROTOCOL

TITLE:	**OPEN-LABEL, DOSE ESCALATION/EXPANSION PHASE IB STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND CLINICAL ACTIVITY OF THE COMBINATION OF RO6870810 AND VENETOCLAX, WITH OR WITHOUT RITUXIMAB, IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)**
PROTOCOL NUMBER:	NP39461
VERSION:	1
EUDRACT NUMBER:	2017-000357-39
IND NUMBER:	123718
TEST PRODUCT:	RO6870810 Venetoclax (GDC-0199; ABT-199; RO5537382) Rituximab (RO0452294)
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
Graf Finckenstein, Friedrich (gra	Company Signatory (Clinical)	28-Apr-2017 19:59:02

PROTOCOL ACCEPTANCE FORM

TITLE:	**OPEN-LABEL, DOSE ESCALATION/EXPANSION PHASE IB STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND CLINICAL ACTIVITY OF THE COMBINATION OF RO6870810 AND VENETOCLAX, WITH OR WITHOUT RITUXIMAB, IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)**
PROTOCOL NUMBER:	NP39461
VERSION NUMBER:	1
EUDRACT NUMBER:	2017-000357-39
IND NUMBER:	123718
TEST PRODUCT:	RO6870810 Venetoclax (GDC-0199; ABT-199; RO5537382) Rituximab (RO045-2294)
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please keep the signed original form in your study files, and return a copy to your local Study Monitor.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABC	Activated B-cell
ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ASCT	Autologous stem cell transplantation
AUC	Area under the curve
BCL	B-cell lymphoma
BET	Bromodomain and extra terminal
BP	Blood pressure
BRCP	Breast cancer resistance protein
BRD	Bromodomain
CBC	Complete blood count
CrCl	Creatinine clearance
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CL	Clearance
CL/F	Apparent clearance
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CNS	Central nervous system
COO	Cell-of-origin
CR	Complete response
CrCl	Creatinine clearance
CRO	Contract research organization
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P450
DDI	Drug-drug interaction
DFS	Disease-free survival

DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicities
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
ECHOP	Etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone
ECOG	Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EFS	Event-free survival
EOT	End of treatment
ESF	Eligibility screening form
EU	European Commission
FDA	Food and Drug Administration
[18F]-FDG PET	Fluoro deoxy glucose positron emission tomography
FEV	Forced expiratory volume
FFPE	Formaldehyde fixed-paraffin-embedded
FL	Follicular lymphoma
FSH	Follicle-stimulating hormone
GCB	Germinal center B-cell
GPA	Granulomatosis with polyangiitis
HBsAg	Hepatitis B surface antigen
HBcAb	Total hepatitis B core antibody
HcAb	Hepatitis C antibody
HCV	Hepatitis C
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICR	Independent radiological central review
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
INR	International normalized ratio
IPI	International prognostic index
IRB	Institutional Review Board
IRR	Infusion-related reaction

ISR	Injection site reaction
IUD	Intrauterine device
IV	Intravenous
IxRS	Interactive (voice/web) response system
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LPLO	Last participant, last observation
LTFU	Long-Term Follow-Up
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCL	Mantle cell lymphoma
MCV	Mean corpuscular volume
MDA	Maximum dose administered
MD	Multiple doses
MDS	Myelodysplastic syndrome
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No-observed-adverse-effect level
NHL	Non-Hodgkin’s lymphoma
NMC	NUT-midline carcinoma
NSAESI	Non-serious adverse event of special interest
NUT	Nuclear protein in testis
NYHA	New York Heart Association
OATP1B1	Organic anion transporting polypeptide 1B1
ORR	Objective response rates
OS	Overall survival
OTC	Over-the-counter
PD	Pharmacodynamic
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time

RDW	Red cell distribution width
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcB	QT corrected for heart rate using the Bazett's correction factor
QTcF	QT corrected for heart rate using the Fridericia correction factor
RBC	Red blood cell
RBR	Research Biosample Repository
RD	Recommended dose
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RR	RR interval
R/R	Relapsed or refractory
SAE	Serious adverse event
SC	Subcutaneous
SD	Single dose
SGOT	Aspartate transaminase
SGPT	Alanine transaminase
SoA	Schedule of activities
SOC	Scientific Oversight Committee
SUSAR	Suspected unexpected serious adverse reactions
t_{max}	Time of maximum concentration observed
TBNK	T- and B-cell and natural killer cell
TLC	Total lung capacity
TLS	Tumor lysis syndrome
TTE	Transthoracic echocardiograms
ULN	Upper limit of normal
US	United States
V_d	Volume of distribution
VAS	Visual analogue scale
V_d/F	Apparent volume of distribution
WBC	White blood cell
WGS	Whole genome sequencing

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**OPEN-LABEL, DOSE ESCALATION/EXPANSION PHASE IB STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND CLINICAL ACTIVITY OF THE COMBINATION OF RO6870810 AND VENETOCLAX, WITH OR WITHOUT RITUXIMAB, IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)**
SHORT TITLE	Open-Label, Dose Escalation/Expansion Phase Ib Study to Evaluate RO6870810 and Venetoclax, with or w/o Rituximab in Patients with R/R DLBCL
PROTOCOL NUMBER:	NP39461
VERSION:	1
TEST PRODUCT:	RO6870810 Venetoclax (GDC-0199; ABT-199; RO5537382) Rituximab (RO045-2294)
PHASE:	Ib

RATIONALE

Patients with diffuse large B-cell lymphoma (DLBCL), relapsed or refractory (R/R) to first-line therapies (including those with Myelocytomatosis oncogene [MYC] and B-cell lymphoma 2 [BCL2] gene aberrations), who are not candidates for high dose therapy with autologous stem cell transplantation (ASCT), or relapse after ASCT, represent a poor prognosis group and may be well suited for the investigative medicine combination proposed for this study.

Bromodomains (BRD) and extra-terminal (BET) proteins (including BRD4) are epigenetic regulators that have been identified as transcription co-factors (activators) for several key oncogenic drivers in DLBCL, including MYC and BCL2. BET protein inhibitors such as RO6870810 therefore may offer novel therapeutic options in DLBCL. Venetoclax, a small molecule BCL2 inhibitor, has demonstrated single agent responses in R/R DLBCL. Additionally, rituximab has demonstrated efficacy in the relapsed setting and may enhance activity within this combination regimen.

This Phase Ib study will therefore explore RO6870810 given with venetoclax (i.e. RO6870810/venetoclax), with or without rituximab co-administration, in patients with R/R DLBCL following failure of a first-line regimen containing an anti-CD20-directed agent. Participants will include patients not considered eligible for curative intent following their first or subsequent regimens, as determined by their treating physician.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Dose-escalation – Part 1:	
• To determine the safety, tolerability and maximum-tolerated doses (MTD) or maximum doses administered (MDA) of RO6870810/venetoclax, and RO6870810/venetoclax co-administered with rituximab.	• Incidence and nature of dose-limiting toxicities (DLTs). • Incidence, nature and severity of adverse events (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events[NCI CTCAE] v4.03). • Changes in vital signs, physical examination and electrocardiogram (ECG) findings, and clinical laboratory results during and following combination administration of RO6870810/venetoclax, and RO6870810/venetoclax co-administered with rituximab.
Recommended Dose [RD] Expansion – Part 2:	
• To evaluate the preliminary clinical activity of RO6870810/venetoclax or RO6870810/venetoclax co-administered with rituximab by estimating complete response rate.	• Complete response (CR) rate, as determined by independent radiological central review (ICR) using modified Lugano response criteria.
Secondary	
Safety – Part 2:	
• To characterize the overall safety profile of RO6870810/venetoclax or RO6870810/venetoclax co-administered with rituximab in this population.	• Incidence, nature and severity of adverse events (graded according to the NCI CTCAE v4.03). • Changes in vital signs, physical examination and ECG findings, and clinical laboratory results during and following combination administration of RO6870810/venetoclax, and RO6870810/venetoclax co-administered with rituximab.
Pharmacokinetic – Parts 1 & 2:	
• To further characterize the pharmacokinetics (PK) of RO6870810 and its potential metabolites when given as RO6870810/venetoclax and RO6870810/venetoclax co-administered with rituximab. In addition, PK of venetoclax and PK of rituximab will be characterized in the double or triple combinations.	• Maximum concentration (C_{max}). • Trough concentration (C_{min}, for all three analytes) pre-dose at Cycle 2 and at the beginning of every subsequent even-number cycles where PK data are available. • Time of maximum concentration (t_{max}). • Clearance (CL) or apparent clearance (CL/F) for drugs given extra-vascular. • Volume of distribution (V_d) or apparent volume of distribution (V_d/F) for drugs given extra-vascular. • Area under the curve (AUC). • Half-life ($t_{1/2}$).

OBJECTIVES AND ENDPOINTS (Cont.)

Objectives	Endpoints
Secondary (Cont.)	
Immunogenicity – Parts 1 & 2: • To characterize the immunogenicity of rituximab when given concomitantly with RO6870810/venetoclax.	• Incidence of anti-drug antibodies (ADA) against rituximab and possible correlation with PK, pharmacodynamics (PD), safety, and efficacy parameters.
Efficacy – Parts 1 & 2: • To evaluate the preliminary clinical activity of RO6870810/venetoclax or RO6870810/venetoclax co-administered with rituximab as per Investigator assessment and ICR.	• CR rate, as determined by the Investigator based on the modified Lugano response criteria. • CR rate, as determined by the ICR and by the Investigator on the basis of CT scans alone. • Objective response rate (defined as a CR or partial response [PR]), as determined by the ICR and by the Investigator on the basis of modified Lugano response criteria. • Objective response rate (defined as a CR or PR), as determined by the ICR and by the Investigator on the basis of CT scans alone. • Duration of response (DoR), defined as the time from the first occurrence of a documented objective response (CR or PR) to the time of progression as determined by the ICR and by the Investigator on the basis of CT scans alone or death from any cause, whichever occurs first. • Progression free survival (PFS), defined as the time from first study treatment to the first occurrence of disease progression or relapse as determined by the Investigator on the basis of CT scans alone or death, whichever occurs first. • Event free survival (EFS), as determined by Investigator on the basis of CT scans alone, initiation of new anti-lymphoma therapy, or death from any cause, whichever occurs first. • Disease-free survival (DFS), defined, among participants who achieve a CR, as the time from the first occurrence of a documented CR to relapse as determined by the Investigator on the basis of CT scans alone, or death from any cause whichever occurs first. Overall survival (OS), defined as the time from initiation of study treatment to death from any cause.

OVERALL DESIGN

Study Design

This study is an open-label Phase Ib study consisting of two sequential parts designed to evaluate the safety, tolerability and clinical activity of RO6870810 in combination with venetoclax and when co-administered with rituximab in participants with R/R DLBCL.

Treatment Groups and Duration

The investigational medicinal products (IMPs) are RO6870810, venetoclax and rituximab.

Study treatments will include RO6870810 in combination with venetoclax or in combination with venetoclax and rituximab. Venetoclax will be administered first orally with a meal, immediately followed by RO6870810. Rituximab will be administered last, when applicable. Treatments will be as follows:

- RO6870810 at planned doses of 0.30, 0.45, or 0.65 mg/kg will be injected subcutaneously (SC) daily (QD) for 14 days within a 21-day cycle.
- Venetoclax at planned doses of 400, 600 or 800 mg will be given per os (PO) QD, for 21 days per cycle. Participants considered to be at high risk for tumor lysis syndrome (TLS) may start treatment with a 3-week dose ramp-up with a weekly dose increase of venetoclax during the first cycle. They may also be hospitalized at the Investigator's discretion for 24-hours after study drug dosing.
- Rituximab at a dose of 375 mg/ m^2 body surface area [BSA]) will be administered intravenously (IV), every week during the first cycle and on Day 1 of all cycles thereafter. Premedication is required prior to administration and all participants should receive prophylaxis for TLS (consisting of appropriate hydration, agents to reduce uric acid and review of laboratory results for clinically significant abnormalities).

This study will consist of a dose-escalation part followed by a dose-expansion part.

Part 1 - Initially, a dose-escalation scheme will be employed to evaluate the combination of RO6870810/ venetoclax. Subsequently, the recommended dose (RD) of RO6870810/venetoclax co-administered with rituximab will be established for further evaluation in Part 2. If this triple regimen is not well tolerated, the RD of the dual combination of RO6870810/venetoclax will be evaluated in Part 2.

Participants will be enrolled in a cohort in a staggered manner, with a minimum of 7 days between the first-dosed and subsequent participants in a given cohort. Up to 6 cohorts with a minimum of 3 participants is planned for the double dose escalation in Part 1.

Furthermore, participants may be enrolled in up to 3 additional cohorts (termed Cohorts 4a, 5a and 6a) to receive RO6870810/venetoclax co-administered with rituximab.

Part 2 – The dose-expansion part will open once the RDs of RO6870810/venetoclax co-administered with rituximab have been established in Part 1. Participants will receive treatments until they experience unacceptable toxicities or until documented disease progression. If, in the opinion of the Investigator, a patient is experiencing clinical benefit despite disease progression, the patient may continue study treatments following discussion with the sponsor.

Dose-Limiting Toxicities

The DLT definitions reflect the known and expected toxicities of RO6870810, venetoclax, and rituximab. Adverse events will be graded according to NCI CTCAE v.4.03.

A DLT is defined as any of the toxicities that (1) occurs during the first 21 days of the first cycle for which the patient receives the full intended combination doses and number of administrations, (2) is considered to be related to study treatment by the Investigator, and (3) is not attributed to disease progression or another clearly identifiable cause.

The full intended number of administrations will be as follows: at least 10 doses of RO6870810, 15 doses of venetoclax, and full doses of rituximab (when applicable).

DLT equivalent toxicities that occur outside of the DLT period during the second and the third treatment cycles will be considered for the determination of the overall tolerability and safety profile and MTD, if reached. During the dose escalation period in Part 1, participants who withdraw before the end of the DLT period for reasons other than DLTs will be replaced to ensure that all participants in each cohort have been assessed for the full DLT period prior to moving to the next dose level. Infusion-related reactions (IRR) due to rituximab that require removal of participants from the study will be considered as treatment limiting toxicities and not DLTs.

Dose modification following DLT will be permitted for RO6870810/venetoclax. Dose modification will not be permitted for participants receiving the triple regimen; however, discontinuation of rituximab treatment may be considered.

DLT Definitions:

Hematological toxicities

- Grade 4 neutropenia lasting $>$ 7 consecutive days despite growth factor support.
- Grade $\geq$ 3 neutropenia associated with single body temperature $>$ 38.3°C or sustained body temperature $\geq$ 38°C for $>$ 1 hour, and/or with documented infection.
- Grade 4 thrombocytopenia lasting $>$ 10 days. Grade 3 or 4 thrombocytopenia requiring platelet transfusion or associated with significant bleeding episodes per Investigator's judgment.
- Grade $\geq$ 3 anemia with hemolysis.

Injection-site reaction (ISR)

- Grade $\geq$ 3 skin ulceration or 'other' skin and subcutaneous tissue disorders considered related to the subcutaneous injection of RO6870810.

Grade $\geq$ 3 non-hematological toxicity, excluding

- Grade 3 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) that resolve to Grade $\leq$ 2 within 3 days.
- Grade 3 bilirubin elevations that resolve to Grade $\leq$ 2 within 3 days.
- Grade 3 laboratory TLS without any clinical manifestation (i.e., creatinine $\geq$ 1.5 $\times$ upper limit of normal (ULN) and/or renal dysfunction, cardiac arrhythmias, seizures, or sudden death).
- Grade 3 nausea, vomiting or diarrhea including their clinical sequelae (e.g., fluid loss with subsequent dehydration, electrolyte loss (sodium, potassium, magnesium, chloride) occurring with sub-optimal prophylactic and curative treatment and that are responding to supportive care within 72 hours.
- A study treatment-related Grade 3 fever that resolves to Grade $\leq$ 2 within 7 days.
- Fatigue, asthenia and malaise that resolve to Grade $\leq$ 2 within 1 week.
- Grade 3 neuropathy if the participant began therapy with a Grade 2 neuropathy at baseline and the neuropathy has not resolved to Grade 2 within 21 days.
- Alopecia.
- IRRs due to rituximab.

Length of Study

For each participant the study will be divided as follows:

- Screening: Up to 28 days prior to first study drug administration.
- Treatment Period: Participants will be treated at the defined doses until disease progression, unacceptable toxicities or withdrawal from treatment for other reasons, or death.

- Safety Follow-Up visit: will be 28 (± 3) days after the last dose of RO6870810 or venetoclax for participants receiving the dual combination. For participants receiving the triple combination, the safety and follow-up visit will take place 28 (± 3) days after the last dose of RO6870810 or venetoclax, or 44 (± 3) days after the last dose of rituximab, depending on which study drug was last administered.
- Long-Term Follow-Up (LTFU): After the safety follow-up visit, participants will be followed every 12 weeks (± 7days) from the date of last dose of study drug for up to 1 year after last dose (unless due to premature termination of the study) to collect data on disease progression, subsequent treatments and survival status. LTFU can be done by telephone call.

End of Study

The end of the study is defined as the date when the last participant last observation is expected to occur. The study will continue until the last data point from the last participant (OS) is recorded in eCRF; or up to twelve months after the last participant discontinued treatment and all participants have completed the safety follow-up visit, whichever comes first.

Independent Radiological Central Review

An independent radiological central review (ICR) will be performed by a vendor to assess all participants for response on the basis of imaging and bone marrow biopsy results. Specific methodological and operational details will be specified in a separate ICR Charter.

PARTICIPANT POPULATION

The participants of this study are patients with DLBCL, relapsed or refractory to first-line or subsequent therapies, who have received at least one prior chemotherapy regimen that included an anti-CD20 targeting agent, with no curative option as determined by the Investigator.

NUMBER OF PARTICIPANTS

In Part 1, maximally six cohorts (Cohorts 1-6) with 3-6 participants per cohort, i.e., a total of 18–36 participants, may be required to establish the MTD/MDA of the RO6870810/venetoclax combination. An additional 9-18 participants may be enrolled in the cohorts of participants administered RO6870810, venetoclax and rituximab. In Part 2 of the study, up to 40 participants will be enrolled.

INCLUSION/EXCLUSION CRITERIA

INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Informed Consent

1. Able and willing to provide written informed consent and to comply with the study protocol according to ICH and local regulations.

Age

2. Age ≥ 18 years.

Type of Participants and Disease Characteristics

3. Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2.
4. Life expectancy > 3 months as per investigator's assessment.
5. Patients with DLBCL relapsed or refractory to ≥ 1 course of chemotherapy including an anti-CD20 monoclonal antibody, and not eligible for ASCT (including due to chemorefractory disease). Patients with transformed follicular lymphoma (FL) are eligible, provided DLBCL histology is biopsy-confirmed prior to study entry and a treatment regimen as described above has been administered. The Sponsor retains the option to limit the number of participants enrolled with transformed FL.
6. Acceptable liver function, as follows:
    - Total bilirubin ≤ 2 times ULN. (Patients with known Gilbert's disease who has serum bilirubin ≤ 3 × ULN may be enrolled).

- Aspartate transaminase (AST; SGOT), alanine transaminase (ALT; SGPT) ≤ 2.5 × ULN, (or ≤ 5 × ULN if tumor involvement (liver) is present).
- Gamma-glutamyl transferase (GGT) alkaline phosphatase ≤ 2.5 × ULN.

7. Acceptable renal function, as follows:
   - Creatinine clearance (CrCl) calculated by Cockroft-Gault formula of ≥ 60 mL/min.
8. Acceptable hematologic status (growth factors cannot be used within the previous 7 days):
   - Absolute neutrophil count (ANC) ≥ 1000 cells/μL
   - Hemoglobin ≥ 9 g/dL
   - Platelet count ≥ 75,000 (platelets/μL)
9. Serum calcium (corrected for albumin) level at or below the ULN (treatment of hypercalcemia is allowed and patient may enroll if hypercalcemia returns to normal with standard treatment).
10. Acceptable coagulation status:
    - Prothrombin time/ partial thromboplastin time (PT/PTT) ≤ 1.2 × ULN (unless receiving anticoagulation therapy, if receiving anticoagulation therapy, eligibility will be based upon international normalized ratio [INR]).
    - INR ≤ 1.6 (unless receiving anticoagulation therapy).
    - If receiving warfarin: INR ≤ 3.0 and no active bleeding (i.e., no bleeding within 14 days prior to first dose of study therapy).

Sex

11. Male and/or female participants

    The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. For all participants, the reliability of sexual abstinence must be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

    a) Male Participants

- During the treatment period and for 4 months after the last dose of RO6870810/venetoclax or for 12 months after last dose of treatment of RO6870810/venetoclax co-administered with rituximab, agreement to:
  - Refrain from donating sperm;
  - Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom with partners who are women of childbearing potential (WOCBP) or pregnant female partners to avoid exposing the embryo.

b) Female Participants

- Women of non-childbearing potential.
- Women of childbearing potential who:
  - Agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for 2 months after the last dose of RO6870810/venetoclax or for 12 months after last dose of treatment of RO6870810/venetoclax co-administered with rituximab. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal occlusion, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices (see Appendix 6).
  - Have a negative pregnancy test (blood) within the 7 days prior to the first study drug administration.

EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Current CNS lymphoma or leptomeningeal infiltration.
2. New York Heart Association (NYHA) Class III or IV cardiac disease, myocardial infarction, within the past 6 months, unstable arrhythmia, or known pericardial disease.
3. Fredericia-corrected QT interval (QTcF) $>$ 470 msec (female) or $>$ 450 msec (male), or history of congenital long QT syndrome.
4. Any electrocardiogram (ECG) abnormality, which in the opinion of the Investigator would preclude safe participation in the study.
5. Active, uncontrolled bacterial, viral, or fungal infections, within 7 days of study entry requiring systemic therapy.
6. Known clinically important respiratory impairment (e.g., diagnosis of obstructive lung disease including patients with forced expiratory volume in the first 1 second of expiration [FEV1] $<$ 60% of the predicted value, diagnosis of restrictive lung disease including patients with total lung capacity [TLC] $<$ 60% of predicted value or history of idiopathic pulmonary fibrosis).
7. Grade $\geq$ 3 sensory or motor neuropathy.
8. Any Grade $>$ 1 (according to the NCI CTCAE 4.03) adverse reaction unresolved from previous treatments and not readily managed and controlled with supportive care. The presence of alopecia (any grade) or Grade $\leq$ 2 peripheral neuropathy without pain is allowed.
9. Serious non-malignant disease that could compromise protocol objectives in the opinion of the Investigator and/or the Sponsor.
10. History of progressive multifocal leukoencephalopathy (PML).
11. History of other malignancy within 2 years prior to screening, except for ductal carcinoma in situ not requiring chemotherapy, appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, low-grade, localized prostate cancer (Gleason score $\leq$ 7) not requiring treatment or appropriately treated Stage I uterine cancer.
12. Completion of ASCT within 100 days prior to Day 1 of Cycle1.
13. Prior standard or investigational anti-cancer therapy as specified below:
    - Radio-immunoconjugate within 12 weeks prior to Day 1 of Cycle 1.
    - Monoclonal antibody or antibody-drug conjugate (ADC) therapy within 3 weeks prior to Day 1 of Cycle 1.
    - Radiotherapy, chemotherapy, or targeted small-molecule therapy within 2 weeks prior to Day 1 of Cycle 1.
14. History of major solid organ transplant (i.e., heart, lungs, liver and kidney).
15. History of an allogeneic bone marrow transplant.
16. Major surgical procedure within 28 days prior to Day 1 of Cycle 1.

Prior/Concomitant Therapy

17. Treatment with systemic corticosteroids $\geq$ 20 mg/day prednisone or equivalent, for non-lymphoma treatment reasons. For lower acceptable doses, documentation of a stable dose for at least 4 weeks prior to Day 1 of Cycle 1 is required. If corticosteroid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, up to 100 mg/day of prednisone or equivalent can be given for a maximum of 5 days. In such cases, all screening tumor assessments should be completed after completion of the steroid, but prior to start of first study treatment.
18. Treatment with strong to moderate CYP3A inhibitors or moderate CYP3A inducers within 7 days prior to the first dose of study treatment.

19. Treatment with strong CYP3A inducers within 14 days prior to the first dose of study treatment of RO6870810/venetoclax.
20. Consumption of grapefruits, grapefruit products, Seville oranges (including marmalade that contains Seville oranges), or star fruit within 3 days prior to the first dose of venetoclax.

Prior/Concurrent Clinical Trial Experience

21. Patients who are currently receiving any other investigational agent or have received an investigational agent within 30 days or 5 half-lives prior to study entry, whichever is longer.
22. Prior treatment with small molecule BET family inhibitor.

Diagnostic Assessments

23. Known to be human immunodeficiency virus (HIV) positive.
24. Presence of positive test results for hepatitis B surface antigen (HBsAg) or hepatitis C antibodies (HcAb) (for patients receiving regimen including rituximab)
    - Patients who are positive for HcAb must be negative for HCV by PCR to be eligible for study participations.
    - Patients with occult or prior HBV infection (defined as positive total hepatitis B core antibody [HBcAb] and negative HBsAg) may be included if HBV DNA is undetectable. These patients must be willing to undergo monthly DNA testing.

Other Exclusions

25. Pregnant or breastfeeding female.
26. Significant allergy to a biological pharmaceutical therapy that, in the opinion of the Investigator, poses an increased risk to the participant.
27. Uncontrolled cancer pain. Participants requiring pain medication must be on a stable regimen at study entry. Symptomatic lesions amenable to palliative radiotherapy should be treated prior to enrollment.
28. History of severe allergic or anaphylactic reaction to humanized or murine monoclonal antibodies (for participants receiving regimen including rituximab).
29. Known sensitivity or allergy to murine products or any component of RO6870810, venetoclax, or rituximab.

CONCOMITANT MEDICATIONS

Patients should be treated for all concomitant medical conditions and adverse events according to accepted standards of medical care at the discretion of the Investigator.

Participants who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use with caution (e.g., oral contraceptives are weak CYP3A4 inhibitors).

For therapies prohibited during the study and for at least 28 days prior to initiation of study treatment, please see the exclusion criteria. Traditional herbal medicines should not be administered.

1.2 SCHEMATIC OF STUDY DESIGN

An overview of Study NP39461 is provided in Figure 1. For details of Part 1 design, dose-escalation, and possible doses combinations for Cohorts 4a-6a, see Figure 2.

Figure 1 Overview of Study NP39461

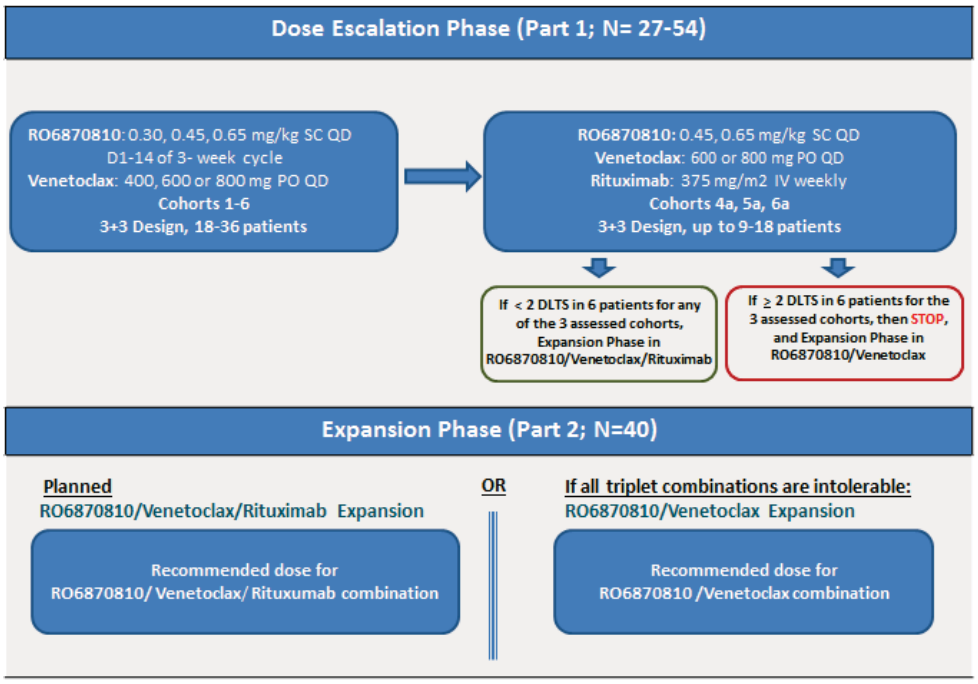
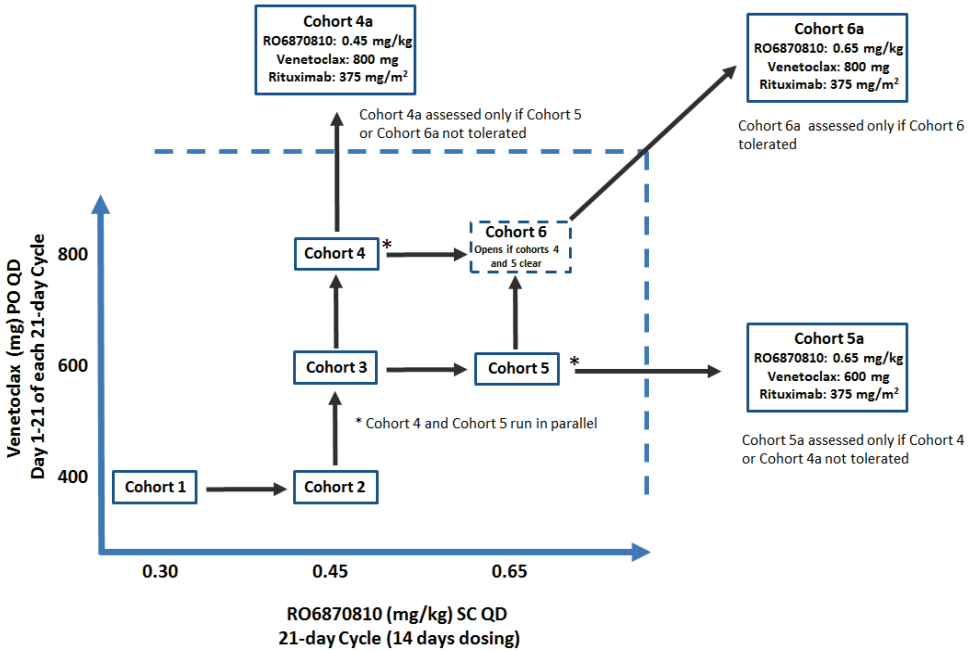


Figure 2 Part 1: Dose Escalation Design



1.3 SCHEDULE OF ACTIVITIES

The schedule of the activities (SoA) is provided in Table 1, Table 2, Table 3 and Table 4.

Table 1 Schedule of Activities – Part 1: RO6870810/Venetoclax, Main Table

Cycle	Screening	Cycle 1[1]				Cycle 2[2]			Cycle 3[2]		Cycle 4[2]		Cycle 5 and all other odd cycles[2]	Cycle 6 and all other even cycles[2]	End of Treatment Visit[19]	Safety Follow Up Visit[20]	Long Term Follow Up Visit[21]
Day	D-28 to D-1	Day 1	Day 2	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 1			
Assessments																	
Informed Consent	X																
Eligibility	X																
Demography	X																
Medical History	X																
B Symptoms[3]	X																
Ann Arbor Staging, IPI	X																
Physical Examination	X															X	
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Anthropometric Measurements[5]	X					X			X		X		X	X	X		
ECOG Performance Status	X	X				X			X		X		X	X	X		
ECG-12 lead[6]	X[6]	7		X	7	2	2	2	2	2	2	2	2	2	X		
Hematology[7]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood Chemistry[7]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation[7]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[7]	X	X				X			X		X		X	X	X	X	
Hepatitis B and C Testing[8]	X																
Serum beta-2 microglobulin (SB2M)		X													X		
Pregnancy Test[9]	X	X				X			X		X		X	X		X	
Pulmonary Fuction (Spirometry)[10]	X																
Echocardiogram[11]	X																
FDG PET Scan[12]	X					X					X			X[14]	X		
Diagnostic Quality CT Scan[12,13]	X					X					X			X[14]	X		
Tumor Assessment	X					X					X			X	X		
Bone Marrow Biopsy/ Aspirate[15]	X								X								
RO6870810 Injection[16]		X		X	X	X	X		X		X		X	X			
Venetoclax Administration[17]		X	X	X	X	X	X	X	X	X	X	X	X	X			
RO6870810 PK Blood Sample		8	X	X	8	2		X			2	X		2	X		
Venetoclax PK Blood Sample		2	X	X	5	X		X			X	X		X	X		
Whole Blood DNA		3	X		X												
Whole Blood RNA		3	X		X												
Blood MRD Assessment		X			X					X			X	X	X		
Flow Cytometry A TBNK Blood Sample		X	X	X	X												
Flow Cytometry B CD11b Blood Sample		X	X	X	X												
Tumor Biopsy (Archival or Fresh)[18]	X																
Post-study Therapy																X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[22]
Previous and Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1 Schedule of Activities – Part 1: RO6870810/Venetoclax, Main Table (cont.)

1. Each cycle is 21 days.
2. Cycle 2 onwards: The start of each cycle must occur within ± 3 days.
3. Unexplained fever > 38°C, night sweats, unexplained weight loss > 10% of body weight over 6 months.
4. Vital Signs will include blood pressure, heart rate, respiratory rate and temperature. See the Detailed Table for all time-points.
5. Height measurement to be performed at screening only. The weight on Cycle 1 Day 1 will be used to determine the dose of RO6870810. Weight must be performed prior to dosing at Day 1 of every cycle and if there is a difference of ± 10% from the Cycle 1 Day 1 weight then, the dose of RO6870810 must be re-calculated.
6. Triplicate ECGs are required at Screening to confirm eligibility. All other ECGs taken during the course of the study will be single ECGs; however, if clinically-required, triplicate ECGs can be done at any time. When ECGs are scheduled at the same time as blood draws, ECGs must be performed first. See the Detailed Table for all time-points.
7. See Appendix 5. If screening tests are performed within 3 days of Cycle 1 Day1, they do not need to be repeated at this visit.
8. Hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), and hepatitis C antibody serology (also HCV and RNA by polymerase chain reaction [PCR] if the patient is HCV antibody positive) required. For hepatitis B core antibody–positive patients, the HBV-DNA titer should be determined using real-time PCR at baseline and monthly until at least 12 months after the last treatment cycle.
9. Blood pregnancy test within 7 days prior to study treatment. Pregnancy test (urine or blood) should be done at Day 1 of each cycle and as clinically indicated during the study.
10. Participants will be carefully monitored for respiratory changes and/or complaints and those participants who develop new onset pulmonary signs or symptoms (e.g., dyspnea, pleuritic chest pain) during the treatment period should have their dose interrupted and supportive measures provided until a proper complete evaluation, including physical examination, repeat pulmonary function test and/or clinically indicated imaging, can be performed and toxicity returns to Grade ≤ 1.
11. Participants who develop new onset cardiac signs or symptoms (e.g., chest pain, pericardial rub on exam, suggestive ECG changes or new pericardial effusion) during the treatment period should have their dose interrupted and supportive measures provided until a proper complete evaluation, including physical examination, clinically indicated imaging (e.g., chest x-ray, transthoracic echocardiogram) and additional laboratory (e.g., cardiac enzymes and markers of inflammation), can be performed and toxicity returns to Grade ≤ 1.
12. During study conduct, response assessments will be determined on the basis of both FDG-PET/CT and diagnostic quality CT scans and bone marrow examinations (if appropriate), by using the modified Lugano Criteria (Cheson et al 2014; see Appendix 8).
13. If contrast is contraindicated (e.g., in participants with contrast allergy or impaired renal function), CT or CT portion of the PET/CT scans without contrast are permitted provided they permit consistent and precise measurement of target lesions during the study treatment period. CT scans should include chest, abdomen, and pelvic scans. CT scans of the neck should be included if clinically indicated (i.e., if evidence of disease upon physical examination) and must be repeated throughout the study if there is disease involvement at baseline.

Table 1 Schedule of Activities – Part 1: RO6870810/Venetoclax, Main Table (cont.)

14. FDG-PET/CT and diagnostic quality CT scan should be performed at Screening, after Cycle 1 (Day1 of Cycle 2, prior to dosing), after Cycle 3 (Day 1 of Cycle 4, prior to dosing), every 4 cycles (C8, C12 and so on) and at End of Treatment. There is a window of –5 days for scans.
15. For participants with bone marrow involvement at Screening, a repeat assessment will be performed whenever there is radiologic evidence of complete response or if clinically indicated (e.g., if there is a clinical suspicion of progressive disease in the bone marrow with no radiologic evidence of progression). Additional bone marrow assessments may be performed at the discretion of the Investigator. Each time it is performed a portion must be sent for exploratory biomarker testing. Unsuccessful attempts at marrow aspiration will not be considered a protocol violation.
16. RO6870810 will be administered as a subcutaneous injection (SC). In Cycle 1, it will be given on Day 1 (omitted on Day 2) and then, every day from Day 3 through to Day 15 inclusive. Starting at Cycle 2: SC administration from Day 1 to Day 14.
17. Venetoclax will be taken orally once a day (QD).
18. Archival tumor tissue specimen will be acceptable within approximately 3 months prior to Day 1 of Cycle 1 if no intervening treatment during that time and prior to first study treatment administration.
19. The End of Treatment visit will be performed when the participant stopped treatment due to progression of disease, toxicities, or other reason.
20. A safety follow-up will take place 28 (± 3) days after the last dose of RO6870810 or venetoclax, whichever was received last.
21. Long-Term Follow-Up: after discontinuation of study treatment and completion of the End of Treatment study visit, participants will be followed every 12 weeks (± 7days) from the date of last dose of study drug for disease progression, subsequent treatment and survival status. After confirmed disease progression, LTFU can be done by telephone call.
22. During the follow-up periods, serious adverse events considered related to study treatment are to be reported (see Section 8.3.1).

Table 2 Schedule of Activities – Part 1: RO6870810/Venetoclax, Detailed Table

Cycle	Day	Scheduled Time (h)	Vital Signs	ECG-12 lead	RO6870810 PK Blood Sample[1, 2]	Venetoclax PK Blood Sample[1, 2]	Whole Blood DNA	Whole Blood RNA	Blood MRD Assessment	Flow Cytometry A TBNK Blood Sample	Flow Cytometry B CD11b Blood Sample
Cycle 1	Day 1	Predose	X	X	X	X	X	X	X	X	X
		0.25		X	X						
		0.5		X	X						
		1		X	X						
		2		X	X						
		4		X	X						
		6		X	X	X	X	X			
		8			X		X	X			
	Day 2	24	X		X	X	X	X		X	X
	Day 8	Predose	X	X	X	X				X	X
	Day 15	Predose	X	X	X	X					
		0.25		X	X						
		0.5		X	X						
		1		X	X						
		2		X	X	X					
		4		X	X	X					
		6		X	X	X					
		8			X	X	X	X	X	X	X
Cycle 2	Day 1	Predose	X	X	X	X					
		0.25		X	X						
	Day 8	Predose	X	X							
		0.25		X							
	Day 15	Predose	X	X	X	X					
		0.25		X							
Cycle 3	Day 1	Predose	X	X							
		0.25		X							
	Day 15	Predose	X	X					X		
		0.25		X							
Cycle 4	Day 1	Predose	X	X	X	X					
		0.25		X	X						
	Day 15	Predose	X	X	X	X					
		0.25		X							
Cycle 5 and all other odd cycles	Day 1	Predose	X	X					X		
		0.25		X							
Cycle 6 and all other even cycles	Day 1	Predose	X	X	X	X			X		
		0.25		X	X						
End of Treatment			X		X[2]	X[2]			X		

1. Each time-point is relative to the start of treatment administration for the specified drug.
2. End of Treatment PK samples are optional.

Table 3 Schedule of Activities – Part 1 & Part 2: RO6870810/Venetoclax/Rituximab, Main Table

Cycle	Screening	Cycle 1[1]				Cycle 2[2]			Cycle 3[2]		Cycle 4[2]		Cycle 5 and all other odd cycles[2]	Cycle 6 and all other even cycles[2]	End of Treatment Visit[20]	Safety Follow Up Visit[21]	Long Term Follow Up Visit[22]
Day	D-28 to D-1	Day 1	Day 2	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 1			
Assessments																	
Informed Consent	X																
Eligibility	X																
Demography	X																
Medical History	X																
B Symptoms[3]	X																
Ann Arbor Staging, IPI	X																
Physical Examination	X															X	
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Anthropometric Measurements[5]	X					X			X		X		X	X	X		
ECOG Performance Status	X	X				X			X		X		X	X	X		
ECG-12 lead[6]	X[6]	7		X	7	2	2	X	2		2		2	2	X		
Hematology[7]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood Chemistry[7]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation[7]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[7]	X	X				X			X		X		X	X	X	X	
Hepatitis B and C Testing[8]	X																
Serum beta-2 microglobulin (SB2M)		X															
Pregnancy Test[9]	X	X				X			X		X		X	X		X	
Pulmonary Fuction (Spirometry)[10]	X																
Echocardiogram[11]	X																
FDG PET Scan[12]	X					X					X			X[14]	X		
Diagnostic Quality CT Scan[12,13]	X					X					X			X[14]	X		
Tumor Assessment	X					X					X			X	X		
Bone Marrow Biopsy/ Aspirate[15]	X								X								
RO6870810 Injection[16]		X		X	X	X	X		X		X		X	X			
Venetoclax Administration[17]		X	X	X	X	X	X	X	X	X	X	X	X	X			
Rituximab Infusion[18]		X[18]		X	X	X			X		X		X	X			
RO6870810 PK Blood Sample		8	X	X	8	2		X	2	X	2	X		2	X		
Venetoclax PK Blood Sample		2	X	X	4	X		X	X	X	X	X		X	X		
Rituximab PK/ADA Blood		2				X			X		X			X	X	X	
Whole Blood DNA		3	X	X	X												
Whole Blood RNA		3	X	X	X												
Blood MRD Assessment		X			X					X			X	X	X		
Flow Cytometry A TBNK Blood Sample		X	X	X	X												
Flow Cytometry B CD11b Blood Sample		X	X	X	X												
Tumor Biopsy (Archival or Fresh)[19]	X																
Post-study Therapy																X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[23]
Previous and Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 3 Schedule of Activities – Part 1 & Part 2: RO6870810/Venetoclax/Rituximab, Main Table (cont.)

1. Each cycle is 21 days.
2. Cycle 2 onwards: The start of each cycle must occur within ± 3 days.
3. Unexplained fever > 38°C, night sweats, unexplained weight loss > 10% of body weight over 6 months.
4. Vital signs will include blood pressure, heart rate, respiratory rate and temperature. See the Detailed Table for all time-points.
5. Height measurement to be performed at screening only. The weight on Cycle 1 Day 1 will be used to determine the dose of RO6870810. Weight must be performed prior to dosing at Day 1 of every cycle and if there is a difference of ± 10% from the Cycle 1 Day 1 weight then, the dose of RO6870810 must be re-calculated.
6. Triplicate ECGs are required at Screening to confirm eligibility. All other ECGs taken during the course of the study will be single ECGs; however, if clinically required, triplicate ECGs can be done at any time. When ECGs are scheduled at the same time as blood draws, ECGs must be performed first. See the Detailed Table for all time-points.
7. See Appendix 5. If screening tests are performed within 3 days of Cycle 1 Day1, they do not need to be repeated at this visit.
8. HBsAg, HBcAb, and hepatitis C antibody serology (also HCV and RNA by polymerase chain reaction [PCR] if the patient is HCV antibody positive) required. For hepatitis B core antibody–positive patients, the HBV-DNA titer should be determined using real-time PCR at baseline and monthly until at least 12 months after the last treatment cycle.
9. Blood pregnancy test within 7 days prior to study treatment. Pregnancy test (urine or blood) can be done anytime during the study if clinically indicated.
10. Participants will be carefully monitored for respiratory changes and/or complaints and those participants who develop new onset pulmonary signs or symptoms (e.g., dyspnea, pleuritic chest pain) during the treatment period should have their dose interrupted and supportive measures provided until a proper complete evaluation, including physical examination, repeat pulmonary function test and/or clinically indicated imaging, can be performed and toxicity returns to Grade ≤ 1.
11. Participants who develop new onset cardiac signs or symptoms (e.g., chest pain, pericardial rub on exam, suggestive ECG changes or new pericardial effusion) during the treatment period should have their dose interrupted and supportive measures provided until a proper complete evaluation, including physical examination, clinically indicated imaging (e.g., chest x-ray, transthoracic echocardiogram) and additional laboratory (e.g., cardiac enzymes and markers of inflammation), can be performed and toxicity returns to Grade ≤ 1.
12. During study conduct, response assessments will be determined on the basis of both FDG-PET/CT and diagnostic quality CT scans and bone marrow examinations (if appropriate), by using the modified Lugano Criteria (Cheson et al 2014; see Appendix 8).
13. If contrast is contraindicated (e.g., in participants with contrast allergy or impaired renal function), CT or CT portion of the PET/CT scans without contrast are permitted provided they permit consistent and precise measurement of target lesions during the study treatment period. CT scans should include chest, abdomen, and pelvic scans. CT scans of the neck should be included if clinically indicated (i.e., if evidence of disease upon physical examination) and must be repeated throughout the study if there is disease involvement at baseline.

Table 3 Schedule of Activities – Part 1 & Part 2: RO6870810/Venetoclax/Rituximab, Main Table (cont.)

14. FDG-PET/CT and diagnostic quality CT scan should be performed at Screening, after Cycle 1 (Day 1 of Cycle 2 prior to dosing), after Cycle 3 (Day 1 of Cycle 4, prior to dosing), every 4 cycles (C8, C12 and so on) and at End of Treatment. There is a window of –5 days for scans.
15. For participants with bone marrow involvement at Screening, a repeat assessment will be performed whenever there is radiologic evidence of complete response or if clinically indicated (e.g., if there is a clinical suspicion of progressive disease in the bone marrow with no radiologic evidence of progression). Additional bone marrow assessments may be performed at the discretion of the Investigator. Each time it is performed a portion must be sent for exploratory biomarker testing. Unsuccessful attempts at marrow aspiration will not be considered a protocol violation.
16. RO6870810 will be administered as a subcutaneous (SC) injection. In Cycle 1, it will be given on Day 1 (omitted on Day 2) and then, every day from Day 3 through to Day 15 inclusive. Starting at Cycle 2: SC administration from Day 1 to Day 14.
17. Venetoclax will be taken orally QD.
18. Rituximab will be administered as intravenous (IV) once a week (QW) in Cycle 1 and on Day 1 of each subsequent cycle starting at Cycle 2 at the recommended dose for non-Hodgkin's lymphoma (NHL) of 375 mg/m^2 body surface area (BSA). Participants at high risk for IRR or TLS complication may, at the Investigator's discretion, receive their initial dose (C1D1) of rituximab split over 2 consecutive days (e.g., 125 mg/m^2 on the first day, 250 mg/m^2 on the second day).
19. Archival tumor tissue specimen will be acceptable within approximately 3 months prior to Day 1 of Cycle 1 if no intervening treatment during that time and prior to first study treatment administration.
20. The End of Treatment visit will be performed when the participant stopped treatment due to progression of disease, toxicities, or other reason.
21. A safety follow-up will take place 28 (± 3) days after the last dose of RO6870810 or venetoclax, or 44 (±3) days after the last dose of rituximab whichever was received last.
22. Long-Term Follow-Up: after discontinuation of study treatment and completion of the End of Treatment study visit, participants will be followed every 12 weeks (±7days) from the date of last dose of study drug for disease progression, subsequent treatment and survival status. After confirmed disease progression, LTFU can be done by telephone call.
23. During the follow-up periods, serious adverse events considered related to study treatment are to be reported (see Section 8.3.1).

Table 4 Schedule of Activities – Part 1 & Part 2: RO6870810/Venetoclax/Rituximab, Detailed Table

Cycle	Day	Scheduled Time (h)	Vital Signs	ECG-12 lead	RO6870810 PK Blood Sample[1, 2]	Venetoclax PK Blood Sample[1, 2]	Rituximab PK/ADA Blood[1, 2]	Whole Blood DNA	Whole Blood RNA	Blood MRD Assessment	Flow Cytometry A TBNK Blood Sample	Flow Cytometry B CD11b Blood Sample
Cycle 1	Day 1	Predose	X	X	X	X	X	X	X	X	X	X
		0.25		X	X							
		0.5		X	X							
		1		X	X							
		2		X	X							
		4		X	X							
		6		X	X	X		X	X			
		8			X			X	X			
		EOI					X					
	Day 2	24	X		X	X		X	X		X	X
	Day 8	Predose	X	X	X	X		X	X		X	X
	Day 15	Predose	X	X	X	X						
		0.25		X	X							
		0.5		X	X							
		1		X	X							
		2		X	X	X						
		4		X	X	X						
		6		X	X	X						
		8			X			X	X	X	X	X
Cycle 2	Day 1	Predose	X	X	X	X	X					
		0.25		X	X							
	Day 8	Predose	X	X								
		0.25		X								
	Day 15	Predose	X	X	X	X						
Cycle 3	Day 1	Predose	X	X	X	X	X					
		0.25		X	X							
	Day 15	Predose	X		X	X				X		
Cycle 4	Day 1	Predose	X	X	X	X	X					
		0.25		X	X							
	Day 15	Predose			X	X						
Cycle 5 and all other odd cycles	Day 1	Predose	X	X						X		
		0.25		X								
Cycle 6 and all other even cycles	Day 1	Predose	X	X	X	X	X			X		
		0.25		X	X							
End of Treatment			X		X[2]	X[2]	X[2]			X		

1. Each time-point is relative to the start of treatment administration for the specified drug.
2. End of Treatment PK samples are optional.