ISRCTN17568633 https://doi.org/10.1186/ISRCTN17568633

A study to evaluate safety, interaction with the body (pharmacokinetics), and clinical activity of combination of RO6870810 and venetoclax, with or without rituximab, in participants with cancer of the white blood cells (lymphoma)

Submission date
12/11/2020

Recruitment status
No longer recruiting

Registration date
01/12/2020

Overall study status
Completed

Last Edited
16/03/2022

Condition category
Cancer

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims:
The B-cell lymphomas are types of lymphoma affecting B cells. Lymphomas are "blood cancers" in the lymph nodes. They develop more frequently in older adults and in immunocompromised individuals. B-cell lymphomas include both Hodgkin's lymphomas and most non-Hodgkin lymphomas.
This open-label, two-part study is designed to evaluate the safety, tolerability and clinical activity of RO6870810/venetoclax, with or without rituximab, in participants with relapsed /refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and/or high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (HGBL-DH/TH). Part 1 is a dose-escalation of RO6870810/venetoclax with or without rituximab. Part 2 will evaluate the preliminary clinical activity at the recommended triple combination doses and explore biomarker endpoints. If the triple regimen is not tolerated, the dual combination of RO6870810/venetoclax will be evaluated in Part 2

Who can participate?
Participants with relapsed/refractory DLBCL and/or high-Grade B-Cell lymphoma and/or high-grade B-Cell Lymphoma with MYC and/or BCL2 and/or BCL6

What does the study involve?
In Part 1, 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 are planned for the double dose escalation in Part 1.

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

The dose-expansion part will open once the RDs of RO6870810/venetoclax co-administered with rituximab have been established in Part 1. Part 2 will consist of two groups: Group 1 N=40 DLBCL participants. Group 2 N=40 DE-DLBCL (expression MYC 40%, BCL2 > 50%) and/or HGBL-DH/TH participants. 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.

Note that due to the early termination of this study, Part 2 was not conducted.

What are the possible benefits and risks of participating?
Patients with DLBCL (including DE-DLBCL) and HGBL-DH/TH who have relapsed or are refractory to first-line regimen and are not eligible for ASCT represent a group with a significant need for novel therapies to be developed. RO6870810, venetoclax, and rituximab have potential for independent anti-tumor effects, and other data suggest potential for synergistic benefit in relapsed or refractory DLBCL and/or HGBL-DH/TH participants.
Based on the safety profiles for RO6870810, venetoclax, and rituximab in B-cell NHL patients, there is potential for some overlapping toxicities. Combined administration of RO6870810 with venetoclax may enhance some of the toxicities associated with each compound, including neutropenia and associated complications, anemia, thrombocytopenia, gastrointestinal (GI) disorders (nausea, diarrhea, vomiting), and fatigue. TLS is a known risk when initiating treatment with venetoclax and to a lower extent with rituximab.

Considering the anticipated activity of the combination, the known safety profile of therapeutic agents and effective measures in place to mitigate and manage toxicities, it is believed that the overall benefit/risk assessment for this combination is favorable and justifies its exploration in relapsed and refractory DLBCL (including DE-DLBCL) and HGBL-DH/TH disease.

Where is the study run from?
Genentech Ltd. (USA)

When is the study starting and how long is it expected to run for?
December 2016 to July 2019

Who is funding the study?
F. Hoffmann-La Roche Ltd

Who is the main contact?
global-roche-genentech-trials@gene.com

Contact information

Type(s)
Public

Contact name
Dr Clinical Trials

Contact details
1 DNA Way
South San Francisco
United States of America
94080
+1 888-662-6728
global-roche-genentech-trials@gene.com

Additional identifiers

EudraCT/CTIS number
2017-000357-39

IRAS number

ClinicalTrials.gov number
NCT03255096

Secondary identifying numbers
NP39461

Study information

Scientific 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 and/or high–grade B cell lymphoma with MYC and/or BCL2 and/or BCL6 gene rearrangements

Study objectives
To evaluate the safety, tolerability and clinical activity of RO6870810 in combination with venetoclax and when co-administered with rituximab in participants with relapse/refractory (R /R) diffuse large B-cell lymphoma (DLBCL) and/or high-grade B-cell lymphoma with myelocytomatosis oncogene (MYC) and/or B-cell lymphoma 2 (BCL2) and/or B-cell lymphoma 6 (BCL6) gene rearrangements (HGBL-DH/TH).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 15/06/2017, Western Institutional Review Board (1019 39th Avenue SE, Suite 120, Pullayup, WA, 98374-2115, USA; +1 3602522500; no email address provided), ref: 20171189

Study design
Interventional non-randomized trial

Primary study design
Interventional

Secondary study design

Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet.

Health condition(s) or problem(s) studied
B-Cell Lymphoma

Interventions
Treatment assignment for both doublet and triplet dosing in Part 1 will be via slot allocation by the Sponsor. Participants will be assigned sequentially to treatment. When Cohorts 4 and 5 are both eligible for recruitment, open slots of Cohort 4 will be filled first. A screening request and approval process will ensure that the correct dose is selected and assigned for participant dosing.

Experimental: Dose Escalation Phase (Part 1)
Participants will receive either RO6870810 and venetoclax or RO6870810 and venetoclax along with rituximab until disease progression, unacceptable toxicities or withdrawal from treatment for other reasons, or death.
Drug: RO6870810
RO6870810 subcutaneously (SC) at dose of 0.30, 0.45, or 0.65 milligram per kilogram (mg/kg) on Days 1-14 of 21-day cycles.

Drug: Venetoclax
Frequency: venetoclax tablets orally at dose of 400, 600 or 800 mg once daily (QD) continuously for 21 days.

Drug: Rituximab
Frequency: rituximab intravenously (IV) at dose of 375 mg/m² weekly during the first 21-day cycle (C1) and on day 1 of each cycle thereafter.

Experimental: Expansion Phase (Part 2)
Participants will receive RO6870810 and venetoclax along with rituximab (or RO6870810 and venetoclax, if the combination of the 3 drugs is not tolerable) at a recommended dose established in dose escalation phase until disease progression, unacceptable toxicities or withdrawal from treatment for other reasons, or death.
Drug: RO6870810
Frequency: RO6870810 subcutaneously (SC) at dose of 0.30, 0.45, or 0.65 milligram per kilogram (mg/kg) on Days 1-14 of 21-day cycles.

Drug: Venetoclax
Frequency: venetoclax tablets orally at a dose of 400, 600 or 800 mg once daily (QD) continuously for 21 days.

Drug: Rituximab
Frequency: rituximab intravenously (IV) at dose of 375 mg/m² weekly during the first 21-day cycle (C1) and on day 1 of each cycle thereafter.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
RO6870810, venetoclax, rituximab

Primary outcome measure
1. Percentage of Participants With Dose-Limiting Toxiciities (DLT)- Part 1 [Time Frame: Cycle (C) 1 (21 days)]
DLT is defined as any of the toxicities- occurs within the first cycle for which the participant receives the full intended combination doses and number of administrations; is considered to be related to study treatment by the investigator; is not attributed to disease progression or another clearly identifiable cause.
2. Percentage of Participants With Adverse Events (AEs) - Part 1 [Time Frame: Up to 36 months]
An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
3. Percentage of Participants With Clinically Significant Changes in Vital Signs, Physical Examination, Clinical Laboratory Results and Electrocardiogram (ECG) Findings- Part 1 [Time Frame: Up to 36 months]
4. Complete Response (CR) Rate as Determined by Independent Radiological Central Review (ICR) Using Modified Lugano Response Criteria- Recommended Dose (RD) Expansion - Part 2 [Time Frame: Up to 36 months]
5. Overall Response (OR) Rate as Determined by Independent Radiological Central Review (ICR) Using Modified Lugano Response Criteria- RD Expansion - Part 2 [Time Frame: Up to 36 months]

Secondary outcome measures
1. Percentage of Participants With Adverse Events (AEs) - Part 2 [Time Frame: Up to 36 months]
An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
3. Percentage of Participants With Clinically Significant Changes in Vital Signs, Physical Examination, Clinical Laboratory Results and Electrocardiogram (ECG) Findings- Part 2 [Time Frame: Up to 36 months]
4. Maximum Concentration (Cmax) of RO6870810 and its Potential Metabolites- Part 1 and Part 2 [Time Frame: Pre-dose Day 1,8,15; 0.25,0.5,1,2,4,6,8 hour (h) post-dose Day 1, 15; Day 2 C1; Pre-dose Day 1,8,15; 0.25h post-dose Day 1,8 C2; Pre-dose Day 1,15 C4; 0.25h post-dose Day 1 C4; Pre-dose, 0.25h post-dose Day 1 of subsequent even Cycles (Up to 36 months)]
5. Trough Serum Concentration (Cmin) of RO6870810 and its Potential Metabolites- Part 1 and Part 2 [Time Frame: Pre-dose Cycle 2 and all other subsequent even Cycles (Up to 36 months)]
6. Time of Maximum Concentration (tmax) of RO6870810 and its Potential Metabolites- Part 1 and Part 2 [Time Frame: Pre-dose Day 1,8,15; 0.25,0.5,1,2,4,6,8 hour (h) post-dose Day 1, 15; Day 2 C1; Pre-dose Day 1,8,15; 0.25h post-dose Day 1,8 C2; Pre-dose Day 1,15 C4; 0.25h post-dose Day 1 C4; Pre-dose, 0.25h post-dose Day 1 of subsequent even Cycles (Up to 36 months)]

7. Clearance (CL) of RO6870810 and its Potential Metabolites- Part 1 and Part 2 [Time Frame: Pre-dose Day 1,8,15; 0.25,0.5,1,2,4,6,8 hour (h) post-dose Day 1, 15; Day 2 C1; Pre-dose Day 1,8,15; 0.25h post-dose Day 1,8 C2; Pre-dose Day 1,15 C4; 0.25h post-dose Day 1 C4; Pre-dose, 0.25h post-dose Day 1 of subsequent even Cycles (Up to 36 months)]
8. Volume of Distribution (Vd) of RO6870810 and its Potential Metabolites- Part 1 and Part 2 [Time Frame: Pre-dose Day 1,8,15; 0.25,0.5,1,2,4,6,8 hour (h) post-dose Day 1, 15; Day 2 C1; Pre-dose Day 1,8,15; 0.25h post-dose Day 1,8 C2; Pre-dose Day 1,15 C4; 0.25h post-dose Day 1 C4; Pre-dose, 0.25h post-dose Day 1 of subsequent even Cycles (Up to 36 months)]
9. Area Under the Curve (AUC) of RO6870810 and its Potential Metabolites- Part 1 and Part 2 [Time Frame: Pre-dose Day 1,8,15; 0.25,0.5,1,2,4,6,8 hour (h) post-dose Day 1, 15; Day 2 C1; Pre-dose Day 1,8,15; 0.25h post-dose Day 1,8 C2; Pre-dose Day 1,15 C4; 0.25h post-dose Day 1 C4; Pre-dose, 0.25h post-dose Day 1 of subsequent even Cycles (Up to 36 months)]
10. Complete Response (CR) Rate as Determined by the Investigator Based on the Modified Lugano Response Criteria- Part 1 and Part 2 [Time Frame: Up to 36 months]
11. Complete Response (CR) Rate, as Determined by the ICR and by the Investigator on the Basis of CT Scans Alone- Part 1 and Part 2 [Time Frame: Up to 36 months]
12. Objective Response Rate, as Determined by the ICR and by the Investigator on the Basis of Modified Lugano Response Criteria- Part 1 and Part 2 [Time Frame: Up to 36 months]
13. Objective Response Rate, as Determined by the ICR and by the Investigator on the Basis of CT Scans Alone- Part 1 and Part 2 [Time Frame: Up to 36 months]
14. Duration of Response (DoR)- Part 1 and Part 2 [Time Frame: Up to 36 months]
15. Progression-Free Survival (PFS)- Part 1 and Part 2 [Time Frame: Up to 36 months]
16. Event-Free Survival (EFS)- Part 1 and Part 2 [Time Frame: Up to 36 months]
17. Disease-Free Survival (DFS)- Part 1 and Part 2 [Time Frame: Up to 36 months]
18. Overall Survival (OS)- Part 1 and Part 2 [Time Frame: Up to 36 months]
19. Half-Life (t1/2) of RO6870810 and its Potential Metabolites- Part 1 and Part 2 [Time Frame: Pre-dose Day 1,8,15; 0.25,0.5,1,2,4,6,8 hour (h) post-dose Day 1, 15; Day 2 C1; Pre-dose Day 1,8,15; 0.25h post-dose Day 1,8 C2; Pre-dose Day 1,15 C4; 0.25h post-dose Day 1 C4; Pre-dose, 0.25h post-dose Day 1 of subsequent even Cycles (Up to 36 months)]
20. Percentage of Ant-Drug Antibodies (ADA) Against Rituximab - Part 1 and Part 2 [Time Frame: Pre-dose, End of Infusion Day 1 Cycle 1; Pre-dose Day 1 Cycle 2, 3, 4 , 6 and all other even Cycles (Up to 36 months)]

Overall study start date
01/12/2016

Completion date
03/07/2019

Eligibility

Key inclusion criteria
1. Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2.
2. Life expectancy >3 months as per investigator's assessment.

Part 1 and Part 2 Group 1:
3. Participants with diffuse large B-cell lymphoma (DLBCL) relapsed or refractory to ≥1 course of chemotherapy including an anti-CD20 monoclonal antibody, and not eligible for autologous stem cell transplantation (ASCT) (including due to chemorefractory disease). Participants with

transformed FL are eligible, provided DLBCL or HGBL-DH/TH 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.

Part 2, Group 2:
4. Patients identified with DE-DLBCL (expression MYC ≥40%, BCL2 >50%) and or HGBL-DH/TH, 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 DE-DLBCL and/or HGBL-DH/TH 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.

Part 1 and Part 2:
5. Willing to provide the protocol specified tumor biopsy(ies): at screening a fresh biopsy (if no archival biopsy tissue of less than 3 months prior to treatment and without intercurrent treatment is available);
Part 2:
6. Willing to provide an additional biopsy on Cycle 2 Day 15 (+2 days).

7. Acceptable liver function, as specified below:
7.1. Total bilirubin ≤2 times upper limit of normal (ULN). (Participants with known Gilbert's disease who has serum bilirubin ≤3 × ULN may be enrolled)
7.2. Aspartate transaminase (AST; SGOT), alanine transaminase (ALT; SGPT) ≤2.5 × ULN, (or ≤5 × ULN if tumor involvement (liver) is present)
7.3. Gamma-glutamyl transferase (GGT) alkaline phosphatase ≤2.5 × ULN
8. Acceptable renal function, as specified below:
8.1. Creatinine clearance (CrCl) calculated by Cockroft-Gault formula of ≥60 mL/min
9. Acceptable hematologic status (growth factors cannot be used within the previous 7 days), as specified below:
9.1. Absolute neutrophil count (ANC) ≥1000 cells/μL
9.2. Hemoglobin ≥9 g/dL
9.3. Platelet count ≥75,000 (platelets/μL)
9.4. Uncontrolled symptomatic hypercalcemia
10. Acceptable coagulation status, as specified below:
10.1. Prothrombin time (PT) and partial thromboplastin time (PTT) ≤1.2 × ULN (unless receiving anticoagulation therapy, if receiving anticoagulation therapy, eligibility will be based upon international normalized ratio [INR])
10.2. INR ≤1.6 (unless receiving anticoagulation therapy)
10.3. If receiving warfarin: INR ≤3.0 and no active bleeding (i.e., no bleeding within 14 days prior to first dose of study therapy).
11. Acceptable method of contraception

Participant type(s)
Patient

Age group
Mixed

Sex
Both

Target number of participants
39

Total final enrolment
39

Key exclusion criteria
1. Current central nervous system (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. Clinically important respiratory impairment
7. Grade ≥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
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 ≤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:
13.1. Radio-immunoconjugate 4 weeks or 5 half-lives, whichever is longer prior to Day 1 of Cycle 1
13.2. Monoclonal antibody or antibody-drug conjugate (ADC) therapy within 3 weeks prior to Day 1 of Cycle 1
13.3. Radiotherapy, chemotherapy, or targeted small-molecule therapy within 2 weeks prior to Day 1 of Cycle 1
13.4. CAR T-cell therapy 30 days 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
17. Treatment with systemic corticosteroids ≥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
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
21. Participants who are currently receiving any other investigational agent ((other than anti-cancer therapy as specified in exclusion criteria number 13) or have received an investigational agent within 30 days or 5 half-lives prior to Day 1 of Cycle 1, whichever is longer

22. Prior treatment with small molecule bromodomain and extra terminal (BET) family inhibitor
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 participants receiving regimen including rituximab)
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

Date of first enrolment
28/08/2017

Date of final enrolment
12/03/2019

Locations

Countries of recruitment
Australia

Denmark

Spain

United States of America

Study participating centre
City of Hope National Medical Center
Duarte
United States of America
91010

Study participating centre
Stanford Cancer Center
Stanford
United States of America
94305-5820

Study participating centre

Weill Cornell Medical College
New York
United States of America
10065

Study participating centre
Levine Cancer Institute
Charlotte
United States of America
28203

Study participating centre
Peter MacCallum Cancer Centre
Melbourne
Australia
3000

Study participating centre
Rigshospitalet
Hæmatologisk Klinik
København
Denmark
2100

Study participating centre
Hospital de la Santa Creu i Sant Pau
Servicio de Hematologia
Barcelona
Spain
08025

Study participating centre
Hospital Duran i Reynals
Servicio de Hematologia
Barcelona
Spain
08907

Study participating centre

START Madrid-FJD
Hospital Fundacion Jimenez Diaz
Madrid
Spain
28040

Sponsor information

Organisation
Genentech, Inc

Sponsor details
1 DNA Way
San Francisco
United States of America
94080
+1 888-662-6728
global-roche-genentech-trials@gene.com

Sponsor type
Industry

Website
www.roche.com/about_roche/roche_worldwide.htm

Funder(s)

Funder type
Industry

Funder Name
Genentech

Alternative Name(s)
Genentech, Inc., Genentech USA, Inc., Genentech USA

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Publication and dissemination plan
Planned publication in a peer-reviewed journal.

Intention to publish date
01/04/2021

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to participant-level data not being a regulatory requirement

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		23/11/2021	15/03/2022	Yes	No