ISRCTN04804337 https://doi.org/10.1186/ISRCTN04804337

Phase I dose-escalation study of oral administration of S55746 in patients with B-Cell Non-Hodgkin Lymphoma

Submission date 31/01/2014	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 21/03/2014	**Overall study status** Completed	
Last Edited 22/11/2019	**Condition category** Cancer	

Plain English summary of protocol
Not provided at time of registration and not expected to be available in the future

Contact information

Type(s)
Scientific

Contact name
Prof Steven Le Gouill

Contact details
Université de Nantes, Hotel-Dieu
Service dhématologie clinique
Place Alexis Ricordeau
Nantes
France
44093

Additional identifiers

ClinicalTrials.gov (NCT)
NCT02920697

Clinical Trials Information System (CTIS)
2013-003779-36

Protocol serial number
CL1-55746-001

Study information

Scientific Title
Phase I dose-escalation study of oral administration of the selective Bcl2 inhibitor S55746 in patients with refractory or relapsed Chronic Lymphocytic Leukaemia and B-Cell Non-Hodgkin Lymphoma

Study objectives
To determine the safety profile and tolerability and establish the recommended Phase II dose of S55746.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics approval was obtained before recruitment of the first participants

Primary study design
Interventional

Study design
Phase I dose-escalation study non-randomized trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Chronic Lymphocytic Leukaemia (CLL) and B-Cell Non-Hodgkin Lymphoma (NHL) including Follicular Lymphoma (FL) , Mantle Cell Lymphoma (MCL), Diffuse Large B-Cell Lymphoma, Small Lymphocytic Lymphoma, Marginal Zone Lymphoma and and Multiple myeloma (MM)

Interventions
Current interventions as of 13/01/2017:
Film-coated tablets containing 50 mg or 100mg of S55746.
This trial is a dose escalation trial. A panel of doses from 50 to 1500 mg could be tested.
Patients, who clearly benefiting from the study treatment, and in the opinion of the investigator it is in the patient's best interest to continue S 55746 may remain on study treatment until evidence of progressive disease, the occurrence of unacceptable toxicity, death or investigator's /patient's decision. Total number of cycles is at the discretion of the investigator.

Interventions from 07/09/2016 to 13/01/2017:
Film-coated tablets containing 50 mg or 100 mg of S55746.
This trial is a dose escalation trial. A modified version of the Continual Reassessment Method (mCRM) will be used for dose allocation process and performed in each arm independently. A panel of doses from 50 to 1500 mg could be tested according to the dose allocation process of the mCRM. Intermediate doses could be tested if needed. Patients will receive at least 2 cycles of treatment. Patients will receive the treatment(s) as long as, in the investigators opinion, they receive benefit according to tumour evaluation. Maximum number of cycles is at the discretion of the investigator.

Original interventions:
Film-coated tablets containing 50 mg or 100 mg of S55746.
This trial is a dose escalation trial. A modified version of the Continual Reassessment Method (mCRM) will be used for dose allocation process and performed in each arm independently. A panel of doses from 50 to 1000 mg could be tested according to the dose allocation process of the mCRM. Doses over 1000 mg and intermediate doses could be tested if needed. Patients will receive at least 2 cycles of treatment. Patients will receive the treatment(s) as long as, in the investigators opinion, they receive benefit according to tumour evaluation. Maximum number of cycles is at the discretion of the investigator.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
S55746

Primary outcome(s)
Current primary outcome measures as of 13/01/2017:
1. Dose Limiting Toxicities (DLTs) in cycle 1
2. Maximum Tolerated Dose, defined as the highest drug dosage that is unlikely (<25% posterior probability) to cause DLTs in more than 33% of the treated patients in the first cycle of S 055746 treatment
3. Safety profile at each visit, assessed by adverse events monitoring, laboratory tests, vital signs and performance status, clinical examination and ECG parameters

Previous primary outcome measures:
1. Maximum Tolerated Dose will be evaluated following Dose Limiting Toxicities at the end of cycle 1 for a given dose measured by adverse events monitoring
2. Safety profile at each visit measured by adverse events monitoring, ECG, cardiac function parameters, physical examination, performance status, vital signs and laboratory tests

Key secondary outcome(s)
Current secondary outcome measures as of 13/03/2018:
1. Pharmacokinetic parameters on blood sample during cycles 1 and 2
2. Preliminary anti-leukaemic activity of S 055746 throughout the study (blood, BMA and biopsy if available)

Previous secondary outcome measures from 13/01/2017 to 13/03/2018:
1. Pharmacokinetic parameters on blood sample during cycles 1 and 2
2. Pharmacodynamic parameters on blood, bone marrow aspiration (BMA) and biopsy if available from cycle 1 to cycle 3 and in any time in case of suspicion of disease progression
3. Optional pharmacogenomic analysis on Cycle 1, D1 pre-dose
4. Preliminary anti-leukaemic activity of S 055746 throughout the study (blood, BMA and biopsy if available)

Secondary outcome measures from 07/09/2016 to 13/01/2017:
1. Pharmacokinetic parameters on blood and urine samples during cycles 1 and 2
2. Assess the influence of food intake on PK profile of S55746

3. Pharmacodynamic parameters from blood samples during cycle 1 or from archival and optional biopsy in case of pharmacodynamic after objective response (complete or partial response)
4. Pharmacogenomic analysis on a blood sample during cycle 1
5. Tumour response based on clinical and radiological evaluation, throughout the study

Original secondary outcome measures:
1. Pharmacokinetics parameters on blood and urine samples during cycles 1 and 2
2. Pharmacodynamics parameters on blood samples and optional biopsy during cycle 1
3. Pharmacogenomics analysis on a blood sample during cycle 1
4. Tumour response based on clinical and radiological evaluation, throughout the study

Completion date
22/10/2018

Eligibility

Key inclusion criteria
Current inclusion criteria:
1. Women or men aged >/=18 years
2. Patients with a measurable histologically confirmed FL, MCL, DLBCL, SLL and MZL (Arm A) or patients with an evaluable immunophenotypically confirmed CLL (Arm B), or patients with a measurable MM t(11;14) (arm A expansion part) according to IMWG criteria
3. Previously treated relapsed after or refractory disease to standard treatments, and require treatment in the opinion of the investigator
4. Estimated life expectancy > 12 weeks
5. WHO performance status 0-2
6. Adequate bone marrow, renal and hepatic functions
7. No evidence or treatment for another malignancy within 2 years prior to study entry. Curatively treated non-melanoma skin cancer, in situ carcinoma, or cervical intraepithelial neoplasia is allowed
Additional eligibility criteria for food interaction cohort:
8. Patients with B¬cell NHL and defined as low risk of TLS according to published criteria (Cairo et al., 2010)
9. Patients not having taken any treatment likely to have an impact on S55746 absorption (antacids, antisecretory including H2-receptor antagonists and proton pump inhibitors) within 7 days prior to first S55746 intake

Previous inclusion criteria as of 13/01/2017:
1. Women or men aged >/=18 years
2. Patients with a measurable histologically confirmed FL, MCL, DLBCL, SLL and MZL (Arm A) or patients with an evaluable immunophenotypically confirmed CLL (Arm B), or patients with a measurable MM t(11;14) (arm A expansion part) according to IMWG criteria
3. Previously treated relapsed after or refractory disease to standard treatments, and require treatment in the opinion of the investigator
4. Estimated life expectancy > 12 weeks
5. WHO performance status 0-2
6. Adequate bone marrow, renal and hepatic functions, normal coagulation profile
7. No evidence or treatment for another malignancy within 2 years prior to study entry. Curatively treated non-melanoma skin cancer, in situ carcinoma, or cervical intraepithelial neoplasia is allowed

Additional eligibility criteria for food interaction cohort:
8. Patients with B¬cell NHL and defined as low risk of TLS according to published criteria (Cairo et al., 2010)
9. Patients not having taken any treatment likely to have an impact on S55746 absorption (antacids, antisecretory including H2-receptor antagonists and proton pump inhibitors) within 7 days prior to first S55746 intake

Inclusion criteria from 07/09/2016 to 13/01/2017:
1. Women or men aged >/=18 years
2. Patients with a measurable histologically confirmed FL, MCL, DLBCL, SLL and MZL (Arm A) or patients with an evaluable immunophenotypically confirmed CLL (Arm B), or patients with a measurable MM t(11;14) (arm A expansion part)according to IMWG criteria
3. Previously treated relapsed after or refractory disease to standard treatments, and require treatment in the opinion of the investigator
4. Estimated life expectancy > 12 weeks
5. WHO performance status 0-1
6. Adequate bone marrow, renal and hepatic functions, normal coagulation profile
7. No evidence or treatment for another malignancy within 2 years prior to study entry. Curatively treated non¬melanoma skin cancer, in situ carcinoma, or cervical intraepithelial neoplasia is allowed
Additional eligibility criteria for food interaction cohort:
8. Patients with B-cell NHL and defined as low risk of TLS according to published criteria (Cairo et al., 2010).
9. Patients not having taken any treatment likely to have an impact on S55746 absorption (antacids, antisecretory including H2-receptor antagonists and proton pump inhibitors) within 7 days prior to first S55746 intake.

Original inclusion criteria:
1. Women or men aged >/=18 years
2. Patients with a measurable histologically confirmed and previously treated FL, MCL, DLBCL, SLL and MZL or patients with an evaluable immunophenotypically confirmed and previously treated CLL
3. Relapsed after or refractory disease to standard treatments, and required treatment in the opinion of the investigator
4. Estimated life expectancy > 12 weeks
5. WHO performance status 0-1
6. Adequate bone marrow, renal and hepatic functions, normal coagulation profile
7. Kaliemia and calcemia within the local normal range
8. No evidence or treatment for another malignancy within 2 years prior to study entry. Curatively treated non-melanoma skin cancer, in situ carcinoma, or cervical intraepithelial neoplasia is allowed

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
Current inclusion criteria:
1. Previous treatment with a BH3 mimetic
2. Previous chemotherapy within 3 weeks before first intake
3. Radioimmunotherapy, radiotherapy within 8 weeks before first intake
4. Major surgery within 3 weeks before first day of study drug dosing
5. Corticosteroids > 20 mg prednisone equivalent per day within 7 days before first intake
6. Anticoagulant oral drugs, aspirin > 325 mg/day within 7 days prior to first S 55746 intake
7. Positive direct antiglobulin test (Coombs test) and haptoglobin below normal value
8. Prior allogenic stem cell transplant
9. Autologous stem cell transplant within 3 months before the first intake of S55746.
10. NHL patients diagnosed with Post¬Transplant Lymphoproliferative Disease, Burkitt's lymphoma, Burkitt-like lymphoma, or lymphoblastic lymphoma/leukaemia
11. Human immunodeficiency virus (HIV)
12. Known acute or chronic hepatitis B or hepatitis C
13. Impaired cardiac function
14. Medications known to prolong QTc interval
15. History or/ clinically suspicious for cancer-related CNS disease
16. Solitary extramedullary plasmacytoma
17. Strong or moderate CYP3A4 inhibitors/inducers (treatment, food or drink products)
18. Treatment highly metabolized by the CYP3A4 or CYP2D6 and/or substrates with a narrow therapeutic index, multienzyme and/or OATP substrates and/or P-gp, or herbal products.
19. Known hypersensitivity to rasburicase
20. G6PD deficiency and other cellular metabolic disorders known to cause haemolytic anaemia
21. Laboratory Signs of Tumor Lysis Syndrome
22. Patients receiving proton pump inhibitor

Previous exclusion criteria as of 13/01/2017:
1. Previous treatment with a BH3 mimetic
2. Previous chemotherapy within 3 weeks before first intake
3. Radioimmunotherapy, radiotherapy within 8 weeks before first intake
4. Major surgery within 3 weeks before first day of study drug dosing
5. Corticosteroids > 20 mg prednisone equivalent per day within 7 days before first intake
6. Anticoagulant oral drugs, aspirin > 325 mg/day
7. Positive direct antiglobulin test (Coombs test) and haptoglobin below normal value
8. Prior allogenic stem cell transplant
9. Autologous stem cell transplant within 3 months before the first intake of S55746.
10. NHL patients diagnosed with Post¬Transplant Lymphoproliferative Disease, Burkitt's lymphoma, Burkitt-like lymphoma, or lymphoblastic lymphoma/leukaemia
11. Human immunodeficiency virus (HIV)
12. Known acute or chronic hepatitis B or hepatitis C
13. Impaired cardiac function
14. Medications known to prolong QTc interval
15. History or/ clinically suspicious for cancer-related CNS disease
16. Solitary extramedullary plasmacytoma

17. Strong or moderate CYP3A4 inhibitors/inducers (treatment, food or drink products)
18. Treatment highly metabolized by the CYP3A4 or CYP2D6 and/or substrates with a narrow therapeutic index, multienzyme and/or OATP substrates or herbal products.
19. Known hypersensitivity to rasburicase
20. G6PD deficiency and other cellular metabolic disorders known to cause haemolytic anaemia
21. Laboratory Signs of Tumor Lysis Syndrome
22. Patients receiving proton pump inhibitor

Exclusion criteria from 07/09/2016 to 13/01/2017:
1. Previous treatment with a BH3 mimetic
2. Previous chemotherapy within 3 weeks before first intake
3. Radioimmunotherapy, radiotherapy within 8 weeks before first intake
4. Major surgery within 3 weeks before first day of study drug dosing
5. Corticosteroids > 20 mg prednisone equivalent per day within 7 days before first intake
6. Anticoagulant oral drugs, aspirin > 325 mg/day
7. Positive direct antiglobulin test (Coombs test) and haptoglobin below normal value
8. Prior allogenic stem cell transplant
9. NHL patients diagnosed with Post¬Transplant Lymphoproliferative Disease, Burkitt's lymphoma, Burkitt¬like lymphoma, or lymphoblastic lymphoma/leukaemia
10. Human immunodeficiency virus (HIV)
11. Known acute or chronic hepatitis B or hepatitis C
12. Impaired cardiac function
13. Medications known to prolong QTc interval
14. History or/ clinically suspicious for cancer¬related CNS disease
15.Solitary extramedullary plasmacytoma
16. Strong or moderate CYP3A4 inhibitors/inducers (treatment, food or drink products)
17. Treatment highly metabolized by the CYP3A4 or CYP2D6 and/or substrates with a narrow therapeutic index, multienzyme and/or OATP substrates or herbal products.
18. Known hypersensitivity to rasburicase
19. G6PD deficiency and other cellular metabolic disorders known to cause haemolytic anaemia
20. Laboratory Signs of Tumor Lysis Syndrome

Original exclusion criteria:
1. Previous treatment with a BH3 mimetic
2. Previous chemotherapy within 3 weeks before first intake
3. Radioimmunotherapy, radiotherapy within 8 weeks before first intake
4. Major surgery within 3 weeks before first day of study drug dosing
5. Corticosteroids > 20 mg prednisone equivalent per day within 7 days before first intake
6. Anticoagulant oral drugs, aspirin > 325 mg/day
7. Positive direct antiglobulin test (Coombs test) and haptoglobin below normal value
8. CLL and NHL prior allogenic stem cell transplant
9. Autologous stem cell transplant within 3 months before first intake
10. NHL patients diagnosed with Post-Transplant Lymphoproliferative Disease, Burkitt's lymphoma, Burkitt-like lymphoma, or lymphoblastic lymphoma/leukaemia
11. Human immunodeficiency virus (HIV)
12. Known acute or chronic hepatitis B or hepatitis C
13. Impaired cardiac function
14. Medications known to prolong QTc interval
15. History or/ clinically suspicious for cancer-related CNS disease
16. Treatment, food or drink products known to inhibit or induce CYP3A4

17. Treatment highly metabolized by the CYP3A4 and with a narrow therapeutic index
18. Known hypersensitivity to rasburicase
19. G6PD deficiency and other cellular metabolic disorders known to cause haemolytic anaemia

Date of first enrolment
26/03/2014

Date of final enrolment
26/12/2017

Locations

Countries of recruitment
United Kingdom

England

Australia

France

Germany

Hungary

Korea, South

Poland

Singapore

Study participating centre
University Hospital of Nantes (Université de Nantes)
Hôtel-Dieu
Nantes
France
44093

Study participating centre
Claude Huriez Hospital (Hospital Claude Huriez)
Rue Michel Polonowski
Lille
France
59000

Study participating centre
Gustave Roussy Institute of Oncology
114 Rue Edouard Vaillant
Villejuif
France
94800

Study participating centre
Lyon-Sud Hospital (Centre Hospitalier Lyon-Sud)
165 Chemin du Grand Revoyet
Pierre-Bénite
France
69310

Study participating centre
Schwabing Hospital
Kölner Platz 1
München
Germany
80804

Study participating centre
University Hospital of Ulm
Ulm
Germany
-

Study participating centre
University Hospital Carl Gustav Carus
Dresden
Germany
-

Study participating centre
National Cancer Center (NCC)
11 Hospital Drive
Singapore
169610

Study participating centre
National University Cancer Institute
Singapore
119074

Study participating centre
National Institute of Oncology
1122 Budapest Ráth György u. 7-9.
Hungary
-

Study participating centre
CRU Hungary Kft
Miskolc
Hungary
-

Study participating centre
Warsaw Institute of Oncology
ul. Roentgena 5
Warsaw
Poland
-

Study participating centre
Medical University of Warsaw
Żwirki i Wigury 61
Warszawa
Warsaw
Poland
-

Study participating centre
St. Mary's Hospital
Seoul
Korea, South
06591

Study participating centre

Severance Hospital
50-1 Yonsei-ro, Seodaemun-gu
Seoul
Korea, South
-

Study participating centre
University College London Hospitals
London
United Kingdom
-

Study participating centre
Freeman Hospital
Freeman Rd
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
The Alfred Hospital Malignant Haematology & Stem Cell Transplantation Services
Level 1, South Block
55 Commercial Road
Melbourne
Australia
VIC 3004

Sponsor information

Organisation
Institut de Recherches Internationales Servier (France)

ROR
https://ror.org/034e7c066

Funder(s)

Funder type

Industry

Funder Name
ADIR

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from https://clinicaltrials.servier.com after Marketing Authorisation has been granted.

A plain English summary of results has been uploaded as an additional file (ISRCTN04804337_ResultsPlainEnglish_16Sep2019)

Previous publication and dissemination plan:
Summary results and a lay summary will be published on www.clinicaltrials.servier.com within 12 months after the end of the study.
IPD sharing plan: The datasets generated during and/or analysed during the current study will be available upon request from www.clinicaltrials.servier.com after the Marketing Authorisation has been granted.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		16/09/2019	22/11/2019	Yes	No
Basic results		16/09/2019	22/11/2019	No	No