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# Phase I dose-escalation study of oral administration of S055746 in patients with Acute Myeloid Leukaemia or Myelodysplastic Syndrome

**Submission date**
01/08/2014

**Registration date**
04/09/2014

**Last Edited**
23/05/2019

**Recruitment status**
Stopped

**Overall study status**
Completed

**Condition category**
Cancer

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

**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 Andrew Wei

**Contact details**
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## Additional identifiers

**EudraCT/CTIS number**
2014-002559-24

**IRAS number**

**ClinicalTrials.gov number**
NCT02920541

### Secondary identifying numbers
CL1-055746-002

# Study information

### Scientific Title
Phase I dose-escalation study of the orally administrered selective Bcl-2 inhibitor S055746 as monotherapy for the treatment of patients with Acute Myeloid Leukaemia (AML) or high or very high risk Myelodysplastic Syndrome (MDS)

### Study objectives
To determine the safety profile and tolerability of S 055746 and establish the recommended Phase II dose.

### Ethics approval required
Old ethics approval format

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

### Study design
Phase I dose-escalation study

### Primary study design
Interventional

### Secondary study design
Dose-escalation study

### Study setting(s)
Hospital

### Study type(s)
Treatment

### Participant information sheet
Not provided at time of registration

### Health condition(s) or problem(s) studied
Acute Myeloid Leukaemia (AML) and Myelodysplastic Syndrome (MDS)

### Interventions
Current interventions as of 13/01/2017:
Film-¬coated tablets containing 50 mg or 100 mg of S055746. This trial is a dose escalation trial. The first daily dose tested will be 100 mg, and then a panel of daily doses from 50 to 2000 mg could be tested. Treatment duration for the participant is until evidence of progressive disease, the occurrence of unacceptable toxicity, death, exercise of investigator discretion, withdrawal of consent or if clinically indicated after discussion between investigator and the sponsor on a case by case basis.

Previous interventions:
Film-coated tablets containing 50 mg or 100mg of S055746. This trial is a dose escalation trial. A modified version of the Continual Reassessment Method (mCRM) will be used for dose allocation process. The first daily dose tested will be 100 mg, and then a panel of daily 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 proposed depending on available results during the study. Treatment duration for the participant is until evidence of treatment failure, the occurrence of unacceptable toxicity, death, exercise of investigator discretion, withdrawal of consent or if clinically indicated after discussion between investigator and the sponsor on a case by case basis

## Intervention Type
Drug

## Phase
Phase I

## Drug/device/biological/vaccine name(s)
S055746

## Primary outcome measure
Current primary outcome measures as of 13/01/2017:
1. Dose Limiting Toxicities in cycle 1
2. Maximum Tolerated Dose, defined as the highest drug dosage that is unlikely (<25% posterior probability) to cause DLT 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. Dose Limiting Toxicities in cycle 1
2. Maximum Tolerated Dose defined as the highest dose administered in the study at which the incidence of DLT is 30%
3. Safety profile at each visit assessed by Adverse events monitoring, laboratory tests, vital signs and performance status, clinical examination and ECG parameters

## Secondary outcome measures
Current Secondary Outcome measures as of 14/03/2018:
1. Pharmacokinetics parameters on blood sample during cycles 1 and 2
2. Preliminary anti-leukaemic activity of S055746 throughout the study (blood, BMA and biopsy if available)

Previous Secondary Outcome Measures:
1. Pharmacokinetics parameters on blood sample during cycles 1 and 2
2. PD parameters on blood, BMA and biospy if available from cycle 1 to cycle 3 and in any time in case of suspicion of disease progression optional pharmacogenomics analysis on Cycle 1, D1 pre-dose
3. Preliminary anti-leukaemic activity of S055746 throughout the study (blood, BMA and biopsy if available)

## Overall study start date

01/01/2015

### Completion date
24/05/2018

# Eligibility

### Key inclusion criteria
Current inclusion criteria as of 13/01/2017:
1. Women or men aged >= 18 years
2. Patients with cytologically confirmed and documented de novo, secondary or therapy¬related AML excluding acute promyelocytic leukaemia :
2.1. With relapsed or refractory disease without established alternative therapy or
2.2. > or = 65 years not previously treated for AML, who are not candidates for intensive chemotherapy or not candidates for standard chemotherapy
3. Patients with cytollogically confirmed and documented MDS or non-proliferative Chronic Myelomonocytic Leukaemia (CMML) patients, in relapse or refractory after previous treatment line including at least one hypomethylating agent (5-azacytidine or decitabine):
3.1. With high or very high risk MDS and without established alternative therapy
3.2. Transformed to AML and without established alternative therapy
4. Ability to swallow oral tablet(s)
5. WHO performance status 0-2
6. Circulating white blood cells < or = 30 x 10^9 /L and < or = 13 x 10^9/L for non-proliferative CMML
7. Adequate renal and hepatic functions
8. Negative serum pregnancy test within 7 days prior to the first day of study drug administration
9. Patients must use effective contraception
10. Written informed consent

Previous inclusion criteria:
1. Women or men aged >= 18 years
2. Patients with cytologically confirmed and documented de novo, secondary or therapy-related AML excluding APL, with relapsed or refractory disease or > or = 65 years not previously treated, who are not candidates for intensive chemotherapy or not candidates for standard chemotherapy
3. Patients with cytollogically confirmed and documented high or very high risk myelodysplastic syndrome who have failed prior hypomethylating therapy
4. WHO performance status 0-2
5. Circulating white blood cells < or = 30 x 10^9 /L
6. For MDS patients:
6.1. Platelets count > 25 10^9/L
6.2. Neutrophils > 0.5 10^9/L
7. Acceptable coagulation parameters according to local laboratory
8. Adequate renal and hepatic functions
9. Negative serum pregnancy test within 7 days prior to the first day of study drug administration
10. Patients must use effective contraception

### Participant type(s)
Patient

### Age group

Adult

## Lower age limit
18 Years

## Sex
Both

## Target number of participants
60 to 80 patients

## Key exclusion criteria
Current exclusion criteria as of 14/03/2018:
1. Foreseeable poor compliance to the study procedures
2. Legally incapacitated person under guardianship or trusteeship
3. Pregnant or breastfeeding women
4. Participation in therapeutic interventional study involving investigational drug intake at the same time or within 2 weeks or at least 5 half-lives or patient already enrolled
5. Previous treatment with a BH3 mimetic
6. Patients who have not recovered to baseline or CTCAE< or = Grade 1 from toxicity due to all prior therapies received for the studied disease
7. Any previous anti¬leukaemic treatment (AML, high or very high risk MDS) within at least 5 half-lives or 2 weeks prior to the study entry except for hydroxyurea
8. Any radiotherapy within 4 weeks before first intake
9. Major surgery within 3 weeks before first intake of S 055746
10. Allogenic stem cell transplant within 6 months before the first intake of S 055746 and for patients who still need immunosuppressive treatment
11. Leukaemic leptomeningeal or leukaemic central nervous system involvement
12. Concomitant uncontrolled infection, organ dysfunction or medical disease likelty to interfere with evaluation of S 055746 safety or study outcome
13. Human immunodeficiency virus (HIV), hepatitis B or active hepatitis C infection
14. Within 6 months prior to the first intake of S 055746, history of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, and/or stenting, ischemic /haemorragic stroke, atrial fibrillation, digestive haemorrhagic risk, deep venous/arterial thromboembolic complication or bleeding diathesis
15. Decreased Left Ventricular Ejection Fraction (LVEF)
16. QTcF prolongation
17. Patients who are receiving QT prolonging drug
18. Coagulopathies with increased risk of bleeding complications
19. Other malignancy within 2 years prior to the first intake
20. Strong or moderate CYP3A4 inhibitors or inducers (treatment, food or drink products) within 7 days prior to the first intake
21. Treatment highly metabolised by the CYP3A4 or CYP2D6 and/or with a narrow therapeutic index, multi-enzymes and/or OATP and/or P-gp substrates or herbal products within 7 days prior to the first intake.
22. Patients receiving proton pump inhibitor
23.Patients having received anticoagulant oral drugs, aspirin > 325 mg/day and antiplatelets within 7 days prior to first S 055746 intake

Current exclusion criteria as of 13/01/2017:
1. Foreseeable poor compliance to the study procedures

2. Legally incapacitated person under guardianship or trusteeship
3. Pregnant or breastfeeding women
4. Participation in therapeutic interventional study involving investigational drug intake at the same time or within 2 weeks or at least 5 half-lives or patient already enrolled
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15. Decreased Left Ventricular Ejection Fraction (LVEF)
16. QTcF prolongation
17. Patients who are receiving QT prolonging drug
18. Coagulopathies with increased risk of bleeding complications
19. Other malignancy within 2 years prior to the first intake
20. Strong or moderate CYP3A4 inhibitors or inducers (treatment, food or drink products) within 7 days prior to the first intake
21. Treatment highly metabolised by the CYP3A4 and with a narrow therapeutic index within 7 days prior to the first intake.
22. Patients receiving proton pump inhibitor

Previous exclusion criteria:
1. Pregnant or breastfeeding women
2. Involvement in therapeutic interventional study at the same time or within 2 weeks prior to first S 055746 intake or patient already enrolled in the study
3. Previous treatment with a BH3 mimetic
4. Patients who have not recovered to baseline or CTCAE< or = Grade 1 from toxicity due to all prior therapies
5. Any previous anti-leukaemic treatment (AML, high or very high risk MDS) within at least 5 half lives or 2 weeks prior to the study entry except for hydroxyurea
6. Any radiotherapy within 4 weeks before first intake
7. Major surgery within 3 weeks before first intake of S 055746
8. Allogenic stem cell transplant within 6 months before the first intake of S 055746 and for patients who still need immunosuppressive treatment
9. Leukaemic leptomeningeal or leukaemic central nervous system involvement
10. Concomitant uncontrolled infection, organ dysfunction or medical disease likelty to interfere with evaluation of S 055746 safety or study outcome
11. Human immunodeficiency virus (HIV)
12. Within 6 months prior to the first intake of S 055746, history of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, and/or stenting, ischemic /haemorragic stroke, atrial fibrillation, digestive haemorrhagic risk, deep venous/arterial

thromboembolic complication or bleeding diathesis
13. QTc prolongation
14. LVEF assessed by echocardiography or Multi-Gated Acquisition scan (MUGA scan)
15. Treatment, food or drink products known to inhibit or induce CYP3A4 within 7 days prior to the first intake
16. Treatment highly metabolised by the CYP3A4 and with a narrow therapeutic index within 7 days prior to the first intake.

### Date of first enrolment
01/01/2015

### Date of final enrolment
26/12/2017

## Locations

### Countries of recruitment
Australia

France

### Study participating centre
**Department of Haematology**
Melbourne
Australia
VIC 3004

### Study participating centre
**Royal Melbourne Hospital**
300 Grattan St
Parkville
Melbourne
Australia
VIC 3050

### Study participating centre
**Institut Paoli Calmettes**
232, boulevard Sainte Marguerite
Marseille
France
13009

### Study participating centre

**Hôpital Lyon-Sud**
165 Chemin du Grand Revoyet
Pierre-Bénite
France
69310

**Study participating centre**
**Hôpital Saint-Louis**
1 Avenue Claude Vellefaux
Paris
France
75010

# Sponsor information

**Organisation**
Institut de Recherches Internationales Servier (France)

**Sponsor details**
50 rue Carnot
Suresnes
France
92284

**Sponsor type**
Industry

**Website**
http://www.servier.com/

**ROR**
https://ror.org/034e7c066

# Funder(s)

**Funder type**
Industry

**Funder Name**
ADIR

# Results and Publications

## Publication and dissemination plan

Current publication and dissemination plan as of 23/05/2019:
Summary results and a lay summary will be published on https://clinicaltrials.servier.com/ within 12 months after the end of the study

## Intention to publish date

24/05/2019

## Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study will be available upon request from https://clinicaltrials.servier.com/ after the marketing authorisation has been granted.

Previous publication and dissemination plan:
The trialists will comply with regulatory requirements. Summary results and a lay summary will be published on https://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 are/will be available upon request from https://clinicaltrials.servier.com after Marketing Authorisation has been granted.

## IPD sharing plan summary

Available on request

## Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Basic results | | | 23/05/2019 | No | No |
| Plain English results | | | 23/05/2019 | No | Yes |