2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Not applicable **Name of Active Ingredient:** S55746		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: 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
Protocol No.: CL1-55746-001
EudraCT No.: 2013-003779-36
The description of the study protocol given hereafter includes the modifications of the 10 substantial amendments to the protocol.

International coordinator
[redacted]

Study centres:
Five countries included 65 patients: France (n = 49), Germany (n = 6), Hungary (n = 1), Poland (n = 2) and Singapore (n = 7).

Publication (reference):
Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 26 March 2014 (first visit first patient) Completion date: 22 October 2018 (last follow-up visit last patient)	Phase I

Objectives:

Primary objectives:
To determine the safety profile and tolerability of S55746 in patients with refractory or relapsed Chronic Lymphocytic Leukaemia (CLL), B-Cell Non-Hodgkin Lymphoma (NHL) including Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Diffuse Large B-Cell Lymphoma (DLBCL), Small Lymphocytic Lymphoma (SLL) and Marginal Zone Lymphoma (MZL) and Multiple Myeloma (MM) with translocation (11;14) (t(11;14)), in terms of Dose-Limiting Toxicities (DLTs), Maximum Tolerated Dose (MTD) of S55746 and establish the Recommended Phase 2 Dose (RP2D) through safety profile (DLT, MTD), PK profile, PD profile and preliminary efficacy.

Secondary objectives:

- To determine the pharmacokinetic (PK) profile of S55746 and metabolites.
- To assess the influence of food intake on PK profile of S55746 in patients with B-cell NHL after single oral administration of a 200 mg dose of S55746, in order to optimize administration and to ensure optimal food recommendations in the ongoing studies.
- To assess the preliminary efficacy of S55746: tumour response according to criteria based on recommendations made by the International Working Group Revised Response Criteria for Malignant Lymphomas for B-Cell NHL patients, according to the guidelines for the diagnosis and treatment of CLL based on the International Workshop on CLL report updating the National Cancer Institute-Working Group 1996 guidelines for CLL patients and according to International Myeloma Working Group (IMWG) Uniform Response Criteria for MM.

Exploratory objectives:

- To determine the pharmacodynamic (PD) profile of S55746 for:
  - CLL or NHL patients with leukemic component on blood samples.
  - All NHL patients on archival tumour sample.
  - MM patients: planned but not done (no MM patients was included).
- To perform an optional pharmacogenomic (PG) analysis of inter-patients variation in genes encoding for proteins involved in absorption/distribution/metabolism/excretion (ADME).

Methodology:
This was a first-in-human, international, multicentre, open-label, non-randomised, non-comparative phase I study. Two dose-escalations were carried out, one in fasting condition, the other one in fed condition.

A modified version of the Continual Reassessment Method (mCRM) was used for dose allocation process in patients dosed in fasting condition. A Bayesian Logistic Regression Method (BLRM) with overdose control (EWOC) was used for dose allocation process in fed condition. Each method was implemented in 2 separate independent arms: arm A for NHL patients and arm B for CLL patients.

This study was performed in strict accordance with Good Clinical Practice.

The Sponsor decided to halt recruitment and discontinue the study during dose escalation. Indeed, the oral formulation of S55746 did not allow reaching the target active exposure despite the introduction of food with the drug intake and the dose escalation up to 1300 mg. In addition, the 100 mg tablet used in the study did not allow for further dose escalation over 1300 mg due to a high pill burden. As a consequence, maximum tolerated dose/recommended dose for expansion was not established and the dose expansion part of the study was not initiated. The recruitment stop was not a consequence of any safety concern and treatment of ongoing patients participating in the trial could continue according to the protocol until the last patient last visit completed date.
In this context, an **abbreviated clinical study report** was written.

Number of patients:
Planned: a maximum of 120 patients
Included: 65 patients including 49 NHL patients (37 fasting patients and 12 fed patients) and 16 CLL patients (12 fasting patients and 4 fed patients)

Of note: it was planned to include MM patients during the expansion part of the study but since this part was not initiated, no MM patients was included.

Diagnosis and main criteria for inclusion:

- Women or men aged ≥ 18 years.
- Patients with a measurable histologically confirmed FL, MCL, DLBCL, SLL and MZL as defined in the World Health Organization (WHO) classification scheme, or patients with an evaluable immunophenotypically confirmed CLL.
- Relapsed after or refractory disease to standard treatments, and required treatment in the opinion of the investigator. MCL and DLBCL patients must be refractory within 3 months after last treatment or in relapse after at least 2 lines of standard treatments.
- Patients with WHO performance status 0-2, adequate bone marrow, renal and hepatic functions.

Test drug:
S55746 was taken orally once a day during a 21-day cycle. Tablets of 50 mg and 100 mg were available.

Test drug administration in Fasting condition including the Food interaction cohort
S55746 was taken once a day without food *i.e.* at least 30 min prior to, or at least 2 hours after a meal.
For the patients of the food interaction cohort, 200 mg of S55746 was taken following an overnight fasting period on week-1day1 (W-1D1) (day of first administration, the week prior to cycle 1 day 1) and then in fed condition (see below) the day after on week-1day2 (W-1D2). After a wash out period from 2 to 7 days, patients of the food interaction cohort started S55746 treatment at cycle 1 day 1 at the last dose of S55746 validated as safe between sponsor and investigators.

Test drug administration in Fed condition
S55746 *was* taken during a moderate meal (400-500 kcal with fat contributing to 150 kcal) lasting maximum 30 minutes. No other food was allowed for at least 2 hours post-dose.

Batch Nos.: [redacted]

Precaution for S55746 administration: patients were hospitalised for duration of at least 3 to 5 days (according to either fasting condition, food interaction cohort or fed condition) and beginning the day before the first intake of S55746 to enable close in-patient Tumor Lysis Syndrome monitoring and management, in accordance with institutional guidelines and published criteria.

Test drug: (Cont'd)

Dose allocation methodology / Fasting condition

For both separate arms, an independent mCRM was used for dose allocation process.
The target toxicity rate was defined as 16 to 30% (*i.e.* the dose for which 16 to 30% of patients experienced a DLT). The arm NHL started first at the initial dose level of 100 mg with a minimum of 2 patients. After having tested the doses of 100 mg, 200 mg and 300 mg, according to PK and safety data, dose skipping of 200 mg maximum was allowed.
The arm CLL started after having tested at least the doses of 100 and 200 mg in the arm NHL. Dose skipping of more than one dose level in arm CLL was allowed according to pre-defined specific criteria.
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.
In each independent arm NHL and CLL:
During dose escalation part, for each new dose level tested and during the first week of the first cycle, S55746 was administered initially to one patient only. If no medically important or life threatening toxicity occurred during a 1-week observation period the other patients of this cohort were allowed to receive S55746. The number of patients per cohort (2 to 6 evaluable patients) depended on safety and PK data observed.
In Arm NHL:
At least 6 B-Cell NHL patients with low risk of Tumour Lysis Syndrome (TLS) were included in a food interaction cohort to evaluate the influence of food intake on S55746 PK profile from W-1D1 to W-1D4 prior patient starting cycle 1 day 1 at the last dose of S55746 validated as safe between sponsor and investigators during end of cohort meeting

Dose allocation methodology / Fed condition

For both separate arms, an adaptive BLRM with EWOC was used to guide dose escalation and estimate the MTD based on occurrence of DLT during cycle 1.
The MTD is 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 S55746 treatment. A minimum of 3 patients were enrolled at each cohort; the total number of patients per cohort (3 to 6 evaluable patients) depended on safety and PK data.
The first dose tested was 200 mg for arm NHL and 100 mg for arm CLL, and a panel of doses from 50 to 1000 mg could be tested according to the dose allocation process of the BLRM. Doses over 1000 mg and intermediate doses could be proposed depending on available results during the study.

In each independent Arm NHL and CLL:
During dose-escalation, if the next dose level defined had not been administered yet during one week to at least one patient of any study evaluating S55746 in monotherapy; the first administration of this new dose level of S55746 was given to only one patient first. If no medically important or life threatening toxicity occurred during a 1-week observation period, the other patients were allowed to receive S55746. A minimum of 6 evaluable patients was needed at the MTD.

During dose escalation for patients both in fasting and fed condition:

- An intra-patient dose escalation, limited to the highest dose that had been confirmed to have an acceptable safety profile and which was lower than the next allocated dose decided during the end of cohort meeting, was permitted in each arm independently according to specific pre-defined criteria.
- Before testing a new dose level, an end of cohort meeting between the sponsor, the coordinator and the investigators was organised to discuss the toxicities in terms of DLT, the safety and PK data observed in all patients, and to decide jointly the next dose level to be tested. The possibility to proceed to intra-patient dose escalation was also discussed during this meeting on a case by case basis.

The expansion part of the study which was planned at the Recommended Dose for Expansion was not started.

Test drug: (Cont'd)

DLT assessment

Toxicities were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v 4.03. A DLT was defined as an adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and occurred during the first cycle and met any of the criteria:

Treatment related:

- Grade ≥ 4 thrombocytopenia persisting for more than 5 days.
- Grade ≥ 4 neutropenia persisting for more than 5 days.
- Grade ≥ 3 neutropenia with fever ≥ 38.5° C persisting for more than 5 days.
- Any grade ≥ 3 non-haematological toxicity.
- Grade ≥ 3 nausea, vomiting, diarrhoea despite optimal medical management.
- Grade ≥ 3 prolongation of the QTcF interval, as determined by a central ECG reading centre.
- Grade ≥ 3 cardiac toxicity (cTnI or T, hypotension, hypertension, left ventricular dysfunction).
- Failure to restart S55746 administration within 1 week of the first missed dose due to delayed recovery from drug-related toxicity.

Comparator:

Not applicable.

Duration of treatment:

Patients received S55746 treatment during the fasting and fed conditions treatment periods. Patients, who benefited from S55746 treatment, which in opinion of the investigator was indicative of positive effect, might continue to receive treatment 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.

The total number of cycles was at the discretion of the investigator.

Criteria for evaluation:

Efficacy measurements:

- Patients with B-Cell NHL were evaluated for clinical response according to criteria based on recommendations made by the International Working Group Revised Response Criteria for Malignant Lymphomas.
- Patients with CLL were evaluated for response according to the guidelines for the diagnosis and treatment of Chronic Lymphocytic Leukemia based on the International Workshop on Chronic Lymphocytic Leukemia report updating the National Cancer Institute-Working Group 1996 guidelines.

Safety measurements:

The safety criteria were DLTs, MTD, adverse events, laboratory tests (biochemistry, haematology with Complete Blood Count (CBC) differential count, coagulation, urine analysis, and thyroid function), vital signs (performance status developed by the Eastern Cooperative Oncology Group [PS-ECOG]), weight, blood pressure and heart rate), 12-lead ECG (central reading), cardiac function (LVEF).

Pharmacokinetic measurements: concentrations of S55746 and potential metabolites in plasma and urine, drug-drug interaction evaluation, 4beta-hydroxycholesterol in plasma.

Pharmacodynamic measurements: results are provided in a separate report.

Pharmacogenomic measurement (optional): not done.

Statistical methods:

Analysis Set:

DLT Evaluable Set (DLTES): all patients of the Safety Set (SS) who were evaluable for DLT according to the DLT assessment at end of cycle 1. A patient was not considered evaluable if:

- He/she did not receive at least 85% (18 doses over 21) of S55746 prescribed doses, unless treatment was stopped for a DLT or,
- He/she did not undergo a DLT assessment at the start of cycle 2 or,
- He/she discontinued during cycle 1 for reason other than DLT.

Efficacy analysis: not performed in the context of the present abbreviated study report.

Study patients: descriptive statistics were provided for patients in each arm (NHL and CLL) as well as by food condition in each arm.

Safety analysis: descriptive statistics were provided for patients overall, for patients in each arm as well as by food condition.

Pharmacokinetic analysis: PK measurements are described in the appendices of the present report.

Pharmacodynamic and Pharmacogenomic analyses: not presented in this study report.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS

Disposition of patients is presented in Table hereafter.

Disposition of patients

Status		NHL patients			CLL patients		
		Fasting (N = 37)	**Fed (N = 12)**	**All (N = 49)**	**Fasting (N = 12)**	**Fed (N = 4)**	**All (N = 16)**
Included	**n**	**37**	**12**	**49**	**12**	**4**	**16**
Withdrawn of treatment due to	**n (%)**	**37 (100)**	**12 (100)**	**49 (100)**	**12 (100)**	**4 (100)**	**16 (100)**
Progressive disease	n (%)	32 (86.5)	11 (91.7)	43 (87.8)	9 (75.0)	3 (75.0)	12 (75.0)
Adverse event	n (%)	2 (5.4)	1 (8.3)	3 (6.1)	2 (16.7)	-	2 (12.5)
Non-medical reason	n (%)	2 (5.4)	-	2 (4.1)	-	1 (25.0)	1 (6.3)
Physician decision	n (%)				1 (8.3)	-	1 (6.3)
Protocol deviation	n (%)	1 (2.70)	-	1 2.0)	-	-	-

N number of patients by food condition; n number of patients; Percentages are based on n

Among patients who entered in the follow-up (FU) period, 30 patients completed the FU period and 5 were lost to FU (including FU stopped due to study discontinuation).

BASELINE CHARACTERISTICS

For ***NHL patients***, median age was 61 years, 51% of patients were female and mostly (76.7%) were Caucasian. Patients in fasting group were older than in the fed group: median age of 64.0 and 51.5 years, respectively.
Staging of the NHL was mainly Ann-Arbor stage 3 (28.6% of patients) and 4 (57.1%) with level 4 more frequent in the fasting group than in the fed group (64.9% and 33.3%, respectively). The mean disease duration since diagnosis was 4.3 ± 4.3 years (median = 2.95 years).
At entry in the study, 59.2% were refractory to previous conventional treatment and 40.8% in relapse.
All NHL patients have received previous drug treatment, 30.6% underwent graft, 16.3% have received radiotherapy and 10.2% underwent surgery. As regards of previous drug treatment, 22.4% of NHL patients have received 1 or 2 treatment lines, 10.2% 3 lines, 49.0% 4-7 lines and 18.4% more than 7 lines (max 14). Previous therapies were of similar profile in fasting and fed groups.

SUMMARY – CONCLUSIONS (Cont'd)

DISPOSITION OF PATIENTS

For ***CLL patients***, median age was 67 years, 81.2% of patients were male and all were Caucasian. These demographic characteristics were similar in the two food condition groups.

Staging of the CLL was mainly Binet stage 'C' (53.3% of patients) and 'B' (40.0%). The mean disease duration since diagnosis was 10.8 ± 6.2 years (median = 9.8 years).

At entry in the study, most of patients were in relapse (87.5%) and a minority (12.5%) were refractory to previous conventional treatment.

All CLL patients have received previous drug treatment with no other therapy: 25.0% of patients have received 2 treatment lines, 25% 3 lines and 50.0% 4-7 lines.

At baseline, most of patients had PS-ECOG equal to 0 (NHL patients: 42.9%, CLL patients: 43.8%) or equal to 1 (53.1% and 50.0%, respectively). All patients had PS-ECOG ≤ 2.

EXTENT OF EXPOSURE

For ***NHL patients***, the median number of cycle was 2.0 and the median treatment duration of S55746 was 6.0 weeks; both were similar in the fasting and fed group. Eight patients (16.3%) reported at least one treatment interruption and 12 patients (24.5%) had at least one cycle delayed. One patient had a single dose reduction. The mean relative dose intensity (RDI) was 97.1 ± 6.3% and 95.9% of patients had a RDI > 85%.

For ***CLL patients***, the median number of cycle was 3.5 and the median treatment duration of S55746 was 10.0 weeks. Four patients (25.0%) reported at least one treatment interruption and 3 patients (18.8%) had at least one cycle delayed. None of patients had dose reduction. The mean RDI was 97.8 ± 4.9% and 93.8% of patients had a RDI > 85%.

EFFICACY RESULTS

Efficacy was part of the secondary objectives of the study. In the context of an abbreviated report, no efficacy analysis was performed.

SAFETY RESULTS

Dose-escalation, MTD and RP2D finding

During the two dose-escalations, the doses tested were:

- NHL disease: 37 fasting patients from 100 mg to 1300 mg and 12 fed patients from 200 mg to 800 mg.
- CLL disease: 12 fasting patients from 100 mg to 700 mg and 4 fed patients at 100 mg.

At the end of cycle 1, 58 patients were evaluable for DLT among whom 3 patients experienced a DLT: 1 DLT [Grade ≥ 4 neutropenia persisting more than 5 days] in a fed NHL patient at 200 mg and 2 DLTs [Grade ≥ 3 non-haematological toxicity], one in a fasting CLL patient at 700 mg and the other in a fed NHL patient at 800 mg.

The maximum tolerated dose/recommended dose for expansion was not established and the expansion part of the study was not initiated.

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Emergent adverse events

The main results of EAEs in overall patients (NHL and CLL disease) are summarised in Table hereafter.

Overall summary for emergent adverse events the Safety Set

		Fasting (N = 49)	Fed (N = 16)	ALL (N = 65)
Patients having reported at least one:				
EAE	n (%)	45 (91.8)	16 (100)	61 (93.8)
Treatment-related EAE	n (%)	14 (28.6)	7 (43.8)	21 (32.3)
Severe* EAE	n (%)	27 (55.1)	8 (50.0)	35 (53.8)
Treatment-related	n (%)	3 (6.1)	3 (18.8)	6 (9.2)
Serious EAE (including death)	n (%)	25 (51.0)	8 (50.0)	33 (50.8)
Treatment-related	n (%)	2 (4.1)	2 (12.5)	4 (6.2)
EAE leading to treatment withdrawal	n (%)	7 (14.3)	4 (25.0)	11 (16.9)
Severe* EAE	n (%)	5 (10.2)	4 (25.0)	9 (13.8)
Serious EAE	n (%)	4 (8.2)	2 (12.5)	6 (9.2)
Treatment-related EAE	n (%)	1 (2.0)	2 (12.5)	3 (4.6)
Treatment-related severe* EAE	n (%)	1 (2.0)	2 (12.5)	3 (4.6)
Treatment-related serious EAE	n (%)	-	2 (12.5)	2 (3.1)
Patients who died during the study	n (%)	18 (36.7)	7 (43.8)	25 (38.5)
During treatment period	n (%)	3 (6.1)	1 (6.3)	4 (6.2)
During the follow-up period	n (%)	15 (30.6)	6 (37.5)	21 (32.3)

** CTCAE grade ≥ 3*

Overall, most of patients (93.8%) reported at least one EAE. The most frequent affected SOCs (≥ 30% of overall fasting and fed patients) were Gastrointestinal disorders (46.2%), General disorders and administration site conditions (41.5%), Blood and lymphatic system disorders (36.9%), [Infections and infestations] and [Respiratory, thoracic and mediastinal disorders] (both SOCs: 32.3%). There was no relevant difference between the fasting and fed groups. In the other SOCs, Metabolism and nutrition disorders was more frequently affected in the fasting group (32.7%) than in the fed group (6.3%).

The ***most commonly reported EAEs*** (≥ 10%) ***in the overall fasting and fed patients*** were anaemia, cough, malignant neoplasm progression (16.9% each), asthenia, constipation, nausea, vomiting, thrombocytopenia (12.3% each), diarrhoea and headache (10.8%, each). Among those EAEs, the following EAEs were less frequent in the fasting group than in the fed group: anaemia and cough (for 14.3% and 25.0%, respectively, for each of the two EAEs), constipation (10.2% and 18.8%, respectively) and diarrhoea (8.2% and 18.8%, respectively).

Of note: among overall patients, the frequency of neutropenia and neutrophil count decreased was 7.7% (all in fasting patients) and 6.2%, respectively. Two NHL patients (3.1%) experienced a febrile neutropenia: both in fasting group, grade 3, considered not treatment-related and recovered while one was non-serious and the other serious.

All ***severe EAEs*** were reported with a frequency < 10%, except malignant neoplasm progression (12.3%). Blood and lymphatic system disorders was the most frequently affected SOC (27.7%) including the following severe EAEs: anaemia (9.2%), thrombocytopenia (7.7%), lymphopenia, neutropenia (6.2% each), febrile neutropenia (3.1%) with the 3 latest severe EAEs reported only in the fasting group.

Overall, 32.3% of patients had at least one ***treatment-related EAE*** with a lower frequency in the fasting group (28.6%) than in the fed group (43.8%). All treatment-related EAEs were reported with a frequency < 5%, except nausea (6.2%). Treatment-related EAE in at least 2 patients in any food condition group were nausea (4 patients [8.2%] in the fasting group, none in the fed group), neutrophil count decreased (1 patient [2.0%] in the fasting group, 2 patients [12.5%] in the fed group), thrombocytopenia and fatigue (for each: 1 patient [2.0%] in the fasting group, 2 patients [12.5%] in the fed group), asthenia and neutropenia (for each: 2 patients [4.1%] in the fasting group, none in the fed group) and diarrhoea (none in the fasting group, 2 patients [12.5%] in the fed group).

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

The ***serious EAEs*** reported in at least 2 patients were malignant neoplasm progression (7 patients, 10.8%), neutropenia (4 patients, 6.2%, only in the fasting group), tumour pain and pulmonary embolism (for each: 3 patients, 4.6%), haemorrhagic anemia, hypercalcaemia, general physical health deterioration and acute kidney injury (for each: 2 patients, 3.1%). Overall, 4 patients (6.2%) reported at least one serious treatment-related EAEs: neutropenia (2 patients), neutrophil count decreased (1 patient) and blood alkaline phosphatase increased, blood bilirubin increased, GGT increased, aspartate aminotransferase increased and jaundice (these 5 events in a single patient).

EAEs leading to IMP withdrawal were reported in 11 patients (16.9%): 7 patients (14.3%) in the fasting group and 4 patients (25.0%) in the fed group. These EAEs were reported in a single patient except malignant neoplasm progression (4 patients: 2 in each fasting and fed group) and neutrophil count decreased (2 patients: 1 in each fasting and fed group). Severe EAEs leading to treatment withdrawal were reported in 9 patients (13.8%): 5 patients (10.2%) in the fasting group and 4 patients (25.0%) in the fed group. Overall, 3 patients (4.6%) experienced 6 treatment-related severe EAE leading to treatment withdrawal**:** 1 patient was in the fasting group (asthenia) and 2 patients in the fed group (5 EAEs: neutrophil count decreased in one patient, blood alkaline phosphatase increased, blood bilirubin increased, GGT increased and jaundice in the other).

A total of 25 patients (38.5%) died during the study: 42.9% in the NHL patients and 25.0% in the CLL patients. In overall patients, 36.7% died in the fasting group and 43.8% in the fed group. Overall, 6 patients (9.2%) experienced a fatal EAE (all not considered as treatment-related, 4 patients died during treatment period and 2 during follow-up period) as follows: malignant neoplasm progression and respiratory distress (each in 1 patient), malignant neoplasm progression (3 patients), pulmonary embolism (1 patient) and general physical health deterioration (1 patient). Other deaths than fatal EAE (n = 19) occurred during the follow-up period for progressive disease.

Blood laboratory tests

For the ***biochemical parameters***, the most frequent emergent grade ≥ 3 values were observed for low phosphate (5 patients, 7.8%) and high GGT (3 patients, 4.6%, all in the fasting group). All these values were grade 3, except for low calcium, high potassium and high acid uric (grade 4 in 1 patient for each).

For the ***haematological parameters***, emergent grade ≥ 3 values were detected for low neutrophils (15.8%), low lymphocytes (15.3%), low platelets (13.8%), low haemoglobin and low white bloods cells (9.2% for each). Among those abnormal values, all were grade 3, except for low neutrophils with grade 4 in 7.9% and low lymphocytes with grade 4 in 3.0%.

Other safety evaluation

Neither clinically relevant changes nor differences between fasting and fed groups in mean values over time were detected for weight and blood pressure. The mean change from baseline in heart rate (highest value) was 16.2 ± 14.9 bpm (median = 14.0 bpm) with emergent value ≥ 100 bpm observed in 31.2% of patients. Four LVEF decreased were reported as EAE in 3 patients (all in the fasting group).

Overall, 51.6% of the patients had their PS-ECOG maintained throughout the study while PS-ECOG worsened (from 0 or 1 at baseline to ≥ 2 post-baseline) in 25.0% of the patients with no relevant difference between the fasting and fed group.

CONCLUSION

In this first-in-human, international, multicentre, open-label, non-randomised, non-comparative, phase I, dose-escalation study, a total of 49 patients with B-Cell Non-Hodgkin Lymphoma (NHL), mostly with Diffuse Large B-Cell Lymphoma, and 16 patients with Chronic Lymphocytic Leukemia (CLL) were treated orally either in fasting condition (49 patients) or in fed condition (16 patients) with a once daily dose of S55746 during a 21-day cycle.

Patients received S55746 treatment for a median of 2 and 3.5 cycles in patients with NHL and CLL, respectively, and all patients withdrew from the treatment, mostly for progressive disease (88% and 75%, respectively). During both dose-escalations in fasting and fed condition, Dose Limiting Toxicity was reported in a total of 3 patients who received S55745 at 200 mg (fed NHL patient), 700 mg (fasting CLL patient) and 800 mg (fed NHL patient).

The most commonly reported emergent adverse events (EAE) (≥ 10% of overall fasting and fed patients) were anaemia, thrombocytopenia, cough, malignant neoplasm progression, asthenia, constipation, nausea, vomiting, diarrhoea and headache. Neutropenia and neutrophil count decreased were reported in 7.7% and 6.2% of overall patients, respectively. EAEs were considered as treatment-related in one third of overall patients and those reported in at least 2 patients were nausea, asthenia, neutropenia, thrombocytopenia, fatigue and diarrhoea. The most frequent serious EAEs were malignant neoplasm progression (10.8%), neutropenia (6.2%), tumour pain and pulmonary embolism (each 4.6%).

The Sponsor decided to halt recruitment and discontinue the study during dose escalation. Indeed, the oral formulation of S55746 did not allow reaching the target active exposure despite the introduction of food with the drug intake and the dose escalation up to 1300 mg. In addition, the 100 mg tablet used in the study did not allow for further dose escalation over 1300 mg due to a high pill burden. As a consequence, maximum tolerated dose/recommended dose for expansion was not established and the dose expansion part of the study was not initiated. The recruitment stop was not a consequence of any safety concern and treatment of ongoing patients participating in the trial could continue according to the protocol until the last patient last visit completed date.

Date of the report: 16 September 2019

Version of the report: Final version