2. SYNOPSIS

Name of Sponsor: Institut de Recherches Internationales Servier (I.R.I.S.) Laboratorios Servier, S.L Servier Research and Development Limited (SDRL)	*(For National Authority Use only)*
Name of finished product: Not applicable **Name of active ingredient:** S65487 (VOB560)	
Title of study: Phase I, open label, non-randomised, non-comparative, multi-center study, evaluating S65487, a BCL-2 inhibitor intravenously administered, in patients with Relapsed or Refractory Acute Myeloid Leukemia, Non-Hodgkin Lymphoma, Multiple Myeloma, or Chronic Lymphocytic Leukemia. Protocol No.: CL1-65487-002 EudraCT No: 2018-004170-97 CT.gov No.: NCT03755154 The description of the study protocol given hereafter includes the modifications implemented through the 4 substantial amendments to the protocol.	
Principal investigator /Coordinating investigator: None assigned	
Number of study centres and countries: Overall, 4 countries and 7 centres were involved. In Spain, 2 centres enrolled 32 patients; in France, 3 centres enrolled 20 patients; in United Kingdom, 1 centre enrolled 6 patients; in Australia, 1 centre enrolled 2 patients.	
Studied period: Initiation date: 17 July 2019 Completion date: 06 November 2023 (last participant last visit) On 14 March 2023, the Institut de Recherches Internationales Servier (I.R.I.S.) decided to discontinue the study recruitment and the study was prematurely terminated as explained in the "Study design" and "Conclusions".	
Phase of development of the study: Phase I	
Publication (reference): Not applicable	
Background and rationale for the study: S65487 is a second-generation, potent and selective B-cell leukemia/lymphoma 2 (BCL-2) inhibitor which is expected to be active in monotherapy or in combination with other therapies for the treatment of patients with either haematological malignancies or solid tumors dependent on BCL-2. S65487 was designed to be compatible with intravenous (IV) administration to achieve higher exposure and decrease inter-patient variability compared to oral administration of other BCL-2-inhibitors. The purpose of this first-in-human (FIH) study was to assess safety, tolerability, pharmacokinetic (PK) and preliminary clinical activity and to estimate the maximum tolerated dose (MTD)/recommended Phase 2 Dose (RP2D) of S65487 as single agent administered intravenously in adult patients with Relapsed (R)/ Refractory (R) Acute Myeloid Leukemia (AML), Non-Hodgkin Lymphoma (NHL), Multiple Myeloma (MM) or Chronic Lymphocytic Leukemia (CLL).	

Objective(s) and endpoint(s):

	Objectives	Endpoints
Primary	Determine the safety profile (including DLT and MTD) and tolerability of S65487 in patients with AML, NHL, MM or CLL and the recommended phase II dose (RP2D) with associated ramp-up scheme according to safety, PK and preliminary efficacy results	- Incidence of DLTs during the first cycle of treatment with single agent S65487 - Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) o Laboratory tests: haematology with differential, blood biochemistry, thyroid function, coagulation, urinary analysis and pregnancy test o Vital signs and performance status o Electrocardiogram (ECG) parameters - Left ventricular ejection fraction (LVEF) assessed by echocardiography or multigated acquisition (MUGA) scan - Dose interruptions, reductions and dose intensity
Secondary	To determine the PK profile in plasma and in urine of S65487 and potential metabolite(s), if relevant. To assess the preliminary anti-tumour activity of S65487 using the appropriate response criteria for each evaluated population (AML, NHL, MM, CLL)	- PK parameters of S65487 and potential metabolite(s) in plasma and urine (e.g., C_{inf}, t_{inf}/t_{end}, AUC_{last}, t_{last}, C_{last}, AUC_{inf}, $t_{1/2,z}$, CL, V_{ss}, Ae, f_e and CL_R) - Best response (BR), overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), Time to progression (TTP), overall survival (OS). Evaluate anti-neoplastic activity using the appropriate response criteria for each evaluated population (AML, NHL, MM, CLL)

Study design:

Phase I FIH, open label, non-randomised, non-comparative, multi-center study.

An adaptative Bayesian Logistic Regression Model (BLRM) guided by an escalation with overdose control (EWOC) method was used to make dose recommendations based on the occurrence of DLT(s) during Cycle 1 and estimate the MTD/RP2D for S65487 administered as a single agent.

This study was designed in two parts: one part for dose escalation to determine MTD and/or RP2D, and one part for dose expansion.

On 14 March 2023, the decision was taken to discontinue recruitment to the CL1- 65487-002 study, based on strategic considerations due to the limited efficacy seen with this treatment in monotherapy. Therefore, the dose expansion part was cancelled, and the study was prematurely terminated. This decision was not based on any safety concerns.

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

Number of patients (planned and analysed):

No formal statistical power calculations to determine sample size were performed for this study.
Planned: overall, around 78 patients.
Dose escalation period: around 58 patients
Dose expansion period: around 20 patients (not performed)
Analysed: 60 patients
Dose escalation period: 60 patients (38 initial schedule – 22 alternative schedule)
Screened: 78 patients
Included set: 60 patients
Safety set: 60 patients

Diagnosis and main criteria for inclusion/exclusion:

Main inclusion criteria:

- Male or female patient aged ≥ 18 years old.
- Patients with cytologically confirmed and documented de novo, secondary or therapy-related AML, excluding acute promyelocytic leukaemia with R/R disease without established alternative therapy.

  Or patients with measurable confirmed MM (IMWG 2014) with R/R disease who had previously received at least three lines of treatment and without established alternative therapy.

  Or patients with histologically and measurable confirmed NHL defined as Diffuse Large B-cell Lymphoma (DLBCL), Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Marginal Zone Lymphoma (MZL), High-Grade B-cell Lymphoma with relapsed or refractory disease who have received at least two lines of therapy (including rituximab) and without established alternative therapy.

  Or patients with CLL who had R/R (except treatment failure), as defined per iwCLL guidelines (Hallek, 2018), including previous venetoclax treatment and without established alternative therapies.
- ECOG (Eastern Cooperative Oncology Group) performance status ≤ 2.
- For NHL, MM patients and CLL patients: haematological function (independent of any growth factor support) based on the last assessment performed before inclusion, defined as:
  - absolute neutrophil count (ANC) ≥ 1×10^9/L,
  - haemoglobin ≥ 8 g/dL,
  - platelet count ≥ 50×10^9/L for NHL and MM patients,
  - platelet count ≥ 30×10^9/L for CLL patients.
- For AML patients: circulating White Blood Cell (WBC) count < 25×10^9/L (with or without use of hydroxycarbamide/leukapheresis) based on the last assessment performed before inclusion.
- Adequate renal function within 7 days before inclusion, defined as creatinine clearance ≥ 50 mL/min/1.73 m², assessed as Glomerular Filtration Rate (GFR) using the Modification of Diet in Renal Disease (MDRD) Formula.
- Adequate hepatic function within 7 days before inclusion, defined as: total serum bilirubin < 1.5 × ULN; AST, ALT ≤ 3 × ULN.

Main exclusion criteria:

- Unlikely to cooperate in the study.
- Pregnancy, breastfeeding or possibility of becoming pregnant during the study.
- Participation in another interventional study at the same time or another interventional study requiring investigational treatment intake within 3 weeks or at least 5 half-lives (whichever is longer) prior to the first S65487 administration.
- Patients who had not recovered from toxicity of previous anticancer therapy, including grade ≥ 2 non-hematologic toxicity, prior to the first Investigational Medicinal Product (IMP) administration.
- Patients in treatment failure to a previous treatment with a BCL-2 inhibitor.
- Major surgery or any radiotherapy within 3 weeks prior to the first IMP administration.
- For AML patients: Allogenic stem cell transplant within 3 months before the first IMP administration and/or patients who still received immunosuppressive treatment within 3 months before the first IMP administration and/or patients with active graft-versus-host disease within 3 months before the first IMP administration and/or patient who received donor lymphocyte infusion within 3 months before the first IMP administration.
- For NHL, MM and CLL patients: prior allogenic stem cell transplant before the first IMP administration and/or autologous stem cell transplant within 3 months before the first IMP administration.
- Corticosteroids > 20 mg prednisone equivalent per day within 7 days before the first IMP administration.
- Severe or uncontrolled active acute or chronic infection.
- Known carriers of hepatitis B surface antigens or infection with hepatitis C virus.

- Known carriers of HIV antibodies.
- Patients with coagulopathy that would increase the risk of bleeding complications.
- Uncontrolled arterial hypertension (systolic blood pressure > 150 mmHg or diastolic blood pressure > 95 mmHg).
- Congestive heart failure (corresponding to New York Heart Association [NYHA] ≥ class II).
- Left Ventricular Ejection Fraction < 50%.
- Congenital or substance-induced long QT defined as QTc interval > 450 ms for males and > 470 ms for females.
- Clinically significant cardiac arrhythmias, complete left bundle branch block, high-grade atrioventricular block (AVB), atrial fibrillation.
- History of myocardial infarction (MI), unstable angina, coronary artery bypass graft (CABG) within 6 months prior the first IMP administration.
- Thromboembolic events within 3 months prior to the first IMP administration.
- Patients with central nervous system (CNS) involvement related to AML, NHL, MM and CLL.
- Recent (less or equal to 3 months) clinically relevant CNS pathology.
- Patients with known peripheral neuropathy grade ≥2 whatever the origin.

Investigational medicinal product/Test drug:

Initial administration Schedule

S65487 administered via IV infusion over 30 minutes once a week on a 3-week cycle via a central or peripheral venous line.

Alternative administration schedule:

S65487 administered via IV infusion over 30 minutes with an alternative administration schedule on a 3-week cycle via a central or peripheral venous line.

- This schedule was implemented in international amendment n°3 and modified in international amendment n°4.
- This schedule included infusions of S65487 on Day 1 (D1), D3, D5, D8 and D15 in each 3-week cycle of treatment.
- The starting total weekly dose of the first week (corresponding to the total dose of the 3 infusions) was equal or lower than the last validated dose tested via the initial weekly schedule and considered to be a safe dose according to the EWOC criterion and the overall safety data.
- During an end-of-cohort meeting, a decision might be made to give S65487 on D1, D2, D3, D4, D5, D8 and D15 of each cycle. If the decision was made to evaluate this more frequent dosing, the initial total dose of S65487 given on D1, D2, D3, D4 and D5 would be equal to a total dose given on D1, D3 and D5 that was below the MTD. No increase was made in the doses given on D8 and D15 when this more intensive schedule was first evaluated.
- The investigator might reduce the intensity of treatment after at least 3 cycles of treatment had been administered and after the patient had achieved a maximal response. A reduction in the intensity of treatment might be made by giving S65487 only once each week or by reducing the number of infusions in the first week of each cycle from 5 to 3.

Precautions for S65487 administration during the first week of treatment:

- **Assessments for and management of Tumor Lysis Syndrome are described in** Section 9.4.1.
- **Infusion related reaction (IRR) prophylaxis is described in** Section 9.4.1.

Dose allocation methodology

In each schedule, an adaptive BLRM with EWOC was applied to guide dose escalation and estimate the MTD(s) based on the occurrence of DLTs during cycle 1, starting from the ramp-up (if applicable), and the data obtained on the four indications were pooled.

The MTD in each indication was defined as the dose with the highest probability to maintain a DLT rate between 16% and 33%, with a limited risk of DLT (<25% posterior probability) for unacceptable toxicity (DLT rate >33%). A minimum of 3 eligible patients were enrolled in each cohort; however, a maximum of 6 evaluable patients per cohort could be recruited to enrich safety and PK data.

The first dose tested in the initial schedule (weekly administration) was 25 mg, and then a panel of doses from 50 to 1350 mg could be tested according to the dose allocation process of the BLRM. Intermediate doses could be proposed depending on available results during the study.

The starting dose in the alternative schedule was based on the data collected from patients treated in the initial schedule. A panel of doses from 12 mg (one dose level below the starting dose) to 1600 mg of S65487 administered daily could be tested according to the dose allocation process of the BLRM. Doses over 1000 mg and intermediate doses could be tested if needed. However, a daily dose of 1600 mg was deemed the maximum dose due to the daily allowance of cyclodextrin (320 mg/kg/day), which is included in the S65487 formulation.

It was decided that intermediate or lower doses could be proposed depending on the available results presented at end-of-cohort meetings during the study.

The starting dose of S65487 in the alternative schedule equalled the total weekly dose previously tested and considered safe in the initial schedule. The projected starting dose for the alternative schedule was 200 mg (total weekly dose) if the dose was considered safe while tested in the initial schedule.

During the dose allocation process, a decision to add two additional doses of S65487 during the first week of each cycle (on D2 and D4) could be made, so that 5 daily doses of S65487 could be given during the first week of treatment. If this decision was taken, unless otherwise justified, it was assumed that increasing the frequency of S65487 might have an effect on patients' safety and dose allocation, which may need to be guided by a new model to account for the possible heterogeneity between the schedules. Therefore, the information (e.g., DLT, etc.) collected from the initial and alternative schedule (S65487 administered on D1, D3, D5, D8 and D15) would be integrated in the new model to enrich the data in a down weighted manner.

To introduce this change in a conservative manner, the starting dose of S65487 given on D1, D2, D3, D4 and D5 would be equal to the total dose given on D1, D3, and D5, which was below the MTD. In addition, it was decided not to reduce the doses given on D8 and D15 with the first cohort of patients to receive 5 consecutive daily doses of S65487. The justification for this decision was that the increase of S65487 on D8 and D15 would not increase more than 2-fold from one dose level to the next, and the new dose level must satisfy the EWOC criteria according to the BLRM.

It might be decided during the conduct of the trial to enrol additional patients to dose levels at or below the MTD in order to better understand the safety, tolerability, PK or PD of S65487.

Irrespective of the treatment arm, before testing a new dose level, an end-of-cohort meeting (EoC) between the Sponsor, the coordinators and the investigators was organised to discuss the toxicities in terms of DLT, safety and PK data observed in all patients, and to decide jointly the next dose level to be tested.

A minimum of 6 evaluable patients should be treated at the MTD(s) in each schedule.

The planned dose expansion part of the study was not initiated.

DLT assessment

Toxicities were assessed according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

A DLT was defined as a clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications, that occurred during the first cycle following the first dose of S65487, and that met any of the criteria defined in the study protocol.

Details of the dose escalation procedure of the BLRM and determination of MTD(s) and/or RP2D(s) are provided in Section 9.7.

Comparator: NA

Duration of treatment:
Screening period: up to a maximum of 21 days prior to C1D-1.

Active treatment period: The planned duration of treatment was until disease progression. Patients might be discontinued from treatment with the study drug earlier due to unacceptable toxicity and/or at the discretion of the investigator or the patient. If the patient had progressive disease but was clearly benefiting from the study treatment in the investigator's opinion, the patient might remain on study treatment if it was in his/her best interest to continue S65487.

Follow-up period: after withdrawal due to any reasons, patients entered a follow-up period of 6 months or until death, whichever came first. During this follow-up period, new treatment received for the studied disease, date of progression and patient's survival were recorded. Since the decision to discontinue recruitment, the 3- and 6-month follow-up period were removed.

Statistical methodology:

Analysis sets:

Screened set: All screened patients.

Included set: All included patients.

Full analysis set (FAS): All included patients who had taken at least one dose of S65487, based on the intention-to-treat (ITT) principal and ICH E9 guideline.

Response evaluable set (RES): All patients of the FAS having at least one post-baseline tumour evaluation with at least one evaluable OR, i.e., OR not equal to not-evaluable (NE) or missing.

Safety set (SS): All patients having taken at least one dose of the IMP. Patients were analysed according to the dose received at C1D1.

DLT evaluable set (DLTES): All patients of the Safety Set who were evaluable for DLT according to the DLT assessment at end of cycle 1

Efficacy analysis was carried out in the FAS and RES. All efficacy parameters were provided in tables and/or graphs for each administration schedule (alternative, initial) and overall.
All **safety analyses** were performed in the SS (resp. DLTES for DLT analysis) for each disease group separately and by pooling patients from all disease groups by dose level and overall. The safety data was also presented for initial and alternative administration schedules, and overall.

Pharmacokinetic analysis: PK analysis is described in a separate PK report.

Pharmacodynamic analysis*:* Exploratory endpoint biomarker including (i) disruption of BCL-2 family protein complexes as a marker of S65487 on-target activity and (ii) detection of markers used to follow the Minimal Residual Disease MRD (disease and patient specific) are described when relevant and analysed overall and per indication, using change from baseline in the Biomarker Evaluable Set (BMKES).

Pharmacogenomic analysis*:* Pharmacogenomic analysis was optional and hence not performed during the study.

Study patients: disposition baseline characteristics and follow-up treatment analysis: Descriptive statistics were provided by dose level and overall.

Summary of results and conclusions

- A total of 78 patients were screened, 18 (23.1%) patients were excluded. Most (16 [20.5%]) of them were excluded due to non-compliance with inclusion / non-inclusion criteria. Two (2.6%) patients withdrew consent.
- A total of 60 patients were enrolled in the study, 48 patients were enrolled in the AML group, 5 patients in the NHL group, and 7 patients in the MM group. No patients were enrolled in the CLL group.
- Of the 60 patients enrolled to the study, 33 (55%) patients were enrolled with protocol deviations before or at inclusion.
- All enrolled patients were treated with S65487.
- All 60 patients were withdrawn from the study. The most common reasons for withdrawal were progressive disease (42 [70.0%] patients) and adverse events (8 [13.3%] patients).

- Overall, 22 (36.7%) patients were withdrawn during follow-up due to death (20 [41.7%] patients in the AML group, no patients in the NHL group, and 2 [28.6%] patients in the MM group) and 18 patients completed follow-up (9 [18.7%] patients in the AML group, 5 [100%] patients in the NHL group, and 4 [57.1%] patients in the MM group).

Demographic and baseline characteristics
Overall, the mean ± standard deviation (SD) age of the 60 patients was 65.9 ± 12.9 years (median = 67.0 years) and most of the patients (66.7%) were more than 60 years old.
More than half of the patients were male (65.0%), and the majority were white (91.1%).

AML
Overall, 48 patients were included with AML disease and classified as follows: 22 patients (45.8%) as 'AML, not otherwise specified', 16 (33.3%) as 'AML with myelodysplasia-related changes', 6 (12.5%) as 'AML with recurrent genetic abnormalities', and 4 (8.3%) as 'therapy-related myeloid neoplasm'.
Twenty-six (54.2%) patients had de novo AML and 22 patients (45.8%) had secondary AML.
The mean disease duration since diagnosis was 2.3 ± 2.0 years (median = 2.0 years).
At entry in the study, 19 (39.6%) patients were in relapse and 29 (60.4%) were refractory to previous treatment.

NHL
Of the 5 NHL patients, 3 (60.0%) patients had follicular lymphoma and 2 (40.0%) had mantle cell lymphoma subtype of NHL.
The mean disease duration since diagnosis was 4.4 ± 2.3 years (median =5.0 years).
At entry in the study, 4 patients (80%) were in relapse and 1 (20%) was refractory to previous treatment.
Overall, the treatment-free interval (defined as: date of first S65487 drug intake – date of end of the last prior therapy) was 323.4 ± 483.3 days (median = 68.0 days).

MM
Overall, 7 patients were included with MM disease and classified as follows: 5 patients (71.4%) as 'plasma cell myeloma', 1 (14.3%) as 'solitary plasmacytoma of bone', and 1 (14.3%) as 'other'.
The mean disease duration since diagnosis was 6.7 ± 1.8 years (median = 6.0 years).
At entry in the study, 3 (42.9%) patients were in relapse and 4 (57.1%) were refractory to previous treatment.
Overall, the treatment-free interval (defined as: date of first S65487 drug intake – date of end of the last prior therapy) was 40.0 ± 30.1 days (median = 33.0 days).

Tumour lysis syndrome
Of all 60 patients, 2 (3.3%) patients had intermediate risk of TLS and 17 (28.3%) patients had low risk of TLS.
IV hydration was performed in 17 (28.3%) patients, oral hydration was performed in 2 (3.3%) patients and anti-hyperuricemic agent was administered in 28 (46.7%) patients for TLS prevention at baseline.

Treatment duration
AML
In the Safety Set, S65487 treatment duration for patients with AML ranged between 1 and 78 weeks with a mean (±SD)13.6 (±15.6) weeks (median 7.3 weeks).

NHL
In the Safety Set, S65487 treatment duration for patients with NHL ranged between 3.1 and 104 weeks with a mean (±SD) of 34.6 (±44.7) weeks (median 6.1 weeks).

MM
In the Safety Set, S65487 treatment duration for patients with MM ranged between 1 and 18.14 weeks with a mean (±SD) 5.1 (±6) weeks (median 2.9 weeks).

Compliance
Overall, 28 (46.7%) patients had at least one treatment interruption, 25 (89.3%) of them had at least one medical reason for one treatment interruption.

Drug concentration
According to the stopping rules, the C_{max} threshold of 10 µg/mL, determined from the 4-week Good Laboratory Practice (GLP) toxicity study in rat, was exceeded in this study in one patient at 134 mg alternate Day 1 (cohort 9), two patients treated at 200 mg once weekly (QW) (cohort 5) and in all patients treated from 268 mg alternate Day 1, except one at 536 mg alternate Day 1 (cohort 6 and cohorts 8 to 15) with no safety concerns. All safety and PK data were analysed, and as no safety concerns were identified, dose escalation resumed as per protocol.

Follow-up duration
The mean (±SD) follow-up duration for 60 patients was 3.3 (±2.8) months (median 2.3 months).

In the context of the study discontinuation and abbreviated Clinical Study Report (CSR), no statistical analyses for efficacy are presented. Individual data listings are presented in Appendix of the CSR.

PK results
Accumulation of S65487 was not observed at the different doses and administration schedules evaluated in this study.

Inter-individual variability on the PK parameters was moderate to very high.

Exposure PK parameters (C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$) increased with an increase in the dose but no clear trend regarding dose linearity was observed. No time or schedule dependencies were observed.

At Day 1, S65487 has a low to moderate plasma clearance (~9-27 L/h), a low to moderate volume of distribution (~26-68 L) and a short terminal elimination half-life, ranging between 1.6 and 4.1 hours. No dose, time or schedule dependencies were observed.

Renal clearance (CL_R) of S65487 was very low (mean < 0.2 L/h) with a mean excreted fraction of the dose (f_e) < 2.0% at Day 1 up to 1200 mg. No dose or schedule dependencies were observed.

Safety results

The primary endpoints of the study were DLTs, incidence and severity of AEs and SAEs, laboratory test, vital signs, ECG, LVEF, dose interruptions and dose intensity.

Dose-limiting toxicity

In the initial schedule DLTs were experienced in the 75 mg, 100 mg, 800 mg, 1200 mg cohorts and in the alternative schedule DLT was experienced in the 1600 mg cohort.

Among 55 evaluable patients, 6 (10.9%) experienced at least one DLT during the dose escalation cycle 1:

- One (25.0%) NHL patient in the 75 mg dosing cohort experienced Grade 4 tumor lysis syndrome.
- One (25.0%) AML patient in the 100 mg dosing cohort experienced Grade 3 proteinuria.
- One (16.7%) AML patient in the 800 mg dosing cohort experienced Grade 2 myocardial infarction.
- Two (50.0%) patients (one AML and one MM) in the 1200 mg dosing cohort experienced DLTs. The MM patient experienced Grade 3 drug-induced liver injury and the AML patient experienced Grade 3 ALT increased, and Grade 4 AST increased.
- One (25.0%) AML patient in the 1600 mg alternative schedule dosing cohort experienced Grade 3 AST increased and Grade 2 blood bilirubin increased.
- The MTD was defined only for the initial schedule at 800 mg QW as the higher tested dose i.e., 1200 mg, was not tolerated. For the alternative schedule (Days 1, 3, 5, 8 and 15), the MTD was not identified as fewer than 6 patients were treated at the highest dose of 1000 mg. The escalation part for the alternative schedule was stopped at 1000 mg once (no DLTs were experienced in 4 evaluable patients).

Adverse events

Overall, 36 (60%) patients died during the study, with 14 (23.3%) deaths occurring during the treatment period.

While 22 patients (36.7%) died during the FU period, Among the deaths during the FU period, 14 (63.6%) were attributed to progressive disease.

During the treatment period, a total of 21 serious Treatment-Emergent Adverse Events (TEAEs) led to the deaths of 16 (26.7%) patients.

It should be noted that 2 fatal TEAEs had onset dates during the treatment period but resulted in death during the follow-up period. Therefore, the number of deaths during the treatment period is due to this fact.

A total of 402 TEAEs were reported in 59 patients in the study. Of these, 90 TEAEs were considered related to the treatment and were observed in 27 patients (45.0%). Out of these, 14 were considered serious TEAEs and occurred in 12 patients (20.0%).

Among the reported TEAEs, 154 were severe and occurred in 51 patients (85.0%). Of these severe TEAEs, 27 were deemed treatment-related and were observed in 15 patients (25.0%).

A total of 25 TEAEs in 16 (26.7%) patients led to study drug withdrawal, with 18 of these in 12 (20.0%) patients being serious TEAEs. Additionally, 8 treatment-related TEAEs in 6 (10.0%) patients led to treatment withdrawal, with 5 of these in 4 (6.7%) patients being serious TEAEs. Thirteen (13) TEAEs in 9 (15.0%) patients led to treatment being delayed, and 1 TEAE in 1 (1.7%) patient led to dose reduction.

TEAEs by severity

The most commonly reported severe TEAEs (affecting ≥5% of the patients overall) were: thrombocytopenia (11 patients [18.3%]), febrile neutropenia (10 patients [16.7%]), anaemia (8 patients [13.3%]); and malignant neoplasm progression and neutropenia (6 patients each [10%]), alanine aminotransferase increased (4 patients [6.7%]) and aspartate aminotransferase increased, hypokalaemia, pneumonia, septic shock (3 patients each [5.0%]).

Death

Overall, 36 (60%) patients died during the study, 14 patients (23.3%) died during the treatment period. Twenty-two patients (36.7%) died during the FU period.

A total of 21 serious TEAEs led to the deaths of 16 (26.7%) patients during treatment. The most common PTs (occurring in ≥3% of patients overall) associated with death were malignant neoplasm progression (6 TEAEs in 6 [10%] patients) and septic shock (2 TEAEs in 2 [3.3%] patients).

SAEs

Among the serious TEAEs reported, the most common (experienced in ≥5% of patients overall) were febrile neutropenia (10 [16.7%] patients), malignant neoplasm progression (6 [10.0%] patients), pneumonia (4 [6.7%] patients), infusion related reaction (3 [5.0%] patients), and septic shock (3 [5.0%] patients).

Discontinuations, dose reduction and dose delay

In total, 16 patients (26.7%) experienced at least one TEAE that led to treatment discontinuation. The main TEAEs leading to study drug discontinuation were related to blood and lymphatic disorders (5 [8.3%] patients), and infections and infestations (4 [6.7%] patients).

Overall, 1 patient (1.7%) had a TEAE that led to dose reduction, and 9 patients (15.0%) had at least one TEAE leading to dose delay. The only TEAE leading to dose reduction was tumor lysis syndrome (1 patient [1.7%]). The only TEAE leading to dose delay reported in more than one patient was gastrointestinal haemorrhage (2 patients [3.3%]).

Clinical laboratory evaluation

There were no meaningful differences in the incidence of shifts to higher toxicity grades (Grade 3 or 4) for haematology, biochemical parameters, coagulation, thyroid function, urinalysis in either disease or dose level groups.

Haematological parameters

Overall, emergent values Grade ≥ 3 were detected for the following haematological parameters: anaemia (35.6%: all Grade 3), high haemoglobin (8.5%, all Grade 3), low neutrophils (15.3% of the patients: 5.1% of the patients rated Grade 3 and 10.2% Grade 4), low white blood cells (18.6% of the patients: 6.8% of the patients rated Grade 3 and 11.9% Grade 4), and low platelets (18.6% of the patients: 10.2% of the patients rated Grade 3 and 8.5% Grade 4).

Biochemistry

Post baseline during treatment, the most common (≥5% of patients) emergent abnormal (high and/or low) Grade 3 or Grade 4 values for biochemical parameters in either disease group, were as following.

Hypercalcaemia ionized: 6 (21.4%) patients

High alanine aminotransferase: 5 (8.3%) patients

High aspartate aminotransferase: 5 (8.5%) patients

Hypokalaemia: 4 (6.7%) patients

Overall, the most frequent (≥ 30% of overall patients) emergent out-of-reference range values were detected for high aspartate aminotransferase (47.5%), high alanine aminotransferase (44.1%), high troponin T (41.2%), high lactate dehydrogenase (38.3%).

Coagulation

Overall, no post-baseline emergent severe abnormal events of Grade 3 or 4 high activated partial thromboplastin time were reported during treatment.

Thyroid function

Overall, post-baseline, 1 (1.9%) patient shifted to high T3 free (> ULN) and 1 (1.8%) to high T4 free (> ULN) and 8 (14.5%) patients switched to high thyroid-stimulating hormone (TSH) (> ULN) from normal values (≥ LLN or ≤ULN) at baseline.

Overall, post-baseline, 8 (15.4%) patients shifted to low T3 free (<LLN), and 8 (14.5%) patients switched to low T4 free (< LLN) from normal values (≥ LLN or ≤ULN) at baseline.

Overall, 8 (14.5%) patients reported post-baseline emergent out of range high TSH level. One (1.9%) patient each reported post-baseline emergent out of range levels of high and low T3 free and 1 (1.8%) patient had reported post-baseline emergent out of range high T4 free level.

Urinalysis and urinary biochemistry

Overall, 11 (37.9%) patients shifted to high microalbuminuria (>ULN) from the normal range (≥ LLN for the lowest value or ≤ULN for the highest value). Overall, of the 29 patients with at least one post-baseline value on treatment, 14 (48.3%) patients shifted to high microalbuminuria (>ULN).

Overall, among patients who were tested negative for urinary biochemical parameters at baseline, 19 (32.8%) tested positive for haematuria, 7 (12.1%) tested positive for glycosuria, 10 (17.2%) tested positive for proteinuria, and 7 (12.1%) tested positive for ketonuria post-baseline.

Vital signs

There were no meaningful changes from baseline in mean systolic and diastolic blood pressure, heart rate, weight and ECOG in any of the disease groups during the study.

Overall, 17 (30.4%) patients who had ECOG 0 at baseline shifted to ECOG scale 1, 2 (3.6%) each shifted to ECOG scale 2 and 3. Five (8.9%) patients who had ECOG 1 at baseline shifted to ECOG scale 2 and 1 (1.8%) patient shifted to ECOG scale 3.

Overall, 22 (37.3%) patients who had systolic blood pressure 90-140 mmHg at baseline shifted to systolic blood pressure ≥140 mmHg post-baseline under treatment.

Overall, 6 (10.2%) patients who had SBP 90-140 mmHg at baseline shifted to SBP <90 mmHg post-baseline under treatment.

Overall, 11 (18.6%) patients who had diastolic blood pressure 60-90 mmHg at baseline shifted to diastolic blood pressure ≥90 mmHg post-baseline under treatment.

Overall, 24 (40.7%) patients who had diastolic blood pressure 60-90 mmHg at baseline shifted to diastolic blood pressure <60 mmHg post-baseline under treatment.

Overall, 19 (32.2%) patients who had heart rate 60-100 beats per minute (bpm) at baseline shifted to heart rate ≥100 bpm post-baseline under treatment.

Overall, 12 (20.3%) patients who had heart rate 60-100 bpm at baseline shifted to heart rate <60 bpm post-baseline under treatment.

ECG and LVEF

Overall, 26 (43.3%) patients had clinically significant emergent ECG abnormality. Nine (15.3%) patients had QTcF value of 450 to 480 msec, 1 (1.7%) patient each had value of 480 to 500 msec and value of >500 msec. A maximum change of QTcF of 30 to 60 msec was seen in 16 (27.1%) patients and > 60 msec in 7 (11.9%) patients.

A total of 23 (47.9%) AML patients had clinically significant emergent ECG abnormality. Nine (19.1%) patients had QTcF value of 450 to 480 msec; 3 (6.4%) patients had value of 480 to 500 msec and 1 (2.1%) patient had value of >500 msec; with a maximum change of QTcF of 30 to 60 msec in 15 (31.9%) patients and > 60 msec in 1 (2.1%) patient.

A total of 2 (40.0%) NHL patients and 1 (14.3%) MM had clinically significant emergent ECG abnormality.

Among 48 AML patients, 43 patients had a mean decrease or no change in LVEF (-2.6±9.7).

Eight (8) AML patients (18.6%) had a change from baseline to worst (lowest) post-baseline value under treatment < - 10% in LVEF, while 35 (81.4%) had a change from baseline to worst (lowest) post-baseline value under treatment of ≥-10%.

Five NHL patients had a mean decrease in LVEF of -7.6±5.5 %. Of the 5 patients, 2 (40%) patients had change from baseline to worst (lowest) post-baseline value under treatment <-10% in LVEF and 3 (60%) had change from baseline to worst (lowest) post-baseline value under treatment ≥-10% in LVEF.

Four MM patients had a mean value of LVEF decreased (-2.3±2.6 %). All 4 MM (100%) patients had change from baseline to worst (lowest) post-baseline value under treatment ≥-10% in LVEF.

Conclusion

- A total of 60 patients were enrolled in the study CL1-65487-002, of whom 48 patients were enrolled in the AML group, 5 patients in the NHL group, and 7 patients in the MM group. No patients were enrolled in the CLL group.
- All **60 patients were withdrawn** from the study. **The most common reasons for withdrawal were progressive disease (42 patients [70.0%])** and adverse events (8 patients [13.3%]). Due to the limited efficacy observed with S65487 treatment in monotherapy, the decision was made to discontinue recruitment to the study. As a result, the expansion phase of this clinical study was not initiated, and the study was prematurely terminated. This decision was not based on any safety concerns.
- Five DLTs were reported in the initial schedule: 1 at 75 mg dose, 1 at 100 mg dose, 1 at 800 mg dose, and 2 at 1200 mg dose, and one DLT was reported in the alternative schedule at 1600 mg dose. **Among 55 evaluable patients, 6 (10.9%) experienced** at least one DLT during the first cycle of dose escalation. These DLT events included tumor lysis syndrome, proteinuria, myocardial infarction, drug-induced liver injury, and elevated liver enzymes.
- The **MTD was** defined only for initial schedule at 800 mg QW; the higher tested dose i.e. 1200 mg, was **not tolerated**. For the alternative schedule (Days 1, 3, 5, 8 and 15), the MTD was not identified as fewer than 6 patients were treated at the highest dose of 1000 mg. The escalation part was stopped at 1000 mg dose (no DLTs in 4 patients).
- The **safety profile of S65487 was generally acceptable in the CL1-65487-002 study**. **No major safety concerns** were observed in terms of TEAEs, clinical laboratory evaluations, or vital signs.
- **No accumulation of S65487** was observed at the different doses and administration schedules evaluated. **Renal clearance of S65487 was very low**. No dose or schedule dependencies were observed.

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