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 the orally administered selective Bcl-2 inhibitor S55746 as monotherapy for the treatment of patients with Acute Myeloid Leukaemia (AML) or high or very high risk Myelodysplastic Syndrome (MDS)

Protocol No.: CL1-55746-002
EudraCT No.: 2014-002559-24
The description of the study protocol given hereafter includes the modifications of the 8 substantial amendments to the protocol.

Coordinators
International coordinator: [redacted]
National coordinator: [redacted]

Study centres:
Five centres located in 2 countries included 48 patients: 2 centres in Australia (21 patients included) and 3 centres in France (27 patients included)

Publication (reference):
Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 22 January 2015 (first visit first patient) Completion date: 24 May 2018 (last visit last patient)	Phase I

Objectives:
Primary objectives:

To determine the safety profile and tolerability of S55746 in patients with AML, and high or very high risk MDS, in terms of Dose-Limiting Toxicities (DLTs), Maximum Tolerated Dose (MTD) of S55746 and determine 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 potential metabolites.
- To evaluate preliminary anti-leukaemic activity of S55746 using the response criteria proposed by 'Clinical Application and Proposal for Modification of the International Working Group response criteria in myelodysplasia' (Cheson, 2006) and the 'Revised Recommendations of the International Working Group for diagnosis standardization of Response Criteria Treatment outcomes and reporting standards for therapeutic trials in AML' (Cheson, 2003) in terms of:
  - Best Response Rate (BRR).
  - Progression-free survival (PFS).
  - Event-free survival (EFS).

Exploratory objectives:

- To determine the pharmacodynamic (PD) profile of S55746 according to:
  - The biological activity of S55746.
  - The relationship between the expression level of Bcl-2 family members in blasts (from blood and bone marrow samples) and the anti-leukaemic activity of S55746.
  - The relationship between gene alterations of Bcl-2 family members and other genes of interest (from blood and bone marrow aspirate) and the anti-leukaemic activity of S55746.
  - The variation of the karyotype induced by S55746 treatment.
- To perform an optional pharmacogenomic (PG) analysis of inter-patient variation in genes encoding for proteins involved in absorption/distribution/metabolism/excretion (ADME).

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

- A mCRM (modified Continual Reassessment Method) was used for dose allocation process in patients dosed in fasting condition.
- A Bayesian Logistic Regression Model (BLRM) with overdose control (EWOC) was used for dose allocation process in patients dosed in fed condition.

After the first patient was enrolled in the dose escalation in fed condition, the enrolment of new patients in fasting condition was ceased. Patients already enrolled continued to be dosed in the same condition (*i.e.* fasting condition).

This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.
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: 60 to 80 patients
Included: 48 patients (34 in the fasting group and 14 in the fed group)

Diagnosis and main criteria for inclusion:

- Women or men aged ≥ 18 years.
- Patients with cytologically confirmed and documented *de novo*, secondary or therapy-related AML (as defined by World Health Organization (WHO) 2008 classification, Vardiman *et al*, 2009) excluding acute promyelocytic leukaemia (APL, French-American-British M3 classification) :
  - With relapsed or refractory disease without established alternative therapy.
  - ≥ 65 years not previously treated for AML, who were not candidates for intensive chemotherapy or not candidates for established alternative chemotherapy

Or

Patients with cytologically confirmed and documented MDS or non-proliferative Chronic MyeloMonocytic Leukaemia (CMML), in relapse or refractory after previous treatment including at least one hypomethylating agent (5-azacytidine or decitabine):

- With high or very high risk (rIPSS > 4.5, Greenberg *et al*, 2012) MDS and without established alternative therapy.
- Transformed to AML and without established alternative therapy.

- Patients with WHO performance status 0-2, circulating white blood cells (WBC) ≤ $30x10^9$/L and ≤ $13x10^9$/L for non-proliferative CMML patients, adequate 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
S55746 *was* taken once a day without food *i.e.* at least 30 min prior to, or at least 2 hours after a meal.
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.

Precaution for S55746 administration: patients were hospitalised for at least 3 days to enable close in-patient Tumor Lysis Syndrome monitoring and management, in accordance with institutional guidelines and published criteria (Cairo *et al*, 2010).

Dose escalation
A minimum of 3 patients who met the eligibility criteria were enrolled at each cohort; the total number of patients per cohort (3 to 6 evaluable patients) depended on safety and PK data.
Before testing a new dose level, an end of cohort meeting 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 was needed at the MTD.
Once MTD was reached, an expansion cohort of up to 24 patients was planned to be evaluated at the MTD or lower dose levels, to gain more information about the safety profile of S55746, to provide additional PK/PD data, anti-leukaemic activity data, and to define the RP2D.
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.

Dose escalation in Fasting condition
A modified version of the Continual Reassessment Method (mCRM) was used for dose allocation process.
The target toxicity rate of 30% (that is the dose for which close to 30% of patients experienced a DLT) had been chosen between the sponsor, the coordinators and the investigators.
The first daily dose tested was 100 mg, and then a panel of doses from 50 to 2000 mg could be tested according to the dose allocation process of the mCRM. Intermediate doses could be proposed depending on available results during the study.

Dose escalation in Fed condition
An adaptive Bayesian Logistic Regression Model (BLRM) with overdose control (EWOC) was used to guide dose escalation and estimate the MTD(s) 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.
The first daily dose tested was 200 mg 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.

DLT assessment
Toxicities were assessed according to 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 non-haematologic DLT.
  - Any grade 3 non-haematologic toxicity not resolving to grade 1 within 7 days of stopping S55746.
  - Any grade 4 non-haematologic 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.
- Any treatment-related death.

Comparator:
Not applicable

Duration of treatment:
Patients received S55746 treatment during the fasting and fed conditions treatment periods. Patients, who had, in opinion of the investigator, clinical benefit from S55746 treatment could receive treatment until evidence of progressive disease, the occurrence of unacceptable toxicity, death, withdrawal of consent, or at the investigator's discretion, if clinically indicated after discussion between investigator and the sponsor on a case by case basis.
The maximum number of cycles administered was at the discretion of the investigator.

Criteria for evaluation:
Efficacy measurements:

- Patients with AML were evaluated for response based on the "Revised Recommendations of the International Working Group for diagnosis standardization of Response Criteria Treatment outcomes and reporting standards for therapeutic trials in AML" (Cheson, 2003).
- Patients with high or very high risk MDS or non-proliferative CMML were evaluated for response based on the "Clinical Application and Proposal for Modification of the International Working Group response criteria in myelodysplasia" (Cheson, 2006).

Safety measurements:
The safety criteria were DLTs, MTD, adverse events, laboratory tests (biochemistry, haematology with CBC differential count, coagulation, urine analysis, and thyroid function), vital signs (performance status (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.

Pharmacodynamic measurements: initially planned were not finally analysed.

Pharmacogenomic measurement (optional): initially planned was not finally analysed.

Statistical methods:
Analysis Set:
DLT Evaluable Set (DLTES): all patients of the 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 a t least 13 doses of 21 prescribed S55746 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 outcome and safety analysis: descriptive statistics were provided overall and by food condition whatever the disease group (AML or MDS).

Pharmacokinetic analysis: PK analyses are described in a separate report.

Pharmacodynamic and Pharmacogenomic analyses: not performed in the context of an abbreviated study report.

SUMMARY - CONCLUSIONS
DISPOSITION OF PATIENTS

Table 1 - Disposition of patients

Status		Fasting (N = 34)		Fed (N = 14)		ALL (N = 48)	
Included	**n**	**34**		**14**		**48**	
Withdrawn of treatment period due to	**n (%)**	**34**	**(100)**	**14**	**(100)**	**48**	**(100)**
Progressive disease	n (%)	24	(70.6)	10	(71.4)	34	(70.8)
Adverse event	n (%)	5	(14.7)	1	(7.1)	6	(12.5)
Physician decision	n (%)	4	(11.8)	2	(14.3)	6	(12.5)
Non-medical reason	n (%)	1	(2.9)	1	(7.1)	2	(4.2)

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

A total of 46 patients entered the follow-up (FU) period during which 33 patients died, 9 completed the FU period and 4 were lost to FU (including FU stopped due to study discontinuation).

BASELINE CHARACTERISTICS

Overall, the median age of patients was 70.0 years, 62.5% were male and mostly white (93.8%). These characteristics were similar in fasting and fed groups.

Forty-three patients were included with **AML disease**: 30 in the fasting group and 13 in the fed group. The diagnosis was AML not otherwise specified for 21 patients (48.8% of AML patients), AML with myelodysplasia related changes for 17 patients (39.5%), AML with recurrent genetic abnormalities for 3 patients (7.0%, all in the fasting group) and AML with therapy-related myeloid neoplasms for 2 patients (4.7%). As regards of the type of disease, 55.8% of patients had *de novo* AML and 44.2% had secondary AML. AML history characteristics were similar in fasting and fed group. The disease duration was 1.2 years (median).

At entry in the study, 3 patients were treatment naive for AML prior to entry in the study. Forty patients received at least one prior treatment drug and the treatment free interval before receiving S55746 was of 53.5 days (median). Among those patients, 31 patients (72.1%) were refractory to a previous treatment and 9 patients (20.9%) were in relapse. The progression free interval of last previous therapy prior to S55746 treatment start was of 6.5 months (median, n = 28).

Five patients were included with **MDS disease**: 4 in the fasting group and 1 in the fed group. The diagnosis was specified as refractory anaemia with excess blasts-1 in 4 patients and anaemia with excess blasts-2 in 1 patient. MDS risk assessment was assessed as high risk in 3 patients and very high risk in 2 patients. The disease duration ranged from 0.3 to 4.9 years. All MDS patients have received previous treatment for the disease. At entry in the study, 1 patient was in relapse and 4 patients refractory to previous treatment.

Most patients (93.8%) had received previous therapy for AML/MDS disease. Among those patients, all have received a drug treatment and few have received previous stem cell transplant (4 patients, 8.3%, all in the fasting group) or previous radiotherapy (3 patients, 6.3%). Overall, 6.3% of patients didn't received any previous treatment, 60.4% of patients have received between 1 or 2 lines of treatment and 33.3% of patients ≥ 3 (max 7) lines. Previous therapies were of similar profile in fasting and fed groups except for stem cell transplant.

At baseline, patients had an ECOG PS of 0 in 29.2% of patients, 1 in 58.3%, and 2 in 12.5%. Frequency of patients with ECOG PS equal to 0 was higher in the fasting group than in the fed group (38.2% and 7.1%, respectively). In contrast, the frequency of patients with ECOG PS 1-2 was lower in the fasting group than in the fed group (1: 52.9% *versus* 71.4% and 2: 8.8% *versus* 21.4%, respectively).

EXTENT OF EXPOSURE

The mean ± SD number of cycle was 4.6 ± 5.2. It was higher in the fasting group (5.3 ± 5.9) than in the fed group (3.1 ± 2.2). The mean treatment duration of S55746 was 13.1 ± 15.7 weeks. It was higher in the fasting group (14.9 ± 17.9 weeks) than in the fed group (8.9 ± 7.0 weeks) and none of the patients had dose reduction. Cycles were delayed in 25.0% of patients with similar frequency in the 2 groups. Overall, the mean relative dose intensity (RDI) was 98.3 ± 8.2%; overall, 91.7% of patients had a RDI > 85% while this percentage was higher in the fasting group than in the fed group (97.1% and 78.6%, respectively).

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 RD finding

During the two dose-escalations, the following dose levels were tested:

- Fasting condition (34 patients): 100 mg (n = 4), 300 mg (n = 5), 500 mg (n = 3), 700 mg (n = 3), 900 mg (n = 3), 1100 mg (n = 4), 1300 mg (n = 12).
- Fed condition (14 patients): 200 mg (n = 3), 400 mg (n = 3), 800 mg (n = 6), 1200 mg (n = 2).

At the end of cycle 1, 44 patients were evaluable for DLT (30 in the fasting group and 14 in the fed group). No DLT was reported in any of those patients.

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

Emergent adverse events

The main results of emergent adverse events are summarised in Table 2.

Table 2 - Overall summary for emergent adverse events in the Safety Set (N = 48)

		Fasting (N = 34)	Fed (N = 14)	ALL (N = 48)
Patients having reported at least one:				
EAE	n (%)	34 (100)	13 (92.9)	47 (97.9)
Treatment-related EAE	n (%)	13 (38.2)	2 (14.3)	15 (31.3)
Severe* EAE	n (%)	31 (91.2)	11 (78.6)	42 (87.5)
Treatment-related	n (%)	4 (11.8)	1 (7.1)	5 (10.4)
Serious EAE (including death)	n (%)	28 (82.4)	10 (71.4)	38 (79.2)
Treatment-related	n (%)	3 (8.8)	1 (7.1)	4 (8.3)
EAE leading to treatment withdrawal	n (%)	9 (26.5)	2 (14.3)	11 (22.9)
Severe* EAE	n (%)	8 (23.5)	1 (7.1)	9 (18.8)
Serious EAE	n (%)	7 (20.6)	2 (14.3)	9 (18.8)
Treatment-related EAE	n (%)	2 (5.8)	-	2 (4.2)
Treatment-related severe* EAE	n (%)	2 (5.8)	-	2 (4.2)
Treatment-related serious EAE	n (%)	2 (5.8)	-	2 (4.2)
Patients who died during the study	n (%)	25 (73.5)	9 (64.3)	34 (70.8)
During treatment period	n (%)	9 (26.5)	2 (14.3)	11 (22.9)
During the follow-up period	n (%)	16 (47.1)	7 (50.0)	23 (47.9)

** CTCAE grade ≥ 3*

Overall, almost all patients (97.9%) reported at least one EAE. The most frequent affected SOCs were Blood and lymphatic system disorders (77.1%), Infections and infestations (70.8%) and Gastrointestinal disorders (60.4%). The last two SOCs were more frequently affected in the fasting group (76.5% and 64.7%, respectively) than in the fed group (57.1% and 50.0%, respectively). In the other SOCs (at least 3 patients affected overall), the frequency was higher in the fasting group than in the fed group, except for vascular disorders which was reported with similar frequency in the 2 groups.

The ***most frequently reported EAEs*** (≥ 20%) ***in the overall study population*** were anaemia (45.8%), thrombocytopenia (31.3%), febrile neutropenia (25.0%), diarrhoea, hypokalaemia, malignant neoplasm progression (22.9% each) and nausea (20.8%). Among those EAEs, the following were more frequent in the fasting group than in the fed group: thrombocytopenia (38.2% and 14.3%, respectively), diarrhoea and hypokalaemia (26.5% and 14.3%, respectively, for each) and nausea (26.5% and 7.1%). Anaemia was less frequent in the fasting group than in the fed group (41.2% and 57.1%, respectively). Febrile neutropenia and malignant neoplasm progression were reported with similar frequency between the 2 groups.
Furthermore, vomiting, asthenia and neutropenia were frequently reported in the fasting group (26.5%, 23.5% and 20.6%, respectively) while they were not reported in the fed group.

Overall, the most frequent (> 10%) ***severe EAEs*** reported were anaemia (41.7% of patients including 39.6% grade 3 and 2.1% grade 4), thrombocytopenia (29.2% including 4.2% grade 3 and 25.0% grade 4), febrile neutropenia (25.0%, all grade 3), malignant neoplasm progression (18.8% including 4.2% grade 3, 2.1% grade 4 and 12.5% fatal), neutropenia (14.6% including 4.2% grade 3 and 10.4% grade 4) and hypokalaemia (12.5%, all grade 3). Among those severe EAEs, thrombocytopenia, neutropenia and hypokalaemia were more frequent in the fasting group (35.3%, 20.6% and 17.6%, respectively) than in the fed group (thrombocytopenia, 14.3%, and none for each other); anaemia was less frequent in the fasting group than in the fed group (35.3% and 57.1%, respectively); febrile neutropenia and malignant neoplasm progression were reported with similar frequency in the 2 groups.
Overall, 31.3% of patients had at least one ***treatment-related EAE*** with a higher frequency in the fasting group (38.2%) than in the fed group (14.3%). Treatment-related EAEs in at least 2 patients were reported only in the fasting group as following: diarrhoea (3 patients, 8.8%), anaemia, thrombocytopenia, asthenia, muscle spasms (2 patients, 5.9%, each). Overall, severe treatment-related EAEs were reported in 5 patients (10.4%) among those 4 patients (11.8%) in the fasting group [thrombocytopenia (2 patients, 5.9%), anaemia, asthenia, renal failure, hepatic failure and right ventricular failure (1 patient, 2.9%, for each)] and 1 patient (7.9%) in the fed group (neutrophil count decreased).

Overall, the most frequent ***serious EAEs*** were febrile neutropenia (25.0%), thrombocytopenia (22.9%), malignant neoplasm progression (20.8%), neutropenia and pneumonia (10.4% each). Among these EAEs, thrombocytopenia and neutropenia were more frequent in the fasting group (26.5% and 14.7%, respectively) than in the fed group (14.3% and none, respectively). Overall, at least one treatment-related serious EAE was reported in 4 patients (8.3%) among those, 3 patients (8.8%) in the fasting group (6 EAEs: thrombocytopenia, anaemia, renal failure, asthenia, right ventricular failure and hepatic failure) and 1 patient in the fed group (neutrophil count decreased).

EAEs leading to IMP withdrawal were reported in 11 patients (22.9%): 9 patients (26.5%) in the fasting group and 2 patients (14.3%) in the fed group. Each of these EAEs was reported in a single patient except malignant neoplasm progression (4 patients in the fasting group) and hemorrhagic stroke (2 patients in the fasting group). Severe EAEs leading to treatment withdrawal were reported in 9 patients (18.8%): 8 patients (23.5%) in the fasting group and 1 patient (7.1%) in the fed group. Overall, 2 patients (4.2%) reported 3 treatment-related severe EAEs leading to treatment withdrawal; these 2 patients (5.9%) were in the fasting group and EAEs were asthenia, hepatic failure and right ventricular failure.

A total of 34 patients (70.8%) died during the study (73.5% in the fasting group and 64.3% in the fed group), of which 11 (22.9%) died under treatment (26.5% and 14.3% respectively). The most frequent reason of death was the progression of the disease: 12.5% during treatment period and 91.3% during follow-up period.

Blood laboratory tests

In the fed group, emergent grade ≥ 3 values were not detected in more than one patient (7.6%) for each ***biochemical parameters***. In the fasting group, emergent grade ≥ 3 values were observed in at least 2 patients (5.9%) for low potassium (17.6%), high GGT (14.7%), low sodium (8.8%), high ALT and low albumin (5.9%, each).

For the ***haematological parameters***, emergent grade ≥ 3 values were detected in more than 20% of overall patients for low haemoglobin (58.3%) and low neutrophils (25.0%). There was no relevant difference between the two groups for low haemoglobin while a more marked difference was observed for low neutrophils (20.6% in the fasting group and 35.7% in the fed group).

Other safety evaluation

Neither clinically relevant changes nor differences between fasting and fed groups in mean values over time were detected for weight, blood pressure and heart rate.

Overall, 43.5% of the patients had their PS ECOG maintained with a lower frequency in the fasting group than in the fed group (27.8%, and 71.8%, respectively) while PS ECOG worsened (from 0 or 1 at baseline to ≥ 2 post-baseline) more frequently in the fasting group than in the fed group (62.5%, and 28.6%, respectively).

CONCLUSION

In this phase I, international, non-randomised, non-comparative, dose-escalation study, a total of 48 patients with acute myeloid leukaemia (43 patients) or high or very high risk myelodysplastic syndrome (5 patients) were treated orally either in fasting condition (34 patients) or in fed condition (14 patients) with a once daily dose of S55746 during 21-day cycles.

Patients received S55746 treatment for an average of 5 cycles, and all patients withdrew from the treatment, mostly for progressive disease (71%). No Dose Limiting Toxicity was reported in any patient during dose-escalations in either the fasting or fed condition.

The most frequently reported emergent adverse events (EAEs) (≥ 20% of overall patients) were anaemia, thrombocytopenia, febrile neutropenia, diarrhoea, hypokalaemia and nausea. Thrombocytopenia, diarrhoea and hypokalaemia were more frequent in the fasting group than in the fed group; anaemia was less frequent in the fasting group. Vomiting, asthenia and neutropenia were commonly reported in the fasting group while none of these occurred in the fed group. The most frequent serious EAEs were thrombocytopenia and febrile neutropenia, both more frequently reported in the fasting group than in the fed group. EAEs were treatment-related in nearly one third of patients with a higher frequency in the fasting group than in the fed group (38% and 14%, respectively). Treatment-related EAEs reported in at least two patients were diarrhoea, anaemia, thrombocytopenia, asthenia and muscle spasms, all were in the fasting group.

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 study 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 on-going patients participating in the trial could continue according to the protocol until the last patient last visit completed date.

Date of the report: 10 January 2019
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