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:** S47445		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**
Title of study: Efficacy and safety of S47445 *versus* placebo as adjunctive treatment of Major Depressive Disorder in patients with an inadequate response to antidepressant therapy. A randomised, double-blind, placebo controlled international, multicentre study. Protocol No.: CL2-47445-014 EudraCT No. 2015-003867-13: The description of the study protocol given hereafter includes the modifications of the two substantial amendments to the protocol.		
National coordinators: [redacted]		
Study centres: 414 patients were included in 54 centres located in 7 countries: Bulgaria (8 centres, 76 patients), Czech Republic (9 centres, 57 patients), Finland (4 centres, 25 patients), Hungary (9 centres, 42 patients), Russia (7 centres, 50 patients) , Slovakia (7 centres, 71 patients), Ukraine (10 centres, 93 patients).		
Publication (reference): Not applicable		
Studied period: Initiation date: 23 March 2016 (date of first visit first patient) Completion date: 06 April 2017 (date of last visit last patient)		**Phase of development of the study:** Phase II

Objectives:

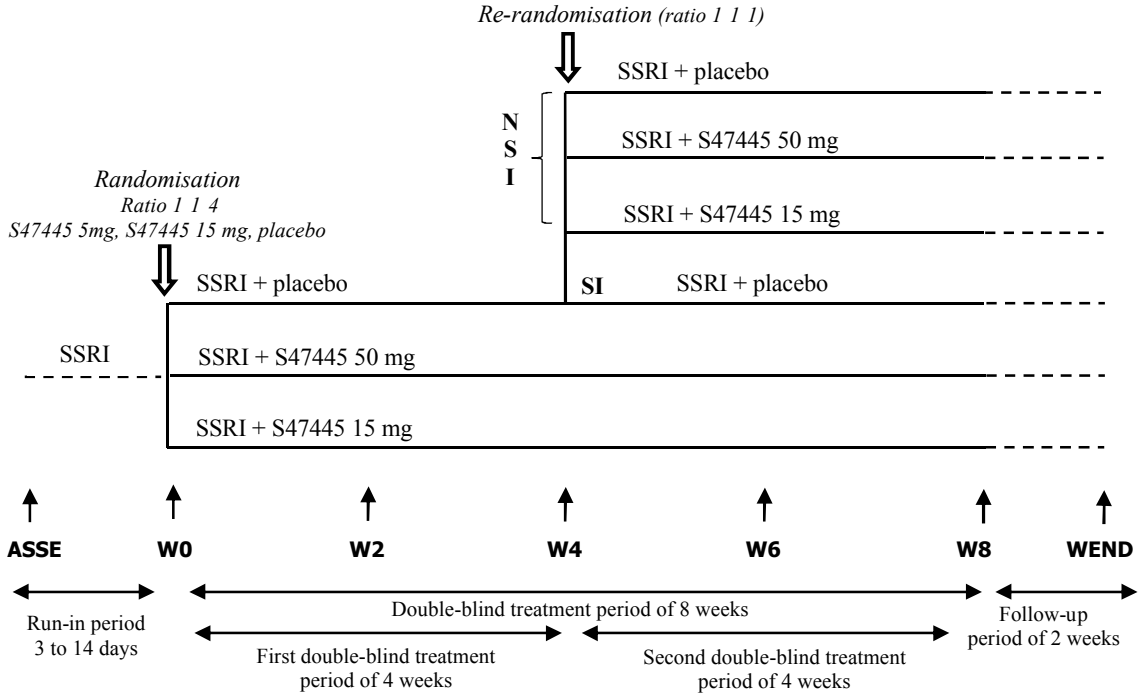
The purpose of the present study was to assess the efficacy and safety of S47445 (15 mg/day or 50 mg/day) compared to placebo in add on to SSRI (except fluvoxamine) in MDD patients with an inadequate response to their current SSRI treatment.

The primary objective of this study was to assess the efficacy of the two doses of S47445 (15 mg/day and 50 mg/day) compared to placebo after two periods of 4-week treatment, using the Hamilton Depression Rating Scale 17 items (HAM-D).

The secondary objectives were:

- To assess the response defined by the HAM-D total score decrease from baseline > 50%.
- To assess the efficacy of the two doses of S47445 as compared to placebo on Global improvement and social functioning using Clinical Global Impression (CGI), Hospital Anxiety and Depression scale (HAD) and Sheehan Disability Scale (SDS).
- To assess the safety and the tolerance of the two doses of S47445 compared to placebo.
- To evaluate the pharmacokinetics of S47445 after repeated oral administration.

Methodology:
This was a phase II, international, multicentre, randomised, double-blind, placebo-controlled study with parallel groups and a sequential parallel comparison (SPC) design.



The re-randomisation at W4 for patients not sufficiently improved (NSI) in the placebo arm was done in double-blind conditions neither the investigator nor the patient knew if and when these treatment changes happened. The re-randomisation criteria at W4 for patients NSI were as follows: HAM-D total score decrease from baseline < 50% and HAM-D total score > 13.
Patients under placebo during the first period and sufficiently improved (SI) at W4 continued under placebo up to W8.

This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.
The study was completed but the development of S47445 was discontinued by the Sponsor: an abbreviated study report was written.

Number of patients:
Planned: 400 patients.
Included: 414 patients.

Diagnosis and main criteria for inclusion:
Target population was patients suffering from moderate to severe major depressive episode according DSM 5 and confirmed by MINI structured interview.

Main inclusion criteria
Outpatients, aged between 18 (or legal age for majority) and 65 years old inclusive, male or female, with an inadequate response to current SSRI after at least 6 weeks of treatment (at appropriate dose for the treatment of a depressive episode) defined by:

- Hamilton Depression Rating Scale: HAM-D total score $\geq$ 20.
- Clinical Global Impression Severity of illness (item 1): 6 $\geq$ CGI-S $\geq$ 4.
- Antidepressant treatment response questionnaire completed by the patient: ATRQ < 50%.

At selection, the maximum SSRI treatment duration for the current episode had to be 4 months, and a stable dosage was required for at least 3 weeks.

Investigational Medicinal Products (IMPs):
Test drug: S47445
Tablets of 15 mg and 50 mg orally administrated, 1 tablet with a glass of water, once a day, during breakfast, starting the day after inclusion visit and ending the day of the 8-week visit.

Comparator: placebo tablets (matching the test drug products for double-blind masking)

Non IMPs (NIMPs):
NIMPs were SSRIs as listed in the study protocol (fluoxetine / citalopram / paroxetine / escitalopram / sertraline). SSRI (not provided by the sponsor) taken by the patient concomitantly to the IMP were managed as recommended in their SmPC for the treatment of a depressive episode. Fluvoxamine was contraindicated.

Duration of treatment:
Run-in period: no study treatment during the 3-14 days of selection period, the current SSRI was maintained at stable dosage.
Treatment period: 8 weeks of study treatment in add on to the current SSRI.
Follow-up period: no study treatment during the 2-week follow up period. The decision to maintain or stop the current SSRI was under the investigator's decision according to patient depression's condition.

Criteria for evaluation:
Efficacy measurements:
Primary endpoint: The HAM-D total score, expressed as change from baseline of the two doses of S47445 (15 mg/day, 50 mg/day) compared to placebo after two periods of 4 weeks of treatment.

Safety measurements: adverse events at each visit, body weight and BMI (ASSE, W4 and W8 visits),blood laboratory tests (W0, W4 and W8 visits), 12-lead ECG (W0, W4 and W8 visits), **v**ital signs (standing and supine systolic and diastolic blood pressure, heart rate) at each visit, Columbia-Suicide Severity Rating Scale (C-SSRS) at each visit except ASSE.

Pharmacokinetic measurements: blood sample was collected at W4 and W8.

Statistical methods:
Analysis Sets

- Randomised Set (RS): all included patients and randomised (according to IRS procedure) at W0.
- Full Analysis Set (FAS): all patients of the RS having taken at least one dose of IMP and having a value at baseline (W0) and at least one post-baseline value for the primary efficacy endpoint.
- Re-randomised Set (RRS): all patients of the FAS, on-going at W4 and re-randomised (according to IRS procedure) at W4.
- Re-randomised Full Analysis Set (RFAS): all patients of the RRS having taken at least one dose of IMP after W4 and having a value at W4 and at least one post-W4 value for the primary efficacy endpoint.
- Safety Set (SS): all included patients having taken at least one dose of IMP.
- Sub-Safety Set (Sub-SS): all patients of the SS on placebo all along the W0-W4 period, on-going at W4 and having taken at least one dose of IMP after W4.

Efficacy analysis:
Primary endpoint
In the context of this sequential parallel comparison design, in order to meet the primary objective of the study, the superiority of at least one dose of S47445 as compared to placebo on depression was assessed after 4 weeks of treatment from the 17-item HAM-D total score expressed in terms of change from baseline (W0) to W4 and of change from baseline (W4) to W8. A Mixed-effects Model for Repeated Measures (MMRM) similar to the model proposed by Doros was used, adapted to the three treatment arms design. All the longitudinal observations at each post-baseline visit on the W0-W8 period of all patients in the FAS were considered.

Statistical methods: (Cont'd)

Primary analysis

The comparisons of each dose of S47445 to placebo associated with the primary analysis were based on the weighted average of W0-W4 and W4-W8 treatment effects, in the FAS and the RFAS respectively. A weight w = 0.5 for each period was used.

The analysis model used all collected data jointly with a series of sub-model. Each sub-model (period 1, period 2 placebo NSI-re-randomised patients, period 2 placebo SI-patients staying under placebo and period 2 active-arms patients staying in the same treatment arm) was adjusted for country and was fitted simultaneously. A complete disjunctive parametrisation by period, individualizing the following interactions and implicitly involving the additive effects of treatment, period, visit and baseline, was used:

- For period 1 the visit-by-baseline and treatment-by-visit interactions.
- For placebo NSI-patients re-randomised in period 2, the visit-by-baseline and treatment-by-visit interactions.
- For the other patients in period 2 who were placebo SI-patients staying under placebo and active-arms patients staying in the same treatment arm, the visit-by-baseline interaction.

An unstructured (co)variance structure was used to model the within-patient errors. The assumptions underlying the model were checked. The step-down Holm procedure was used to control the family wise error rate, since 2 doses of S47445 were compared to placebo. To assess the robustness of the results of the primary analysis, sensitivity analyses to the method of handling missing data and to the modelisation were performed.

Study outcome: descriptive statistics provided by treatment group for each period.

Safety analysis:

Descriptive statistics were provided by treatment group:

- On the ASSE-W4/WEND period in the SS.
- On the ASSE-W8/WEND period in patients of the SS having received the same IMP during all study.
- On the W4-W8/WEND period in patients initially on placebo, entering in the W4-W8 period and having taken at least one dose of IMP on this period.

Pharmacokinetic analysis: the PK analysis initially planned was finally not performed.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Overall, 520 patients were selected for the study. Of them, 414 patients were included and randomly assigned to one of the 3 treatment groups at W0: 70 patients in the S47445 15 mg group, 66 in the S47445 50 mg group and 278 in the placebo group. The planned unbalanced distribution with 1:4 ratio for each S47445 group *versus* placebo group was reached.

During the first 4-week double-blind treatment period in the RS (N = 414), 15 patients (3.6%) were withdrawn: 7 patients for non-medical reason (1 patient in the S47445 15 mg group, 1 in the S47445 50 mg group and 5 in the placebo group) and 4 patients for adverse event (1 patient in the S47445 15 mg group and 3 in the placebo group). Overall, 399 patients (96.4%) completed the W0-W4 period.

During the second 4-week double-blind treatment period in the RRS (N = 227), among patients initially on placebo, those not sufficiently improved and still on-going at W4 were re-randomised. One patient sufficiently improved at W4 was wrongly re-randomised. Overall, 227 patients were re-randomised with a well-balanced distribution to one of the 3 treatment groups and entered in the W4-W8 period: 74 patients in the S47445 15 mg group, 77 in the S47445 50 mg group and 76 in the placebo group. Of note, the rate of patients not sufficiently improved at W4 among those initially on placebo (82.4%, 229 of 278 randomised to placebo) was higher than expected (70%). All patients completed the W4-W8 period, except one who withdrew for non-medical reason in the S47445 15 mg group.

During the 8-week double-blind treatment period in the RS, a total of 187 patients were not re-randomised at W4. These patients were randomised at W0 to one of the 3 groups: 70 patients in the S47445 15 mg group, 66 patients in the S47445 50 mg group and 51 patients in the placebo group. Of those, 92.0% completed the W0-W8 period and all patient withdrawals occurred during the W0-W4 period.

SUMMARY – CONCLUSIONS (Cont'd)

BASELINE CHARACTERISTICS

At baseline, the mean (± SD) age was 46.7 ± 11.6 years. Most patients were female (69.6%). The proportion of female was slightly lower in the S47445 50 mg group (62.1%) than in the S47445 15 mg and placebo groups (70.0% and 71.2%, respectively). There was no clinically relevant between-groups difference. No relevant differences between treatment groups were observed for alcohol consumption and smoking, weight, blood pressures and ECG parameters. Orthostatic hypotension (calculated) was observed in 9 patients, mostly in the placebo group (7 patients).

All included patients fulfilled DSM-5 criteria for MDD diagnosis confirmed by MINI. In all, 78.5% of patients were diagnosed as having recurrent MDD. The MDD was rated as moderate in 84.3% of patients and severe in 15.7%. MDD lasted on average 8.2 ± 8.2 years and the current episode on average 3.4 ± 1.9 months. The mean number of previous episodes was 2.2 ± 2.0. Regarding above characteristics of MDD, there was no relevant between-groups difference.

The HAM-D total score was on average (± SD) of 24.6 ± 2.4, CGI Severity of 4.4 ± 0.5, HAD depression score of 15.4 ± 2.7, HAD anxiety score of 8.2 ± 3.2 and SDS total score of 20.3 ± 3.4. No relevant between-groups difference was evidenced for any parameter.

Based on C-SSRS at baseline, 11 patients (2.7%) had suicidal ideation during their recent history (2 patients in S47445 15 mg group [2.9%], 2 patients in S47445 50 mg group [3.0%] and 7 patients in placebo group [2.5%]) and none had suicidal behaviour.

In the RS over W0-W4, mean treatment duration was 27.7 ± 2.6 days (median = 28.0 days). The mean compliance was 99.1 ± 5.8% with 99.0% of patients having compliance between 70% and 130%. There was no relevant between-group difference. Similar results were observed in the Safety Set.

At baseline (i.e. last value before first study drug intake on W4-W8) in the RRS, the ratio female/male was similar in the 3 treatment groups. The efficacy criteria scores were slightly lower compared to those at inclusion in RS, meaning potential improvement of patients after W0-W4 treatment period (placebo and IMP were in add on current SSRI): HAM-D total score was on average (± SD) of 20.0 ± 3.5, CGI Severity of 3.8 ± 0.7, HAD depression score of 12.1 ± 3.3, HAD anxiety score of 6.7 ± 3.5 and SDS total score of 16.7 ± 4.2.

Other demography and characteristics of the disease were similar to those observed in RS patients at W0.

Baseline characteristics of the patients in FAS were the same as RS over W0-W4. Those of RFAS patients were the same as RRS over W4-W8.

EXTENT OF EXPOSURE

In the RRS over W4-W8, mean treatment duration was 28.0 ± 1.6 days (median = 28.0 days). The mean compliance was 99.4 ± 3.5% with 99.6% of patients having compliance between 70% and 130%. There was no relevant between-group difference. Similar results were observed in the Sub-Safety Set.

During W0-W8, in patients of SS having taken the same IMP all along the study, mean treatment duration was 53.9 ± 8.8 days (median of 56 days). The mean compliance was 98.7 ± 7.1% with 98.5% of patients having compliance between 70% and 130%. There was no relevant between-groups difference.

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS

Primary criterion

HAM-D total score - Change from baseline during W0-W4 and W4-W8 periods
Difference between S47445 doses and placebo

		S47445 15 mg	S47445 50 mg	Placebo
FAS - Period 1: W0-W4 (N = 414)				
Baseline (W0)	Nobs	70	66	278
	Mean ± SD	24.6 ± 2.3	24.1 ± 2.3	24.7 ± 2.5
W4 - baseline	Nobs	69	65	272
	Mean ± SD	-5.6 ± 4.1	-4.9 ± 4.0	-6.2 ± 4.6
RFAS - Period 2: W4-W8 (N = 227)				
Baseline (W4)	Nobs	74	77	76
	Mean ± SD	19.9 ± 3.6	20.0 ± 3.0	20.2 ± 3.8
W8 - baseline	Nobs	73	77	76
	Mean ± SD	-5.9 ± 4.0	-6.8 ± 4.5	-6.7 ± 5.2
Statistical analysis				
FAS - Period 1: W0-W4				
Change from baseline to W4	E (SE) (1)	0.33 (0.57)	1.30 (0.58)	
	95% CI (2)	[-0.78 ; 1.45]	[0.16 ; 2.44]	
RFAS - Period 2: W4-W8				
Change from baseline to W8	E (SE) (3)	0.93 (0.73)	0.02 (0.72)	
	95% CI (4)	[-0.50 ; 2.36]	[-1.39 ; 1.44]	
FAS/RFAS - Period 1-2: W0-W4/W4-W8				
Primary statistical analysis				
Change from baseline (weighted)	E (SE) (5)	0.63 (0.46)	0.66 (0.46)	
	95% CI (6)	[-0.27 ; 1.53]	[-0.24 ; 1.57]	
	p-value (to be compared to 0.025) (7)	1.000	1.000	

The comparison of each dose of S47445 to placebo was based on the weighted average of W0-W4 (period 1) and W4-W8 (period 2) treatment effects, in the FAS and the RFAS respectively. A weight w=0.5 for each period was used S47445 doses minus placebo. Mixed-effects Model for Repeated Measures with a complete disjunctive parameterization by period, individualizing the following interactions and implicitly involving the additive effects of treatment, period, visit and baseline For period 1 the visit-by and treatment-by-visit interactions; for placebo SI-patients staying under placebo in period 2 the visit-by-baseline interaction; and for active-arms patients staying in the same treatment arm in period 2, the visit-by-baseline interaction.

(1) Period 1 treatment effects estimate (standard error)
(2) Period 1 two-sided 95% CI of the estimate
(3) Period 2 treatment effects estimate (standard error)
(4) Period 2 two-sided 95% CI of the estimate
(5) Weighted average treatment effects estimate (standard error)
(6) Two-sided 95% CI of the weighted average treatment effects estimate (without Holm adjustment)
(7) One-sided adjusted p-value taking into account Holm procedure for multiplicity adjustment (to be compared to 0.025)

No statistically significant superiority to placebo was demonstrated for any of the S47445 doses on HAM-D total score. Results were confirmed by sensitivity analyses.

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS

Adverse events

Summary for emergent adverse events over the first 4-week treatment period in the Safety Set

		S47445 15 mg (N = 70)	S47445 50 mg (N = 66)	Placebo (N = 278)
Patients having reported at least one:				
EAE	n (%)	14 (20.0)	11 (16.7)	60 (21.6)
Treatment-related EAE	n (%)	8 (11.4)	4 (6.1)	28 (10.1)
Serious EAE	n (%)	-	-	1 (0.4)
Treatment-related serious EAE	n (%)	-	-	1 (0.4)
EAE leading to treatment withdrawal	n (%)	1 (1.4)	-	3 (1.1)
Serious EAE leading to treatment withdrawal	n (%)	-	-	1 (0.4)
Treatment-related EAE leading to treatment withdrawal	n (%)	-	-	3 (1.1)
Treatment-related serious EAE leading to treatment withdrawal	n (%)	-	-	1 (0.4)
Patients who died	n (%)	-	-	-

In the Safety Set (SS) during the first 4-week treatment period (N = 414), the percentage of patients with at least one EAE was similar between the S47445 15 mg group and the placebo group. It tended to be slightly lower in the S47445 50 mg than in the placebo group.

The most frequently affected SOC (> 10% of patients) was Nervous system disorders with higher frequency in the S47445 50 mg group than in the placebo group (7.1% in the S47445 15 mg group, 12.1% in the S47445 50 mg group and 6.5% in the placebo group).

The most frequently reported EAE was headache with higher frequency in the S47445 groups (5.7% in the S47445 15 mg group and 6.1% in the S47445 50 mg group) than in the placebo group (2.9%). Other EAE reported by at least 2 patients in the S47445 groups were nasopharyngitis (2.9% and 1.5%, respectively in the S47445 15 mg and 50 mg groups, and 0.4% in the placebo group) and somnolence (none and 3.0%, respectively in the S47445 15 mg and 50 mg groups, and 0.4% in the placebo group).
All EAEs were mild or moderate, except one (headache) which was severe in the placebo group.

The frequency of treatment-related EAEs was similar between S47445 15 mg group (11.4%) and placebo group (10.1%) . It tended to be slightly lower in the S47445 50 mg group than in the S47445 15 mg group (6.1%). Headache treatment-related tended to be higher in the S47445 15 mg group than in the placebo group (5.7% *vs* 2.2%) while it was similar between the S47445 50 mg group and the placebo group (1.5% *vs* 2.2%).

No S47445-treated patients reported a serious EAE. One patient in the placebo group reported a serious EAE vision blurred considered as treatment-related and leading to treatment withdrawal.
Four patients reported at least one EAE (including serious events) leading to treatment withdrawal during W0-W4: 1 patient (1.4%) in the S47445 15 mg group and 3 patients (1.1%) in the placebo group.

Summary for emergent adverse events over the second 4-week treatement period in the Sub-Safety Set

		S47445 15 mg (N = 74)	S47445 50 mg (N = 77)	Placebo (N = 116)
Patients having reported at least one:				
EAE	n (%)	11 (14.9)	17 (22.1)	17 (14.7)
Treatment-related EAE	n (%)	1 (1.4)	8 (10.4)	4 (3.4)
Serious EAE	n (%)	1 (1.4)	-	1 (0.9)
Treatment-related serious EAE	n (%)	-	-	-
EAE leading to treatment withdrawal	n (%)	-	-	-
Patients who died	n (%)	-	-	-

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

In the Sub-Safety Set (Sub-SS) during the second 4-week treatment period (N = 267), the percentage of patients with at least one EAE was similar between the S47445 15 mg group and the placebo group. It was slightly higher in the S47445 50 mg than in the placebo group.

The SOC Nervous system disorders was the most frequently affected in the S47445 50 mg, with a higher frequency than in both S47445 15 mg and placebo groups (7.8% *vs* 2.7% and 0.9%, respectively). Likewise, headache was the most frequent reported EAE: 2 patients (2.7%) in the S47445 15 mg, 3 patients (3.9%) in the S47445 50 mg and 1 patient (0.9%) in the placebo group.

No adverse events were severe in any treatment groups. The frequency of treatment-related EAEs was higher in the S47445 50 mg group than in S47445 15 mg group and placebo group (10.4%, 1.4% and 3.4%, respectively). Treatment-related EAEs in more than 2 patients was headache (none in S47455 15 mg group, 3.9% in the S47445 50 mg group and 0.9% in placebo group).

Two patients reported at least one serious EAE: one patient had spinal pain not treatment-related in the S47445 15 mg group and the other patient had acute vestibular and syndrome and diarrhoea (both not treatment-related) in the placebo group.

No adverse events (including serious events) led to treatment withdrawal during W4-W8.

Summary for emergent adverse events over the 8-week treatment period in patients having taken same IMP during study in the SS

		S47445 15 mg (N = 70)	S47445 50 mg (N = 66)	Placebo (N = 127)
Patients having reported at least one:				
EAE	n (%)	14 (20.0)	15 (22.7)	33 (26.0)
Treatment-related EAE	n (%)	8 (11.4)	4 (6.1)	15 (11.8)
Serious EAE	n (%)	-	-	2 (1.6)
Treatment-related serious EAE	n (%)	-	-	1 (0.9)
EAE leading to treatment withdrawal	n (%)	1 (1.4)	-	3 (2.6)
Serious EAE leading to treatment withdrawal	n (%)	-	-	1 (0.9)
Treatment-related EAE leading to treatment withdrawal	n (%)	-	-	3 (2.6)
Treatment-related serious EAE leading to treatment withdrawal	n (%)	-	-	1 (0.9)
Patients who died	n (%)	-	-	-

In the patients of SS having taken same IMP during study during the 8-week treatment period (N = 263), the percentage of patients with at least one EAE tended to be slightly lower in both S47445 groups than in the placebo group.

The distribution of affected SOCs on W0-W8 was similar to those observed in patients of SS on W0-W4. Nervous system disorders was the most frequent affected SOC with higher frequency in the S47445 50 mg group than in the placebo group. Headache was the most frequent EAE during W0-W8. In comparison with the SS during W0-W4, the frequencies in the S47445 groups were closer those of the placebo group. Two EAEs were severe: 1 headache in the placebo group and 1 gastroenteritis eosinophilic in the S47445 50 mg group. The frequency of treatment-related EAEs was similar between S47445 15 mg group and placebo group. It was slightly lower in the S47445 50 mg group than in the S47445 15 mg group (6.1% *vs* 11.4%, respectively).

Two patients in the placebo group reported at least one serious EAE (one during W0-W4, the other during W4-W8, see above).

Four patients reported at least one EAE (including serious events) leading to treatment withdrawal. All these events occurred during W0-W4 in the SS.

Laboratory tests

Changes in mean value over time

Neither clinically relevant changes nor differences between groups from baseline to last post-baseline value on treatment were detected for biochemical and haematological parameters during the first 4-week treatment period in the SS, the second 4-week treatment period in the Sub-SS as well as during the 8-week treatment period in patients having taken same IMP in the Sub-SS.

Emergent potentially clinically significant abnormal (PCSA) values

During first 4-week treatment period in the SS, emergent PCSA biochemical value was reported in at most one patient in the S47445 groups, except for high total cholesterol more frequently observed in the S47445 50 mg group than in the placebo group (4.6% *vs* 1.1%), for low HDL cholesterol and high LDL cholesterol both more frequently observed in the S47445 15 mg group than in placebo group (4.4% *vs* 1.5% and 5.9% *vs* 1.6%, respectively). As regards of emergent PCSA haematological values, these were sparse in all groups and for each parameter.

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Emergent potentially clinically significant abnormal (PCSA) values(Cont'd)

During the second 4-week treatment period in the Sub-SS, emergent PCSA biochemical and haematological values were sparse in the S47445 groups for each parameter.

During the 8-week treatment period in patients having taken same IMP in the Sub-SS, emergent PCSA biochemical values were sparse in the S47445 groups and for each parameter, except for high total cholesterol, low HDL cholesterol, high LDL cholesterol (higher frequency in the S47445 15 mg group than in the placebo group: 10.3% in *vs* 1.7%,) and high creatine phosphokinase (higher frequency in the S47445 50 mg group than in the placebo group: 4.6% *vs* 1.6%). As regards of emergent PCSA haematological values, these were sparse in all groups, except for low haematocrit more frequently observed in the S47445 15 mg group than in placebo group (4.5% *vs* 1.6%).

Other safety evaluation

Neither clinically relevant changes nor between-groups differences were detected in vital signs or clinical examination during any of the treatment periods. Of note, no orthostatic hypotension was reported as adverse event by the investigator.

Neither clinically relevant changes nor between-groups differences were observed regarding quantitative ECG parameters. No QTcF values greater than 480 ms were detected on treatment. None of the patients had an emergent clinically significant ECG abnormality.

CONCLUSION

This international, multicentre, randomised, double-blind, placebo-controlled phase II study conducted in patients suffering from major depressive disorder with inadequate response to their current antidepressant therapy did not show superiority for any of the S47445 doses *versus* placebo as adjunctive treatment to SSRI on total score of Hamilton depression rating scale.

Emergent adverse events were no more frequent with S47445 than with placebo. Headache was the most common adverse event on S47445 with a higher frequency than with placebo. No concerns were observed regarding other safety assessments, especially orthostatic hypotension was not reported as adverse event. This study demonstrated a good safety profile of S47445 in association with SSRI.

Date of the report: 30 January 2018

Version of the report: Final version