Document title	**Clinical Study Report Synopsis**
Study title	**Safety and efficacy of S 33138 versus risperidone in schizophrenic patients with predominant positive symptoms: A pilot phase IIa, international, multicentre, randomised, double-blind, parallel-group, controlled study**
Study drug	**S 33138**
Studied indication	**Schizophrenia**
Development phase	**Phase IIa**
Protocol code	**CL2 - 33138 - 007**
Study initiation date	**21 July 2005**
Study completion date	**17 October 2006**
Main coordinator	[redacted] **Germany**
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France** **Laboratorios Servier (S.L.)** **Avenida de los Madronos, 33** **28043 Madrid - Spain** **Servier Research & Development Limited (SRDL)** **International Centre of Therapeutic Research** **Gallions, Wexham Springs** **Framewood Road - Wexham** **Slough SL3 6RJ - United Kingdom**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 25 February 2008**

~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study:
Safety and efficacy of S 33138 versus risperidone in schizophrenic patients with predominant positive symptoms: A pilot phase IIa, international, multicentre, randomised, double-blind, parallel-group, controlled study.
Protocol No.: CL2-33138-007

International coordinator: [redacted] Germany) (was also national coordinator for Germany)
National coordinators: [redacted]) in Australia, [redacted] (London) in Great Britain, [redacted] Italy, [redacted] Poland, [redacted] in Spain, [redacted] Hungary, [redacted] Bulgaria, [redacted] Austria (added by Amendment No. 2).

Study centres: 33 centres located in 9 countries were opened, and 32 included at least one patient: Australia (2 centres, 2 patients included), Austria (1 centre, 1 patient included), Bulgaria (added by Amendment No. 5 ; 7 centres, 56 patients included), Germany (3 centres, 7 patients included), Hungary (added by Amendment No. 1 ; 5 centres, 42 patients included), Italy (5 centres, 11 patients included), Poland (5 centres, 28 patients included), Spain (4 centres, 32 patients included), Great Britain (1 centre, no patient selected).

Publication (reference): None

Studied period:	**Phase of development of the study:**
Initiation date: 21 July 2005 *(date of first visit)* Completion date: 17 October 2006 (*date of last visit*)	IIa

Objectives:
Primary objective: to assess the clinical and biological safety of S 33138 after 8 weeks of oral administration in schizophrenic patients with predominant positive symptoms.
Secondary objectives: to assess the efficacy of S 33138, to get an evaluation of patient's subjective well-being, and to assess the pharmacokinetics of S 33138 and S 35424.

Methodology:
This was a pilot, phase IIa, international, multicentre, randomised, double-blind, four-parallel-group, controlled study. This study tested 3 fixed doses of S 33138 (5, 10, and 20 mg/d) *versus* flexible dose of risperidone (4 or 6 mg/d) for 8 weeks.

Number of patients:
Planned: 160 patients (40 by group)
Included: 179 patients (47 in the S 33138 5 mg group, 40 in the S 33138 10 mg group, 47 in the S 33138 20 mg group, 45 in the risperidone group)

Diagnosis and main criteria for inclusion:
Patients of both genders, aged between 18 and 65 years with DSM-IV-TR criteria for an acute first episode or a relapse of schizophrenia paranoid type (295.30) or schizoaffective disorder (295.70) or provisional schizophreniform disorder (295.40) or schizophrenia undifferentiated type (295.90), a total score of at least 60 for the 30-item Positive and Negative Syndrome Scale (PANSS), a score of at least 4 on three or more items of the PANSS positive subscale, a (PANSS positive subscale score - PANSS negative subscale score) > 0, a Clinical Global Impression (CGI) Severity of Illness score of at least 4 (moderately ill), and normal results for physical examination and vital signs.

Study drug:
S 33138 5 mg or 10 mg tablets in capsules. Patients randomly received 3 fixed doses of S 33138 (5, 10, or 20 mg/d), *i.e.* one capsule (+ 1 placebo capsule) or two capsules p.o. once a day in the morning before breakfast. Patients treated with S 33138 20 mg had a titration period, and received a half dose (10 mg/d) for 1 week. At each visit from W1 to W6, according to investigators' judgement, patients could have a double-blind dose adaptation, and received one placebo capsule in the evening before dinner.
Batch No. L0005808, L0005972, L0006131, L0006658, L0011317.

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Reference product:
Risperidone 2 mg tablet in capsule. Patients randomly received 4 mg/d, *i.e.* two capsules p.o. once a day in the morning before breakfast. Patients had a titration period, and received a half dose (2 mg/d) for 2 days. At each visit from W1 to W6, there was a flexible dose adaptation according to investigators' judgement. Patients could have a double-blind dose adaptation (6 mg/d), and received a third capsule in the evening before dinner.

Duration of treatment:
Wash-out period: 2 to 7 days between the selection visit and the first study drug intake, the day after inclusion visit (W0).
Double-blind treatment period: 8 weeks, from W0 to W8 visits.
Follow-up period: 2 to 4 weeks with a treatment free period of 3 to 7 days.

Criteria for evaluation:
Safety measurements:
Adverse events: at each visit.
Simpson-Angus Scale (SAS) and **Barnes Akathisia Scale (BAS)** were assessed at W0, W1, W2, W4, W6, and W8 visits, and at the withdrawal visit in case of premature treatment withdrawal.
UKU side effect rating scale (UKU) was assessed at W0, W4, and W8 visits, and at the withdrawal visit in case of premature treatment withdrawal.
Clinical laboratory testing: blood biochemistry, haematology, and endocrinology (prolactin for all patients selected, and PSA, Testosterone, LH, and FSH for male patients; added by Amendment No 2) were performed at the selection visit, at W4, and W8 visits, at the withdrawal visit in case of premature treatment withdrawal, and at the study end visit.
Physical examination, including neurological and mental status examinations, and vital signs (body temperature, body weight, supine systolic blood pressure, supine diastolic blood pressure and supine heart rate) were assessed at all visits during the whole study (at the selection visit, at W0, W1, W2, W4, W6, W8, at the withdrawal visit in case of premature treatment withdrawal, at the follow-up visit, and at the study end visit). Height was only measured at the selection visit.
12-lead ECGs were recorded at the selection visit, at W1, W4, and W8 visits, at the withdrawal visit in case of premature treatment withdrawal, at the follow-up visit, and at the study end visit. At W1, W4, and W8, 4 recordings were performed, prior to, 1h, 3h and 6h after study drug administration. ECG readings were centralised.
Other assessments not specifically related to efficacy or safety:
Subjective Well-being under Neuroleptics - short form (SWN): Patients self-assessed subjective well-being over the past 7 days at W0, W2, W4, and W8 visits.
Efficacy measurements:
PANSS and **CGI** were completed at each visit from the selection visit to the last visit of the double-blind treatment period (W0, W1, W2, W4, W6, W8), and at the withdrawal visit in case of premature treatment withdrawal. CGI Global Improvement and CGI Efficacy Index were assessed from W1.
Pharmacokinetic measurements: at W4 and W8 visits (prior to, 1h, 3h and 6h after study drug administration), at the follow-up visit, and at the study end visit. Plasma levels of S 33138 and its main metabolite S 35424 were centrally assayed.

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Statistical methods:

Safety assessment of S 33138 was the primary objective of the study. No particular safety measurement was considered as primary criterion.

Safety analysis

All safety parameters were described by treatment group in the Safety Set over the W0 - W8 period, and the follow-up period.

Efficacy analysis

PANSS and CGI scales were described by treatment group over the W0-W8 period in the FAS and the OCW8S. For the change from baseline to last post-baseline value of the PANSS total score, estimate of the difference between each dose of S 33138 and risperidone as well as associated standard error and 95% two-sided confidence interval were provided using a two-way analysis of covariance on factors treatment and centre (random effect) with baseline as covariate.

For both parameters, response to treatment was defined: decrease from baseline of PANSS total score ≥ 20%, or 30%, and CGI global improvement score = 1 or 2.

Other analysis: SWN scale

Descriptive statistics over the W0-W8 period.

Pharmacokinetic analysis

Descriptive statistics were to be performed on the plasma concentrations for both S 33138 and S 35424. Secondly, plasma S 33138 and S 35424 concentrations were to be analysed using a compartmental population approach. Finally, the relationship between pharmacodynamic data (score results) and plasma concentrations was to be analysed by a graphical approach. If applicable, this relationship was to be modelised with an appropriate pharmacokinetic/pharmacodynamic (PK/PD) population model.

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

		S 33138 5 mg	**S 33138 10 mg**	**S 33138 20 mg**	**Risperidone**	**All**
Included (randomised)		**47**	**40**	**47**	**45**	**179**
Lost to follow-up		-	-	-	-	-
Withdrawn due to		**24**	**16**	**20**	**7**	**67**
Adverse event		0	2	3	0	5
Protocol deviation		6	1	0	1	8
Lack of efficacy		10	7	11	2	30
Non medical reason		8	6	6	4	24
Completed at W8		**23**	**24**	**27**	**38**	**112**
Attended the follow-up visit		**37**	**32**	**39**	**44**	**152**
Attended the end of study visit		**40**	**36**	**42**	**43**	**161**
Safety Set	**n (%)**	47 (100.0%)	40 (100.0%)	47 (100.0%)	44 (97.8%)	178 (99.4%)
Full Analysis Set (FAS)	**n (%)**	45 (95.7%)	40 (100.0%)	45 (95.7%)	43 (95.6%)	173 (96.6%)
Observed cases W8 Set (OCW8S)	**n (%)**	26 (55.3%)	26 (65.0%)	28 (59.6%)	38 (84.4%)	118 (65.9)

% % according to Randomised Set

In all, 179 patients were included, and randomly assigned to one of the 4 groups: 47 patients in the S 33138 5 mg group, 40 in the S 33138 10 mg group, 47 in the S 33138 20 mg group, and 45 in the risperidone group. Among them, 112 patients (62.6%) completed the study with a lower frequency in the S 33138 groups than in the risperidone group: 23 patients (48.9%) in the S 33138 5 mg group, 24 (60.0%) in the S 33138 10 mg group, and 27 (57.4%) in the S 33138 20 mg group *versus* 38 (84.4%) in the risperidone group.

In all, 152 patients (84.9%) attended the follow-up visit, and 161 (89.9%) attended the end of study visit.

Overall, 67 patients (37.4%) were withdrawn. The rate of withdrawals was higher in the S 33138 groups than in the risperidone group: 24 patients (51.1%) in the S 33138 5 mg group, 16 (40.0%) in the S 33138 10 mg group, and 20 (42.6%) in the S 33138 20 mg group *versus* 7 (15.6%) in the risperidone group.

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This difference was mainly related to the rate of withdrawals due to lack of efficacy which was higher in the S 33138 groups: 10 patients (21.3%) in the S 33138 5 mg group, 7 (17.5%) in the S 33138 10 mg group, and 11 (23.4%) in the S 33138 20 mg group *versus* 2 (4.4%) in the risperidone group.
In the RS, the mean treatment duration over the W0-W8 period was 42.5 ± 19.4 days, median 55.0 days. The treatment duration was shorter in the S 33138 groups than in the risperidone group as shown by the mean duration (39.0 ± 20.5, 41.6 ± 19.4 and 40.0 ± 20.4 days in the S 33138 5 mg, 10 mg, and 20 mg groups, respectively *versus* 49.7 ± 15.2), and the distribution of patients at Q1 (22.0, 21.0, and 20.0 days in the S 33138 5 mg, 10 mg, and 20 mg groups, respectively *versus* 54.0 days). In the OCW8S, the mean treatment duration over the W0-W8 period was 55.4 ± 2.2 days, median 56.0 days, and did not differ between groups.

In the RS, the mean age was 38.7 ± 10.0 years, ranging from 18 to 64 years. The male patients were slightly over-represented (55.9%). According to DSM-IV TR criteria, most patients (87.7%) had a paranoid type schizophrenia. Undifferentiated type schizophrenia was diagnosed in 3.4% of patients. Schizoaffective disorder was diagnosed in 6.1% of patients, and schizophreniform disorder in 2.8% of patients.
Schizophrenia lasted for 10.9 ± 9.3 years on average (median 8.7 years), and the current episode for 2.7 ± 7.5 months (median 1.2 months). Most patients (89.4%) reported a schizophrenia lasting for at least 6 months.
All patients but 3 (98.3%) had been previously treated by antipsychotic treatment. The most frequent treatments were risperidone (59.8%), haloperidol (49.7%), and olanzapine (49.2%).
At inclusion, in the RS, the mean SAS total score was 1.4 ± 2.6, median 0. The most frequent extrapyramidal symptom was abnormal gait in 25% of patients. The mean BAS global clinical assessment of akathisia score was 0.2 ± 0.4, median 0. The mean UKU total score was 6.7 ± 6.2, median 5.5. As regards the mean sub-scores, psychic score was higher than the other scores (4.6 ± 4.2 *versus* 0.7 ± 1.2 for neurologic score, and 0.8 ± 1.5 for autonomic score).
At inclusion, in the RS, the mean PANSS total score was 89.2 ± 11.6. On average, the positive score was higher than the negative score (26.3 ± 3.9 *versus* 19.1 ± 3.9, respectively). The mean CGI severity of illness score was 4.8 ± 0.6 corresponding to markedly ill patients, on average.
In the RS, demography, disease characteristics, as well as safety and efficacy scales showed no clinically relevant differences between groups.
The baseline characteristics in the FAS and OCW8S were similar to those in the RS but the mean PANSS total score in the OCW8S which was smaller in the S 33138 10 mg group (84.1 ± 7.5) than in the other groups (90.2 ± 9.5, and 87.9 ± 13.0 in the S 33138 5 and 20 mg groups, respectively, and 90.3 ± 12.7 in the risperidone group).

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SAFETY RESULTS (cont'd)
- Emergent adverse events

Summary of emergent adverse events

		S 33138 5 mg (N=47)	S 33138 10 mg (N=40)	S 33138 20 mg (N=47)	Risperidone (N=44)
Patients having reported					
at least one emergent adverse event	n (%)	25 (53.2)	18 (45.0)	18 (38.3)	27 (61.4)
at least one treatment-related emergent adverse event	n (%)	12 (25.5)	9 (22.5)	10 (21.3)	14 (31.8)
at least one emergent headache*	n (%)	4 (8.5)	-	1 (2.1)	2 (4.5)
at least one emergent akathisia*/ **	n (%)	1 (2.1)	2 (5.0)	-	4 (9.1)
at least one emergent weight decrease*	n (%)	1 (2.1)	-	3 (6.4)	-
At least one emergent extrapyramidal disorder**	n (%)	2 (4.3)	1 (2.5)	2 (4.3)	4 (9.1)
Patients having experienced					
at least one serious adverse event	n (%)	1 (2.1)	1 (2.1)	1 (2.1)	-
at least one treatment-related serious adverse event	n (%)	-	1 (2.1)	1 (2.1)	-
Patients with premature treatment discontinuation					
due to an emergent non serious adverse event (excluding schizophrenia)	n (%)	-	1 (2.1)	1 (2.1)	-
due to an emergent serious adverse event	n (%)	-	1 (2.1)	1 (2.1)	-
due a treatment-related adverse event	n (%)		2 (5.0)	2 (4.3)	
due a treatment-related serious adverse event	n (%)	-	1 (2.1)	1 (2.1)	-
Patients who died	n (%)	-	-	-	-

** most frequent emergent adverse event excluding schizophrenia with the 5, 10, and 20 mg dose, respectively*
*** most frequent emergent adverse event excluding schizophrenia on risperidone*

On S 33138, the percentage of patients with at least one emergent adverse event during the treatment period was higher in the S 33138 5 mg group, and lower in the S 33138 20 mg group. All these percentages were lower to that in the risperidone group: 53.2% in the S 33138 5 mg group, 45.0% in the S 33138 10 mg group, and 38.3% in the S 33138 20 mg group *versus* 61.4% in the risperidone group.

The most frequent system organ class affected during the treatment period was psychiatric disorders in all groups. The other system organ classes affected in at least 10% of patients were nervous system disorders in all groups but the S 33138 10 mg group, and infections and infestations in all groups but the S 33138 5 mg group. Then, they were related to gastrointestinal disorders in the S 33138 5 mg group, and investigations in the risperidone group. For all these system organ classes but gastrointestinal disorders, the incidence was lower in the S 33138 groups than in the risperidone group.

Excluding schizophrenia which was the most frequent emergent adverse event in all groups, the emergent adverse events reported in at least 5% of patients were headache in the S 33138 5 mg group (8.5%), akathisia and drug abuser in the S 33138 10 mg group (5.0% each), and weight decreased in the S 33138 20 mg group (6.4%). For these emergent adverse events as well as for the other events, the incidence did not increase with the dose.
In the risperidone group, the most frequent emergent adverse events were extrapyramidal disorders, akathisia, and nasopharyngitis (9.1% each), and insomnia and anxiety (6.8% each). For all these emergent adverse events, the incidence was lower in the S 33138 groups than in the risperidone group.

The percentage of patients with at least one emergent adverse event considered to be related to the study product by the investigator was higher in the S 33138 5 mg group (25.5%) than in the other S 33138 groups (22.5% and 21.3% with 10 and 20 mg, respectively). All these percentages were lower to that in the risperidone group (31.8%).

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SAFETY RESULTS
- Emergent adverse events (cont'd)

Extrapyramidal symptoms, reported as adverse events, were few in the S 33138 groups, and less frequent than in the risperidone group (at most 2 patients by symptom on S 33138 *versus* 4 on risperidone). All but one symptom was mild or moderate. All symptoms but one resolved on S 33138. The exception was 1 moderate extrapyramidal disorder in the S 33138 5 mg group. In the risperidone group, 2 extrapyramidal disorders, and 2 akathisia resolved with sequelae. All these symptoms but one extrapyramidal disorder in the S 33138 5 mg group were considered related to the study treatment by the investigator.

No death was reported during the study. In all, 3 patients experienced a serious adverse event during the treatment period, one patient in each S 33138 dose group. One suicide attempt in the S 33138 5 mg group, one angioneurotic oedema in the S 33138 10 mg group in one patient who had had a previous allergic reaction with Quinke's oedema, and skin reaction possibly related to seroquel and/or abilify intake about one month before, and one allergic dermatitis in the S 33138 20 mg group. Both allergic reactions were considered related to the study treatment by the investigator. Both led to a premature drug discontinuation. All patients recovered.

Excluding patients prematurely withdrawn because of schizophrenia (10 patients), 2 patients prematurely discontinued the study drug due to non serious emergent adverse events, both on S 33138: one for akathisia with the 10 mg dose, and one for vomiting with the 20 mg dose. Both were considered treatment related by the investigator. Both resolved after symptomatic treatment.

- Biological safety

- ***Laboratory tests***

Neither clinically relevant changes nor differences between groups over time were detected on treatment for all biochemical and haematological parameters in the Safety Set.
Emergent potentially clinically significant abnormal (PCSA) biochemical values were sparse in all groups, except for triglycerides, and CPK in all groups without difference between them:

- Triglycerides: 3 PCSA values in the S 33138 5 mg group, and 2 in the other dose groups, and the risperidone group. Among these values, 2 in the S 33138 groups (1 value each in the 5 and 10 mg groups), and 2 in the risperidone group corresponded to a worsening of out-of-reference-range value already reported at baseline.
- CPK: 1 PCSA value each in the S 33138 5 and 10 mg groups, and 3 values each in the S33138 20 mg group, and risperidone group. Among these values, 1 in the S 33138 5 mg group, 2 in the S 33138 20 mg group, and 1 in the risperidone group corresponded to a worsening. PCSA values ranged between 3N and 10N in the S 33138 groups, and between 4N and 26N in the risperidone group.

Emergent PCSA haematological values were sparse in all groups.

- ***Endocrinological parameters***

In the Safety Set, the mean prolactin decreased between the baseline and the last post-baseline value on treatment in the three S 33138 groups, particularly with the 5 and 10 mg doses (-29.6 ± 46.7 µg/L, -26.8 ± 36.9 µg/L, -7.9 ± 25.0 µg/L in the 5 mg, 10 mg, and 20 mg groups, respectively) whereas it increased in the risperidone group (+ 30.8 ± 40.8 µg/L). For the other endocrinological parameters, there were neither clinically relevant changes over time nor differences between groups on treatment in male patients.
On S 33138, patients with emergent out-of-reference-range values were reported for prolactin, FSH, LH and total testosterone with the three doses but FSH with the 10 mg dose. One emergent high PSA value was reported at the 20 mg dose, only. There was no increase according to the dose for all parameters. In the risperidone group, emergent out-of-reference-range values were reported for prolactin, FSH, and total testosterone. The percentage of patients with emergent high prolactin values was lower in the S 33138 groups than in the risperidone group.

In all, 2 emergent PCSA endocrinological values were reported, both in the S 33138 20 mg group: 1 high PSA value, and 1 high FSH value, this latter already abnormally high at baseline.

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SAFETY RESULTS (cont'd)

- Safety scales

SAS

In the Safety Set, there were no clinically relevant changes of the mean SAS total score between the baseline and the last post-baseline value on treatment in all groups, nor between groups after 8 weeks (-0.2 ± 2.5, -0.5 ± 1.7, and –0.7 ± 2.0 in the S 33138 5, 10, and 20 mg groups, respectively, and 0.1 ± 3.8 in the risperidone group).

BAS

At the last post-baseline value on treatment over the W0-W8 periods, the percentage of patients with mild to severe akathisia was lower in the S 33138 mg groups than in the risperidone group (4.3%, 2.6%, and none in the S 33138 5, 10, and 20 mg groups, respectively *versus* 9.1%). These percentages were similar to those at baseline in the S 33138 5 and 10 mg groups, lower than that at baseline in the S 33138 20 mg group, and higher in the risperidone group. They showed no increase with the S 33138 dose.

UKU

At the last post-baseline assessment on treatment, the mean UKU total score showed no clinically relevant difference between groups (5.5 ± 7.1, 3.0 ± 4.5, and 4.5 ± 5.9 in the S 33138 5, 10, and 20 mg groups, respectively, and 4.6 ± 5.3 in the risperidone group). As at baseline, psychic score was higher than the other scores. In all groups, all mean scores at the last post-baseline assessment on treatment were lower than at baseline.

- Vital signs

Weight and BMI

In the Safety Set, the mean weight decreased between the baseline and the last post-baseline value over the W0-W8 period in the S 33138 5 mg group (-1.06 ± 3.29 kg), was stable in the S 33138 10 mg group (-0.14 ± 2.99 kg) and 20 mg group (-0.79 ± 2.69 kg), and increased in the risperidone group (1.35 ± 2.79 kg). However, the magnitude of change was small. BMI modification followed weight changes.

Blood pressure, and heart rate

In the Safety Set, the mean supine blood pressure and heart rate showed no clinically relevant change between the baseline and the last post-baseline value on treatment over the W0-W8 period in all groups.

- ECG

In the Safety Set, there were no clinically relevant mean changes between the baseline and last-post baseline value on treatment for any ECG parameters in all groups. Same results were observed at W1, W4 and W8, and at the follow-up visit, as well as between pre and post dose administration (1, 3, and 6 hours).

The percentage of patients with QTc ≤ 450 ms at selection, and at least one QTc > 450 ms on treatment was lower in the S 33138 mg groups than in the risperidone group according to Bazett's formula (8.5%, 7.5%, and 10.6% in the S 33138 5, 10, and 20 mg groups, respectively *versus* 22.7% in the risperidone group), or showed no relevant difference between groups according to Fridericia's formula (2.1%, 5.0%, and 2.1% in the S 33138 5, 10, and 20 mg groups, respectively, and 2.3% in the risperidone group). All values were isolated on S 33138 according to Fridericia's formula, and for 3/4 patients, 1/3, and 3/5 in the S 33138 5, 10, and 20 mg groups according to Bazett's formula. All of these patients but two in the risperidone group had QTc ≤ 480 ms with both formulae. No patient had a QTc > 500 ms with both formulae.

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- ECG (cont'd)

The percentage of patients with at least one prolongation of QTc > 30 ms on treatment was lower in the S 33138 mg groups than in the risperidone group with both formulae (Bazett's formula: 27.7%, 30.0%, and 38.3% in the S 33138 5, 10, and 20 mg groups, respectively *versus* 56.8% in the risperidone group, and Fridericia's formula: 19.1%, 15.0%, and 23.4% in the S 33138 5, 10, and 20 mg groups, respectively *versus* 34.1% in the risperidone group). Among these prolongations of QTc, few were longer than 60 ms according to Bazett's formula, only. It was reported in 1 patient in the S 33138 5 mg group, and 2 patients in the S 33138 20 mg group, and 4 patients in the risperidone group. The prolongation was associated with a high QTcB which ranged between 450 ms and 480 ms (both excluded) in 1 patient in each S 33138 dose group, and associated with a QTcB > 480 ms in 2 patients in the risperidone group.

In all, 2 patients (one in the S 33138 10 mg group, and one in the risperidone group) had one emergent ECG abnormality considered as clinically significant. Both abnormalities concerned T wave pattern. Patients recovered.

EFFICACY RESULTS

- PANSS

In the FAS, the mean total score decreased between the baseline and the last post-baseline assessment in all groups. The mean decrease was higher with the 20 mg dose (-15.9 ± 21.6) than with the other S 33138 doses (-13.9 ± 25.8, and –13.8 ± 26.0 in the S 33138 5 and 10 mg groups, respectively). In the three S 33138 groups, the mean decrease was smaller than in the risperidone group (-27.6 ± 19.8) as showed the estimated difference between S 33138 20 mg and risperidone (E (SE) = 12.7 (4.6), 95%CI = [3.6 ; 21.7]). In the OCW8S, the mean decrease from baseline showed no difference between the three doses of S 33138, and the risperidone at the end of the treatment period. The estimated difference between S 33138 20 mg and risperidone was E (SE) = 1.8 (4.0), 95%CI = [-6.1 ; 9.7].

In the FAS, the percentage of responders to treatment according to the two definitions (decrease from baseline of PANSS total score ≥ 20%, or 30%) was lower in the S 33138 20 mg group than in the risperidone group at the last assessment (60.0% *versus* 81.4% for response 1, and 37.8% *versus* 53.5% for response 2). In the OCW8S, the percentage of responders to treatment according to both definitions showed no relevant difference between the S 33138 20 mg, and risperidone groups at the end of the treatment period (89.3% and 86.8% for response 1, and 57.1% and 57.9% for response 2).

In the FAS, the mean PANSS positive and negative scores decreased between the baseline and the last post-baseline assessment in all groups. Both mean decreases were higher with the S 33138 20 mg dose (-7.3 ± 8.4, and -2.2 ± 4.5, respectively) than with the other S 33138 doses (-6.6 ± 8.5 and -1.0 ± 6.0 in the S 33138 5 mg group, and –6.8 ± 8.9 and –1.7 ± 6.7 in the S 33138 10 mg group) with a dose effect for the negative score. In the three S 33138 groups, the mean decreases were smaller than in the risperidone group (-11.8 ± 6.7 for the positive score, and –2.8 ± 5.6 for the negative score).

In the OCW8S, the mean decrease from baseline in the PANSS positive score showed no relevant difference between the S 33138 20 mg, and the risperidone groups at the end of the treatment period (-12.2 ± 4.5, and -12.8 ± 5.9, respectively), and the mean decrease from baseline in PANSS negative score was higher with the S 33138 20 mg dose than with the risperidone (-3.7 ± 4.5 *versus* -2.8 ± 5.6).

- CGI

In the FAS, the mean CGI severity of illness, and global improvement scores decreased throughout the visits in all groups. At the last assessment, both mean scores in the S 33138 groups were lower with the 20 mg dose than with the other doses. In the three S 33138 groups, both mean scores were higher than in the risperidone group. The percentage of responders to treatment (CGI global improvement score = 1 or 2) at the last assessment was higher in the S 33138 20 mg group than in the other dose groups (46.7% and 52.5% in the S 33138 5 and 10 mg groups, respectively *versus* 57.8%), and was lower in the S 33138 20 mg group than in the risperidone group (57.8% *versus* 76.7%).

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In the OCW8S, the mean CGI severity of illness score was lower in the S 33138 10 and 20 mg groups at the end of the treatment period (2.9 ± 1.4 or 0.9, respectively) than in the S 33138 5 mg group (3.2 ± 1.4). There was no relevant difference between the S 33138 10 and 20 mg group, and the risperidone group at the end of the treatment period (3.0 ± 0.9). The mean global improvement score was lower with the S 33138 20 mg dose (1.7 ± 0.8) than with the other doses (2.3 ± 1.5, and 2.2 ± 1.4 with the 5 and 10 mg doses, respectively), and with the risperidone at the end of the treatment period (1.9 ± 1.1). The percentage of responders according to CGI global improvement increased with the S 33138 doses at the end of the treatment period (65.4%, 76.9%, and 89.3%). The percentage of responders was higher in the S 33138 20 mg group than in the risperidone group (89.3% *versus* 84.2%).

CONCLUSION

This pilot study in schizophrenic patients with predominant positive symptoms treated for 8 weeks, designed to assess the clinical and biological safety of three doses of S 33138 (5, 10, and 20 mg), has shown that general safety was satisfactory with the three doses. Incidence of adverse events did not increase with the dose. There were few extrapyramidal symptoms with the three S 33138 doses, and fewer than on risperidone despite its flexible dose. Biological safety, including endocrinological parameters, was good. There was no hyperprolactinaemia on S 33138. Cardiological recordings showed that safety of S 33138 was better than that of risperidone. Indeed, QTc did not exceed 480 ms on S 33138, regardless of the formula, and no prolongation > 60 ms was reported according to Fridericia's formula.

Improvement of patients was shown according to PANSS, and CGI scale with the three S 33138 doses at the last assessment in the FAS and OCW8S. The best activity was observed with the S 33138 20 mg dose in both sets but was nevertheless lower than in the risperidone group in the FAS. On the other hand, in the OCW8S, the therapeutic benefit of the S 33138 20 mg dose and risperidone showed no relevant difference at the end of treatment on the whole and positive PANSS symptoms, and on the severity of illness assessed by the CGI scale. Moreover, improvement in negative PANSS symptoms was better with the S 33138 20 mg dose than with the risperidone as well as the CGI global improvement.

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