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<b>Sponsor/company:</b>	sanofi-aventis	<b>ClinialTrials.gov Identifier:</b>	NCT00126009
<b>Generic drug name:</b>	Amisulpride, haloperidol, valproate	<b>Study Code:</b>	C_8428
		<b>Date:</b>	21/June/2007
<b>Title of the study:</b>	A 3-month, open, randomised trial comparing the efficacy and safety of the association valproate-amisulpride to the association valproate-haloperidol in Bipolar I patients suffering from a manic episode		
<b>Investigators:</b>	This was a multicentric study conducted in 40 centres, 6 countries. The principal investigator was Pr Pierre THOMAS.		
<b>Study centre:</b>	Pr Pierre THOMAS, Hôpital Fontan, Rue André Verhaeghe, 59037 Lille		
<b>Publication (reference):</b>			
<b>Study period:</b>	<b>Phase of development: II</b>		
Date first patient enrolled: 13th May 2004			
Date last patient completed: 30th March 2006			
<b>Objectives:</b>	<p><u>Primary objectives</u> To compare the efficacy of the association valproate-amisulpride (400 to 800 mg/day) to the association valproate-haloperidol (5 to 15 mg/day) in Bipolar I patients suffering from a manic episode according to DSM IV TR (APA 2000) treated for a 3-month period</p> <p><u>Secondary objectives</u> To evaluate the clinical and biological safety of the association valproate-amisulpride to the association valproate-haloperidol To assess the patient status 3 weeks and 3 months after inclusion To assess patient satisfaction 3 months after inclusion.</p>		
<b>Methodology:</b>	Open study comparing two parallel groups of patients allocated to a flexible association of either valproate and amisulpride or valproate and haloperidol for 3 months after a 1-3 days washout phase.		
<b>Number of patients:</b>	Planned: 120	Included: 126	Randomised: 123 Treated: 121
<b>Evaluated:</b>	Efficacy: ITT: 120, PP: 102 Safety: 121		
<b>Diagnosis and criteria for inclusion:</b>	<ul style="list-style-type: none"> <li>• In-patients,</li> <li>• Aged 18 to 65 years inclusive,</li> <li>• Able to comply with the protocol,</li> <li>• Having given their written informed consent (with a legal representative or a person of trust),</li> <li>• With a current diagnosis of Bipolar I Disorder (296) according to DSM IV,</li> <li>• Having had at least one manic episode in the past,</li> <li>• Suffering from a manic episode (296.42, 296.43, 296.44),</li> <li>• With a minimum total score on the Y-MRS of 20 on D-3 and D0,</li> <li>• With a score <math>\geq 3</math> for 2 of the following Y-MRS items: <ul style="list-style-type: none"> <li>- elevated mood</li> <li>- increased motor activity energy</li> <li>- sleep</li> <li>- content (grandiosity).</li> </ul> </li> <li>• With a score <math>\geq 5</math> on the Clinical Global Impression Severity Scale (CGI-BP) at D0.</li> </ul>		

**Investigational product:** amisulpride

Dose: 400 to 800 mg/day (breakable tablets dosed at 400 mg)

Administration: according to the daily dose prescribed:

- 1 tablet in the evening (400 mg/day)
- ½ tablet in the morning and 1 tablet in the evening (600 mg/day)
- 1 tablet in the morning and 1 tablet in the evening (800 mg/day)

Amisulpride was administered in association with valproate (local valproate prescribed in accordance with the SMPc of each country). The initial dose was 600 mg/d administered from D1 to D4. Then, from D5 to M3, the posology could be adapted by step of 200 mg with a total daily dose ranging from 400 to 800 mg/d.

**Duration of treatment:** 3 months

**Duration of observation:** 3 months

**Reference therapy:** haloperidol

Dose: 5 to 15 mg/day (tablets dosed at 5 mg)

Administration: according to the daily dose prescribed:

- 1 tablet in the evening (5 mg/day)
- 1 tablet in the morning and 1 tablet in the evening (10 mg/day)
- 1 tablet in the morning and 2 tablets in the evening (15 mg/day)

Haloperidol was administered in association with valproate (local valproate prescribed in accordance with the SMPc of each country). The initial dose was 10 mg/d administered from D1 to D4. Then, from D5 to M3, the posology could be adapted by step of 5 mg with a total daily dose ranging from 5 to 15 mg/d.

**Criteria for evaluation:****Efficacy:**

Primary criterion: combined criterion defined by:

- Percentage of responders defined by a decrease of at least 50% of the Y-MRS between D0 and D END and
- Completion of the 3-month treatment period.

Secondary criteria:

- Changes in Y-MRS Scores between D0 and D21,
- Changes in Y-MRS Scores between D0 and D END,
- The percentage of remission defined as the Young Mania Rating Scale  $\leq 12$  at D END,
- The percentage of responders defined by a decrease of at least 50% of the Y-MRS between D0 and D END,
- Changes in the Brief Psychiatric Rating Scale (BPRS) Scores between D0 and D 21,
- Changes in the Brief Psychiatric Rating Scale (BPRS) Scores between D0 and D END,
- Changes in Clinical Global Impressions Scale for Bipolar Disorder (CGI-BP) between D0 and D END,
- Change in the Global Assessment Scale (GAS) between D0 and D END,
- Change in the Montgomery and Asberg Depression Rating Scale (MADRS) between D0 and D END,
- Satisfaction patients questionnaire at M3,
- Survival analysis of sustained response defined by a Y-MRS score  $\leq 12$  and a MADRS score  $\leq 15$  at two consecutive visits from D7 visit,
- Percentage of patients presenting a switch to depression between D0 and D END defined by (2 definitions):
  - \* a CGI-BP depression subscale score worsened by  $\geq 1$  point (dimension severity of illness) and a MADRS score  $\geq 15$
  - \* a CGI-BP depression subscale score worsened by  $\geq 2$  points (dimension severity of illness) and a MADRS score  $\geq 15$ .
- Percentage of patients presenting a relapse into manic episode between D0 and D END defined by an increase of at least 25% YMRS total score following a sustained response

**Criteria for evaluation (continued):****Safety:**

- Incidence of adverse events, TEAEs and SAEs considering all spontaneously reported adverse events and the clinical examination at each visit.
- Laboratory measurements (haematology and coagulation parameters, blood biochemistry, serum concentration of valproic acid)
- Vital parameters (SBP, DBP, heart rate and body weight)
- Neurological examinations:
  - \* The Simpson Angus Scale for measurement of parkinsonian-like extrapyramidal symptoms (EPSs)
  - \* The Barnes Akathisia Scale for measurement of akathisia-type EPSs
  - \* The Abnormal Involuntary Movement Scale (AIMS) to measure the dyskinetic involuntary muscle movements
- ECG measurement.

**Statistical methods:**Description of the populations analysed:

All the efficacy analyses (primary and secondary endpoints) were performed on both the Intent-to-treat (ITT) and Per protocol (PP) principles.

- N = 120 patients were included in the ITT population. The ITT population corresponds to all patients randomised at visit D0, who received at least one dose of active study combination and who achieved at least one post baseline visit.
- N = 102 patients from the ITT population who have presented no major protocol violations at the time of inclusion and during the study were included in the PP population.

All the safety endpoints were analysed on the Safety population. N = 121 randomised patients who received at least one dose of active study combination were included in the Safety population.

Descriptive statistics:

Continuous variables were described using: number of observations (N), mean (Mean), standard deviation (S.D.), median (Median), minimum (Min), maximum (Max) and number of missing values (Nmiss).

Categorical and ordinal variables were presented using: frequencies (N), percentages (%) and number of missing values (Nmiss).

Statistical analysis:

Both efficacy and safety analyses compared the two treatment groups using univariate statistical tests according to the nature of the variables:

- Qualitative variables: Pearson Chi-square test (or a Fisher's Exact test)
- Quantitative variables: Student t test (or a Wilcoxon-Mann-Whitney test).

For the primary efficacy endpoint, a one-sided statistical test on the  $\alpha = 5\%$  significance level was performed in order to demonstrate the superiority of the efficacy of the association valproate-amisulpride compared to the association valproate-haloperidol.

Other statistical tests were two-tailed and the level of significance was  $\alpha = 5\%$  (unless otherwise stated).

Two-sided 95% Confidence Intervals (95% CI) were provided whenever appropriate.

**Summary:****Efficacy results:****Table R1: Percentage of patients meeting the primary efficacy endpoint in the course of the study (ITT)**

Treatment groups		Group Amisulpride (N = 62)	Group Haloperidol (N = 58)	P-value~	Total (N = 120)
Patients meeting the primary efficacy endpoint*	N	62	58	0.402	120
	No	17 (27.4%)	20 (34.5%)		37 (30.8%)
	Yes	45 (72.6%)	38 (65.5%)		83 (69.2%)

\* The primary efficacy endpoint of this study is defined as the percentage of patients meeting:

- a decrease of at least 50% of the Y-MRS between D0 and D-END

**AND**

- completion of the 3-month treatment period

~ Pearson Chi<sup>2</sup> test (Two-sided)

The percentages of patients meeting the primary efficacy endpoint are not significantly different between the two treatment groups (p = 0.402): 72.6% in the group Amisulpride vs 65.5% in the group Haloperidol.

**Table R2: Statistical comparison between treatment groups for the mean percent changes in Y-MRS total scores from baseline (visit D0) to visit D-END, LOCF method (ITT)**

Statistical comparison Group Amisulpride vs Group Haloperidol	Means difference	95% IC~	P-value&
Y-MRS change (%) between D0 and D-END#	+ 4.02	[-7.15 , +15.20]	0.477

# Last visit performed by the patient - Last Observation Carried Forward (LOCF) method

~ 95% Confidence Interval

& Analysis of variance ANOVA with the study treatment as a factor

The Y-MRS total scores decrease significantly after the 3-month treatment period (between D0 and D-END) for both treatment groups (p < 0.001). The evolutions of the Y-MRS total scores after the 3-month treatment period are not significantly different between the two treatment groups (p = 0.477).

**Table R3: Percentage of patients in remission at visit D-END (ITT)**

Treatment groups		Group Amisulpride (N = 62)	Group Haloperidol (N = 58)	P-value~	Total (N = 120)
Patients in remission* at D-END	N	62	58	0.352	120
	No	10 (16.1%)	6 (10.3%)		16 (13.3%)
	Yes	52 (83.9%)	52 (89.7%)		104 (86.7%)

\* Remission at D-END is defined as: Y-MRS score  $\leq$  12 at visit D-END

~ Pearson Chi<sup>2</sup> test (Two-sided)

The percentages of patients in remission at D-END are not significantly different between the two treatment groups (p = 0.352): 83.9% in the group Amisulpride vs 89.7% in the group Haloperidol.

**Summary (continued):****Efficacy results (continued):****Table R4: Percentage of responder patients at visit D-END (ITT)**

Treatment groups		Group Amisulpride (N = 62)	Group Haloperidol (N = 58)	P-value§	Total (N = 120)
Responder patients* at D-END	N	62	58	0.366	120
	No	8 (12.9%)	4 (6.9%)		12 (10.0%)
	Yes	54 (87.1%)	54 (93.1%)		108 (90.0%)

\* Response at D-END is defined as: decrease = 50% of the Y-MRS score between D0 and D-END

§ Fisher exact test (Two-sided)

The percentages of responder patients at D-END are not significantly different between the two treatment groups ( $p = 0.366$ ): 87.1% in the group Amisulpride vs 93.1% in the group Haloperidol.

**Table R5: Statistical comparison between treatment groups for the mean percent changes in GAS total scores from baseline (visit D0) to visit D-END, LOCF method (ITT)**

Statistical comparison Group Amisulpride vs Group Haloperidol	Means difference	95% IC~	P-value&
GAS change (%) between D0 and D-END#	- 1.99	[-34.55 , +30.58]	0.904

# Last visit performed by the patient - Last Observation Carried Forward (LOCF) method

~ 95% Confidence Interval

& Analysis of variance ANOVA with the study treatment as a factor

The GAS total scores increase significantly after the 3-month treatment period for both treatment groups ( $p < 0.001$ ). The evolutions of the GAS total scores after the 3-month treatment period are not significantly different between the two treatment groups ( $p = 0.904$ ).

**Table R6: Statistical comparison between treatment groups for the mean percent changes in MADRS total scores from baseline (visit D0) to visit D-END, LOCF method (ITT)**

Statistical comparison Group Amisulpride vs Group Haloperidol	Means difference	95% IC~	P-value&
MADRS change (%) between D0 and D-END#	- 27.21	[-75.35 , +20.93]	0.265

# Last visit performed by the patient - Last Observation Carried Forward (LOCF) method

~ 95% Confidence Interval

& Analysis of variance ANOVA with the study treatment as a factor

The MADRS total scores don't decrease significantly after the 3-month treatment period in any of the two treatment groups ( $p > 0.05$ ). Nevertheless, the decrease seem to be higher for the group Amisulpride. The evolutions of the MADRS total scores after the 3-month treatment period are not significantly different between the two treatment groups ( $p = 0.265$ ).

**Summary (continued):****Efficacy results (continued):****Table R7: Percentage of patients presenting a sustained response during the study (ITT)**

Treatment groups		Group Amisulpride (N = 62)	Group Haloperidol (N = 58)	P-value~	Total (N = 120)
Sustained response* during the study	N	62	58	0.165	120
	No	16 (25.8%)	9 (15.5%)		25 (20.8%)
	Yes	46 (74.2%)	49 (84.5%)		95 (79.2%)

\* Sustained response during the study is defined as: Y-MRS score = 12 and MADRS score = 15 observed at two consecutive visits from the visit D7

~ Pearson Chi<sup>2</sup> test (Two-sided)

The percentages of patients presenting a sustained response during the 3-month treatment period are not significantly different between the two treatment groups (p = 0.165): 74.2% in the group Amisulpride vs 84.5% in the group Haloperidol.

**Table R8: Percentage of patients presenting a switch to depression between D0 and D-END (ITT)**

Treatment groups		Group Amisulpride (N = 62)	Group Haloperidol (N = 58)	P-value~	Total (N = 120)
<b>Switch to depression between D0 and D-END</b>					
Criterion ①*	N	62	58	0.239	120
	No	55 (88.7%)	47 (81.0%)		102 (85.0%)
	Yes	7 (11.3%)	11 (19.0%)		18 (15.0%)
Criterion ②**	N	62	58	0.223	120
	No	56 (90.3%)	48 (82.8%)		104 (86.7%)
	Yes	6 (9.7%)	10 (17.2%)		16 (13.3%)

\* Switch to depression between D0 and D-END (criterion ①) is defined as: CGI-BP depression subscale score worsened by = 1 point (dimension severity of illness) and MADRS score = 15

\*\* Switch to depression between D0 and D-END (criterion ②) is defined as: CGI-BP depression subscale score worsened by = 2 points (dimension severity of illness) and MADRS score = 15

~ Pearson Chi<sup>2</sup> test (Two-sided)

The percentages of patients presenting a switch to depression during the 3-month treatment period are not significantly different between the two treatment groups neither for the criterion ① (p = 0.239) nor for the criterion ② (p = 0.223). Nevertheless, these frequencies appear to be in favour of the group Amisulpride.

**Safety results:****- Adverse events**

A total of 92 patients (76.0%) presented at least one TEAE during the 3-month treatment period (between D0 and M3): 41 patients (66.1%) in the group Amisulpride and 51 patients (86.4%) in the group Haloperidol, with a significant difference between the two treatment groups showing a better tolerance in favour of the group Amisulpride (p = 0.009).

**Summary (continued):****Safety results (continued):****- Adverse events (continued)**

Among these 92 patients, 82 patients (67.8%) presented at least one TEAE related to study treatment according to the investigator's judgment: 34 patients (54.8%) in the group Amisulpride and 48 patients (81.4%) in the group Haloperidol, with a significant difference between the two treatment groups in favour of the group Amisulpride ( $p = 0.002$ ).

Moreover, 22 patients (18.2%) withdrew from the study because of a TEAE occurred during the 3-month treatment period: 7 patients (11.3%) in the group Amisulpride and 15 patients (25.4%) in the group Haloperidol, with a significant difference between the two treatment groups in favour of the group Amisulpride ( $p = 0.044$ ).

The most affected organ systems were the nervous system disorders (72 patients), the psychiatric disorders (20 patients), the gastrointestinal disorders (18 patients), the general disorders and administration site conditions (10 patients) and the infections and infestations (8 patients).

Extrapyramidal disorders (45 patients), akathisia (22 patients), depression (12 patients) and tremor (11 patients) were the most frequent TEAEs during the 3-month treatment period. Moreover, extrapyramidal symptoms and akathisia were less frequent in the group Amisulpride than in the group Haloperidol.

No death was reported during the study.

TEAEs rated as "Serious" concerned a total of 8 patients and 9 events in the 3-month treatment period. Among the 9 serious TEAEs, 4 serious TEAEs were notified by the investigator with possible link to study treatment in the group Haloperidol (anxiety or depression). Moreover, 4 serious TEAEs resulted in patient discontinuation in the group Haloperidol (depression). No serious TEAE occurred in the group Amisulpride was related to study treatment or resulted in patient discontinuation.

**- Biological Safety**

Concerning biological Safety, the highest frequencies of PCSA (Potentially Clinically Significant Abnormal) values were recorded for total bilirubin levels (16.1% of patients in the group Amisulpride, 5.1% in the group Haloperidol) and for conjugated bilirubin levels (12.9% of patients in the group Amisulpride, 6.8% in the group Haloperidol). No PCSA laboratory test results led the investigators to report them as serious TEAEs, TEAEs of severe intensity or TEAEs resulting in patient discontinuation.

**- Vital signs**

Concerning the vital signs, the highest frequencies of PCSA values were recorded for systolic blood pressure (6.5% in the group Amisulpride, 11.9% in the group Haloperidol) and for body weight (8.1% in the group Amisulpride, 5.1% in the group Haloperidol). No PCSA vital parameter values led the investigators to report them as serious TEAEs or TEAEs resulting in patient discontinuation.

**- Neurological examinations**

The mean absolute changes from baseline (visit D0) in Simpson Angus total scores as well as in AIMS total scores were significantly different between the two treatment groups in favour of the group Amisulpride ( $p < 0.05$ ). The same conclusion is to be done with the Barnes Akathisia mean global scores at D-END which were significantly different between the two treatment groups in favour of the group Amisulpride ( $p < 0.001$ ).

**Date of the report:** Final Version dated 11<sup>th</sup> January 2007