



European Medicines Agency

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**WITHDRAWAL ASSESSMENT REPORT
FOR
ABILIFY**

**International Nonproprietary Name:
aripiprazole**

Procedure No. EMEA/H/C/0471/II/0063

This withdrawal Assessment Report is based on the latest assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the “Question and Answer” document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

I. RECOMMENDATION

Based on the CHMP review of the data on safety and efficacy, the CHMP considers that the variation application (EMA/H/C/471/II/63) for Abilify, intended to extend the indication to the following: *'ABILIFY is indicated for the treatment of major depressive episodes as adjunctive treatment in patients who have had an inadequate response to at least one antidepressant monotherapy (see section 5.1)'* is not approvable unless the MAH can provide satisfactory responses in writing and in an oral explanation to the objections and concerns.

II. EXECUTIVE SUMMARY

II.1 Problem statement

Major depressive disorder is an illness characterized by the presence of either a depressed mood or a loss of interest or pleasure in daily activities consistently for at least a 2-week period. Additional symptoms must accompany these hallmark features (such as weight/appetite changes, insomnia/hypersomnia, agitation/retardation, fatigue, worthlessness/guilt, decreased concentration, suicidal ideation).

Despite numerous treatment options, major depression remains a widespread, debilitating illness. Two-thirds of patients who are initially prescribed medications do not experience a timely remission, as conventionally defined by an absolute score below a specified cut-off level on measures of severity of depression. Forty to 50% of patients do not experience a timely response, as conventionally defined by achieving a minimal 50% reduction in symptom severity. Furthermore, 10 to 20% of care-seeking depressed patients remain significantly symptomatic after 2 years.

Large numbers of patients do not experience an adequate response to antidepressant treatment. More than 60% of patients with major depression do not achieve remission following treatment with an adequate course of at least one antidepressant (ADT). Unresolved symptoms are associated with chronicity of symptoms and poorer outcomes. Specifically, residual symptoms are associated with an increased risk of relapse, impaired social and occupational functioning, worsened prognosis, and chronicity of course. Based on these findings, reducing symptom burden as much as possible with the aim of achieving a remission is a commonly accepted therapeutic goal.

In this type II variation, the MAH applied for an extension of indication of Abilify as follows:

'ABILIFY is indicated for the treatment of major depressive episodes as adjunctive treatment in patients who have had an inadequate response to at least one antidepressant monotherapy (see section 5.1).'

II.2 About the product

Aripiprazole, a dihydrocarbostyryl (quinolinone) derivative, is an antipsychotic agent. Aripiprazole (Abilify) has been authorised in the European Union (EU) on 04 June 2004. Aripiprazole tablets, orodispersible tablets and oral solution are currently approved in the European Union (EU) for the treatment of schizophrenia with recommended starting dose of 10 mg or 15 mg/day and target dose of 15 mg/day administered on a once-a-day schedule without regard to meals. These formulations are also indicated for the treatment of moderate to severe manic episodes in Bipolar I disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

Aripiprazole intramuscular (7.5mg/ml, solution for injection) is specifically indicated for the treatment of the rapid control of agitation and disturbed behaviours in patients with schizophrenia or in patients with manic episodes in Bipolar I Disorder, when oral therapy is not appropriate.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

The development program completed to support the proposed extension of indication consisted of:

- Two Phase I studies to investigate the pharmacokinetic effects of daily doses of aripiprazole when co-administered with venlafaxine (**CN138-462**) and escitalopram (**CN138-463**) and safety of aripiprazole in healthy subjects;
- Three randomised, double-blind, placebo controlled, 14-week, Phase III studies (**CN138-139**, **CN138-163** and **CN138-165**) to assess efficacy, safety, and pharmacokinetics of aripiprazole in patients with diagnosis of Major Depressive Episode (according to DSM-IV-TR) and with 1-3 incomplete responses to prior antidepressant regimens in current episode and inadequate response to prospective treatment (8 weeks).
- An open-label, 52-week study (**CN138-164**), designed to provide additional data on long term safety data of aripiprazole and maintenance of the efficacy in patients with diagnosis of Major Depressive Episode (according to DSM-IV-TR) and inadequate response to 1 - 4 historical antidepressant regimens in current episode. Patients entered this study either as de novo patients or after having completed the placebo-controlled studies CN 138-139 or CN 138-163.

In March 2005, while the pivotal studies were on-going, the MAH sought Scientific Advice on the program to establish whether the planned clinical program could support a claim for adjunctive therapy in treatment resistant depression based on the Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Depression (CPMP/EWP/518/97, Rev. 1). As a result of this advice, the MAH decided not to pursue a request for EU approval of a claim for treatment of resistant depression. Instead, the MAH proposed the use of adjunctive aripiprazole proposed for an indication more consistent with the population in the pivotal studies (ie. patients with a major depressive episode).

II.4 General comments on compliance with GMP, GLP, GCP

The clinical studies were conducted in accordance with GCP as stated by the MAH.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Not applicable

III.2 Non clinical aspects

Environmental risk assessment (ERA)

Within the variation (EMEA/H/C/471/II/48), the MAH provided further ERA update with currently available data on ecotoxicity and fate, which included new data on the Collembola Reproduction test ISO 11267. Following this update, the PEC/PNECsoil ratio changed from 0.0051 to 0.12. Although the value of the PEC/PNEC soil ratio (<1), the CHMP considered that the terrestrial fate and effect analyses should be completed prior any conclusions are made on the terrestrial impact of aripiprazole.

Within this variation (EMEA/H/C/471/II/63), further concerns were raised by the CHMP in relation with the PEC refinement.

III.3 Clinical aspects

Pharmacokinetics

- **Pharmacokinetic interaction studies**

- 1) Study CN138462

The primary objective was to assess the effects of daily 10 to 20 mg oral doses of aripiprazole on the steady-state pharmacokinetics of venlafaxine in healthy subjects.

A total of 38 subjects were enrolled in this study and 27 subjects completed the study per protocol including pharmacokinetic assessments on Days -1 and 14. Eleven (11) subjects discontinued, of which 6 subjects discontinued due to adverse events (AEs) and 5 subjects withdrew consent.

There was a small increase in venlafaxine C_{max} (14.8%) and AUC(TAU) (18.3%) in the presence of aripiprazole. Although there was no pre-specified statistical criteria for concluding a lack of drug-drug interaction, under the usual definition of interaction effect (90% confidence limits for the geometric mean ratios contained entirely within 80%-125%), there was no meaningful increase in exposure. This suggested that a clinically important pharmacokinetic drug-drug interaction between venlafaxine and aripiprazole is unlikely.

Based on point estimates and 90% confidence intervals, there were no increases or decreases in O-desmethylvenlafaxine C_{max} and AUC(TAU) values, when aripiprazole was co-administered with venlafaxine.

- 2) Study CN138463

The primary objective was to assess the effects of daily 10 mg oral doses of aripiprazole on the steady-state pharmacokinetics of escitalopram in healthy subjects.

A total of 25 subjects were enrolled in this study, and 17 subjects completed the study per protocol including pharmacokinetic assessments on Days -1 and 14. Eight (8) subjects discontinued study therapy; 3 subjects due to an AE and 4 subjects withdrew informed consent, possibly due to the side

effects of study treatment. One (1) subject was discontinued at the discretion of the Investigator due to a pre-existing undisclosed psychiatric condition. There was 1 serious adverse event (SAE) of syncope of moderate intensity.

The relationship between plasma concentrations of escitalopram and its safety and efficacy is poorly defined. There is high between-subject variability in the pharmacokinetics of this agent and the dose range required across patient population is wide (the therapeutic dose can vary by 3 or more fold). Thus, a wide range of systemic exposures to escitalopram is observed in clinical practice and small changes in the systemic exposures are unlikely to be clinically meaningful. Given the variability in doses and concentrations of escitalopram in clinical practice, the standard confidence interval of 0.8 to 1.25 was not considered to be applicable to conclude a pharmacokinetic interaction. Consequently, the approach of using point estimates to assess pharmacokinetic effects of aripiprazole on escitalopram PK parameters within 20% with a high degree of certainty was chosen.

There was a small increase in escitalopram C_{max} (4%) and AUC(TAU) (7%) in the presence of aripiprazole. If powered *a priori* as a prospective drug interaction study, the usual criterion of interaction effect (90% confidence intervals of geometric mean ratios contained entirely within 80%-125%) would have been met to conclude no interaction. This suggested that a pharmacokinetic drug-drug interaction between escitalopram and aripiprazole is unlikely.

- **Additional pharmacokinetic analyses**

The three Phase 3 efficacy studies (**CN138139, CN138163 and CN138165**) had similar designs. Plasma concentration data from population pharmacokinetic samples from patients who had an incomplete/partial response at the end of 8 weeks of ADT alone (Phase B) who were randomized to receive either aripiprazole or placebo for 6 weeks (Phase C) were analysed to examine the pharmacokinetic drug-drug interactions for the ADTs that may have been precipitated by adding aripiprazole to the ADT.

The data from each study were analyzed separately and the data from CN138139 and CN138163 were also combined and a pooled analysis was performed in order to provide a more robust assessment with larger numbers of patients taking each ADT. The results of the statistical analyses on antidepressant plasma concentrations and important metabolites in Phase C compared with Phase B for CN138139, CN138163, CN138165 and the pooled analysis (studies CN138139 and CN138163) are summarized in Tables 1, 2 and 3, respectively.

Table 1: Results of Statistical Analyses on Antidepressant Plasma Concentrations in Phase C Compared to Phase B (CN138139)

Antidepressant Analyte	Therapy	Treatment in Phase C	Number of Patients with Evaluable Data	Phase C to Phase B Geometric Mean Plasma Concentration Ratio	
				Point Estimate	90% Confidence Interval
Citalopram		Aripiprazole	44	1.009	(0.942, 1.081)
		Placebo	45	0.926	(0.853, 1.006)
Fluoxetine		Aripiprazole	24	1.171	(1.045, 1.312)
		Placebo	22	1.047	(0.912, 1.202)
Norfluoxetine		Aripiprazole	24	1.390	(1.215, 1.590)
		Placebo	22	1.148	(1.062, 1.240)
Paroxetine		Aripiprazole	13	0.899	(0.790, 1.023)
		Placebo	11	0.911	(0.812, 1.021)
Sertraline		Aripiprazole	30	0.940	(0.866, 1.019)
		Placebo	29	0.966	(0.883, 1.057)
Desmethylsertraline		Aripiprazole	30	0.985	(0.915, 1.062)
		Placebo	29	1.054	(0.992, 1.119)
Venlafaxine		Aripiprazole	37	0.965	(0.864, 1.078)
		Placebo	47	0.865	(0.767, 0.976)
O-Desmethylvenlafaxine		Aripiprazole	37	0.940	(0.868, 1.019)
		Placebo	47	1.007	(0.942, 1.076)

Table 2: Results of Statistical Analyses on Antidepressant Plasma Concentrations in Phase C Compared to Phase B (CN138163)

Antidepressant Analyte	Therapy	Treatment in Phase C	Number of Patients with Evaluable Data	Phase C to Phase B Geometric Mean Plasma Concentration Ratio	
				Point Estimate	90% Confidence Interval
Citalopram		Aripiprazole	42	0.931	(0.836, 1.037)
		Placebo	32	0.904	(0.826, 0.991)
Fluoxetine		Aripiprazole	4	1.301	(0.747, 2.266)
		Placebo	5	0.839	(0.685, 1.028)
Norfluoxetine		Aripiprazole	4	1.158	(0.906, 1.480)
		Placebo	5	1.080	(0.921, 1.266)
Paroxetine		Aripiprazole	6	0.693	(0.478, 1.005)
		Placebo	7	0.909	(0.822, 1.005)
Sertraline		Aripiprazole	15	0.994	(0.834, 1.185)
		Placebo	16	1.026	(0.800, 1.316)
Desmethylsertraline		Aripiprazole	15	1.071	(0.955, 1.202)
		Placebo	16	0.974	(0.855, 1.110)
Venlafaxine		Aripiprazole	35	0.965	(0.846, 1.101)
		Placebo	33	0.917	(0.786, 1.069)
O-Desmethylvenlafaxine		Aripiprazole	35	0.993	(0.913, 1.081)
		Placebo	33	0.981	(0.872, 1.103)

Table 3: Results of Statistical Analyses on Antidepressant Plasma Concentrations in Phase C Compared to Phase B (CN138165)

Antidepressant Analyte	Therapy	Treatment in Phase C	Number of Subjects with Evaluable Data	Phase C to Phase B Geometric Mean Plasma Concentration Ratio	
				Point Estimate	90% Confidence Interval
Citalopram		Aripiprazole	51	1.029	(0.961, 1.101)
		Placebo	47	0.928	(0.867, 0.993)
Fluoxetine		Aripiprazole	27	1.002	(0.876, 1.147)
		Placebo	20	1.244	(1.158, 1.337)
Norfluoxetine		Aripiprazole	27	1.188	(1.086, 1.300)
		Placebo	20	1.291	(1.210, 1.377)
Paroxetine		Aripiprazole	8	0.970	(0.704, 1.336)
		Placebo	17	0.817	(0.682, 0.979)
Sertraline		Aripiprazole	20	0.958	(0.861, 1.056)
		Placebo	26	0.964	(0.827, 1.123)
Desmethylsertraline		Aripiprazole	20	1.023	(0.951, 1.100)
		Placebo	27	1.077	(1.011, 1.147)
Venlafaxine		Aripiprazole	36	0.902	(0.784, 1.037)
		Placebo	39	0.943	(0.830, 1.070)
O-Desmethylvenlafaxine		Aripiprazole	36	0.931	(0.848, 1.022)
		Placebo	39	0.952	(0.876, 1.035)

For the pooled analysis, escitalopram, sertraline, desmethylsertraline, venlafaxine, and O-desmethylvenlafaxine, the proximity of the Phase C to Phase B geometric mean plasma concentration ratios to 1.0 and the similarity of the ratios and their 90% CIs between the aripiprazole-treated patients and the placebo-treated patients indicate that there was no substantial effect of aripiprazole treatment on plasma exposure to any of the ADTs, or where applicable their respective metabolites. The Phase C to Phase B geometric means of the plasma concentration ratios for fluoxetine and norfluoxetine were 16.9% and 22.5% higher, respectively, in aripiprazole treated patients as compared to the placebo-treated patients. These differences in fluoxetine and norfluoxetine concentration ratios between the aripiprazole and placebo groups were relatively small and may have been due to the long half-lives of these analytes (4 to 6 days and 4 to 16 days, respectively) resulting in non-steady state conditions at early timepoints in Phase B. The plasma concentration ratio of paroxetine was 17.9% lower in aripiprazole-treated as compared with placebo-treated patients, which was a relatively small difference.

- **Discussion on pharmacokinetic aspects**

The two Phase 1 drug-drug interaction studies and the population pharmacokinetic analysis from three Phase 3 safety and efficacy studies showed no meaningful pharmacokinetic changes for the 5 ADTs studied (escitalopram, fluoxetine, paroxetine CR, sertraline, or venlafaxine XR), when aripiprazole was added to steady-state ADT.

Based on the *in vitro* profile of aripiprazole, no metabolically-based interaction resulting from the addition of aripiprazole to the 5 ADTs was expected. Clinical metabolic drug-drug interaction studies have shown that aripiprazole does not substantially alter the metabolic activity of CYP2C9 (warfarin); CYP2C19 (omeprazole, warfarin), CYP2D6 (dextromethorphan O-demethylation), or CYP3A4 (dextromethorphan N-demethylation).

Thus, aripiprazole was considered unlikely to affect the pharmacokinetics of the ADTs used in the clinical program supportive of the proposed indication.

The above MAH conclusions are endorsed by the CHMP.

Clinical efficacy

- **Main clinical studies**

- 1. Short Term Efficacy**

Three randomised, double-blind, placebo controlled, 14-week, Phase III studies (**CN138-139**, **CN138-163** and **CN138-165**) were conducted to assess efficacy, safety, and pharmacokinetics of aripiprazole in patients with diagnosis of Major Depressive Episode (according to DSM-IV-TR) and with 1-3 incomplete responses to prior antidepressant regimens in current episode and inadequate response to prospective treatment (8 weeks).

All these Phase III studies were multicenter and conducted in the US.

METHODS

Inclusion Criteria

Patients who enrolled had a previous medical history of inadequate response to prior antidepressant treatment in the current episode of depression. For the purpose of this clinical program, at least 1 treatment failure was documented by patient history and another was confirmed by an 8 week, single-blind, prospective antidepressant treatment phase.

Patients were eligible to participate in the studies if they had, by history, a failure of 1 to 3 adequate treatments with a marketed ADT in the current episode of depression. Historical treatment failure was defined as < 50% reduction in depressive symptoms severity, as assessed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ). An adequate ADT trial in the questionnaire was defined as a treatment period for at least 6 weeks duration, or at least 3 weeks for combination treatments, at a minimum dose as specified in the ATRQ.

Patients entered a screening phase (Phase A) to assess eligibility and to allow for washout of their previous ADT and prohibited concomitant medications.

Treatment period

Eligible patients from Phase A then entered an 8-week prospective treatment phase (Phase B), receiving single-blind placebo and 1 of 5 open-label ADTs (escitalopram, sertraline, venlafaxine XR, fluoxetine, or paroxetine CR). ADT was assigned by the investigator with the guidance to limit any one ADT to 40% of patients entering Phase B. The ADTs consisted of escitalopram (10 to 20 mg/day),

fluoxetine (20 to 40 mg/day), either paroxetine (20 to 40 mg/day) or paroxetine CR (25 to 50 mg/day), sertraline (50 to 150 mg/day) or venlafaxine XR (37.5 to 225 mg/day). The choice of ADT was determined by the investigators after considering each patient's antidepressant treatment history. Unless it was clinically warranted to do otherwise based on the opinion of the investigator, ADTs with which a patient had reported either an inadequate response or lifetime intolerability were excluded.

If patients responded adequately to ADT treatment plus placebo in Phase B, they were continued on single-blind ADT plus placebo (Phase B+) to maintain the patient blind and prevent potential rater bias.

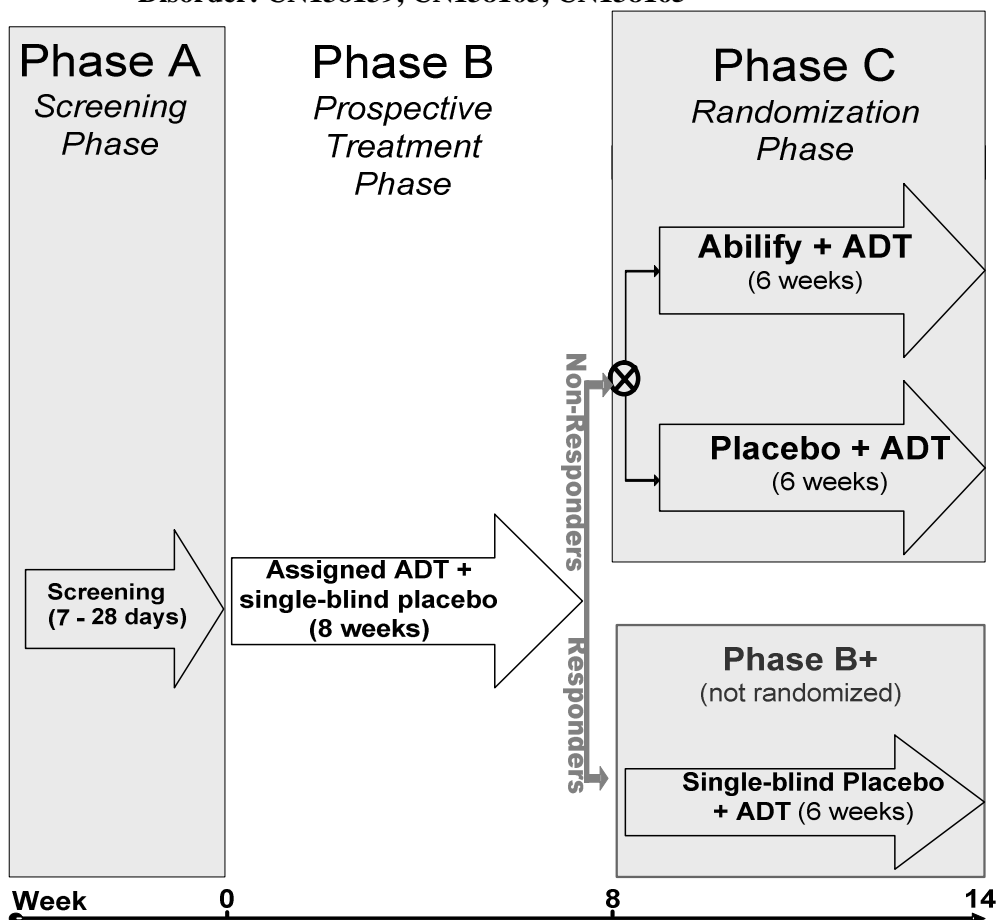
If patients had an inadequate response in Phase B to ADT treatment plus placebo, as prospectively defined (< 50% decrease on Hamilton Depression Rating Scale-17 [HAM-D17] Total Score versus the end of Phase A, HAM-D17 Total Score \geq 14, and Clinical Global Impression [CGI]-Improvement Score \geq 3), they were randomized to double-blind treatment with either aripiprazole-plus-ADT or placebo-plus-ADT in a 6-week randomization phase (Phase C).

In Phase C, aripiprazole dosing was started at 5 mg. The dose could be adjusted in 5-mg increments weekly (through Week 12). The maximum dose of aripiprazole was 20 mg/day when used in combination with escitalopram, sertraline, or venlafaxine XR, and 15 mg/day, in combination with fluoxetine or paroxetine CR. If a patient did not tolerate the 5-mg aripiprazole dose, the dose could be decreased to 2 mg/day, and if appropriate, subsequently increased back to 5 mg. Investigators were guided to titrate to at least 10 mg/day, if well tolerated.

Study design

The design of these multicenter, randomised, placebo-controlled studies is shown in **Figure 1**.

Figure 1: Study Design of Placebo-Controlled Studies in Major Depressive Disorder: CN138139, CN138163, CN138165



Primary efficacy endpoint

The primary efficacy endpoint was the mean change from end of Phase B (Week 8) to end of Phase C (Week 14, LOCF) in the Montgomery Asberg Depression Rating Scale (MADRS) Total Score.

Secondary efficacy endpoints

Secondary efficacy endpoints included: MADRS response (defined as at least a 50% reduction from end of Phase B in MADRS Total Score) and remission (defined as a MADRS Total Score of 10 or lower and at least a 50% reduction from end of Phase B) rates at Week 14 (LOCF); the mean change from end of Phase B (Week 8) to end of Phase C (Week 14, LOCF) in the CGI-Severity (CGI-S) Score, the mean change from end of Phase B (Week 8) to end of Phase C (Week 14, LOCF) in the HAM-D17 Total Score, Inventory of Depressive Symptomatology (IDS-SR) Total Score, and Quick Inventory of Depressive Symptomatology (QIDS-SR) Total Score.

The mean change from end of Phase B (Week 8) to end of Phase C (Week 14, LOCF) Sheehan Disability Scale (SDS) Mean Score was a key secondary outcome measure.

Sample size

The planned sample size of 332 evaluable patients (166 randomized to placebo and 166 randomized to aripiprazole) would provide 90% power to detect a difference of 3.75 between placebo-plus-ADT and aripiprazole-plus-ADT, in mean change from the end of Phase B to the end of Phase C in MADRS Total Score. This calculation assumed a standard deviation of 10.5 and a 2-sided t-test to be interpreted at the 0.05 significance level.

RESULTS

Patient characteristics

Among patients who entered the prospective treatment phase (Phase B) of the studies, the frequency of ADT selection in declining order was: venlafaxine XR (29.5%), escitalopram (27.9%), sertraline (19.1%), fluoxetine (14.5%), and paroxetine CR (9.0%). The assignment and proportion of patients assigned to each ADT was similar in all studies.

There were 360 patients in CN138139, 381 patients in CN138163, and 349 patients in CN138165 who completed Phase B and were randomized to double-blind treatment in Phase C. Within each study, the percentage of patients who completed treatment was similar between the treatment groups. Overall completion rates for the 3 studies combined were also similar for the placebo group (87.2%) and the aripiprazole group (85.3%). The most frequent reason for discontinuation in the aripiprazole group was AE (4.4%), whereas in the placebo group it was withdrawal of consent (3.7%).

The mean age of patients was approximately 45 years. More females than males were randomized to treatment, and most patients were white.

Overall, the randomized patient samples in the 3 studies had similar psychiatric histories. Any differences were not considered to be clinically meaningful. Greater than 65% of all patients had 1 adequate trial prior to entry into the study, with approximately 25% having 2 adequate trials. An adequate trial was defined as a treatment period of at least 6 weeks duration, or at least 3 weeks for combination treatments, at a minimum dose as specified in the ATRQ.

Across all trials, selective-serotonin reuptake inhibitors (SSRIs) were the most common previous adequate antidepressant medication used.

Efficacy Results

These are summarised below (see Table 4).

Table 4: Summary of Efficacy Results at Endpoint (Week 14): Placebo-Controlled Studies in Major Depressive Disorder, LOCF Data Set, Efficacy Sample

Variable	CN138139		Treatment Group CN138163		CN138165	
	Placebo	Aripiprazole	Placebo	Aripiprazole	Placebo	Aripiprazole
PRIMARY ENDPOINT						
MADRS Total Score	N = 172	N = 181	N = 184	N = 185	N = 169	N = 174
Mean End of Phase B (Week 8)	25.65	25.88	26.55	24.59**	26.72	26.22
Mean Change End of Phase C (Week 14)	-5.77	-8.78**	-5.65	-8.49**	-6.39	-10.12**
SECONDARY ENDPOINTS						
Patients (%) in MADRS Response at Week 14	N= 172 41 (23.8)	N = 181 61 (33.7)*	N = 184 32 (17.4)	N = 185 60 (32.4)**	N = 169 45 (26.6)	N = 174 81 (46.6)**
Patients (%) in MADRS Remission at Week 14	27 (15.7)	47 (26.0)*	28 (15.2)	47 (25.4)*	32 (18.9)	64 (36.8)**
CGI-Severity Score	N = 172	N = 181	N = 184	N = 185	N = 169	N = 174
Mean End of Phase B (Week 8)	4.11	4.08	4.07	4.02	4.20	4.10
Mean Change End of Phase C (Week 14)	-0.64	-1.03**	-0.63	-1.10**	-0.69	-1.14**
CGI-Improvement Score	N = 172	N = 181	N = 184	N = 185	N = 169	N = 174
Mean at End of Phase C (Week 14)	2.81	2.49**	2.91	2.42**	2.79	2.42**
HAM-D17 Total Score	N = 147	N = 152	N = 170	N = 181	N = 156	N = 155
Mean End of Phase B (Week 8)	19.73	19.68	19.64	18.75*	19.96	19.75
Mean Change End of Phase C (Week 14)	-4.89	-7.17**	-4.41	-6.77**	-5.12	-7.64**
IDS-SR Total Score	N = 172	N = 181	N = 184	N = 187	N = 169	N = 174
Mean End of Phase B (Week 8)	34.04	34.43	32.34	30.27	33.04	32.72
Mean Change End of Phase C (Week 14)	-5.16	-6.95	-4.55	-6.03	-5.36	-6.93
QIDS-SR Total Score	N = 172	N = 181	N = 184	N = 187	N = 169	N = 174
Mean End of Phase B (Week 8)	12.71	12.94	12.33	11.60	12.81	12.96
Mean Change End of Phase C (Week 14)	-2.28	-2.58	-1.80	-2.30	-2.13	-2.83
SDS Mean Score ^a	N = 164	N = 167	N = 168	N = 180	N = 160	N = 160
Mean End of Phase B (Week 8)	5.35	5.69	5.35	5.06	5.89	5.67
Mean Change End of Phase C (Week 14)	-0.65	-1.11	-0.73	-1.31*	-0.80	-1.22

** (p ≤ 0.01), * (0.01 < p ≤ 0.05), compared with placebo, a: key secondary outcome measure

The aripiprazole group showed statistically significantly greater improvement than placebo on the primary efficacy measure, the mean change from end of Phase B to end of Phase C (LOCF) in MADRS Total Score.

The percentages of patients who achieved response were statistically significantly greater for the adjunctive aripiprazole group than the adjunctive placebo group in all 3 studies. At Week 14 (LOCF), the relative risk (RR) for response (aripiprazole over placebo) was 1.45 in CN138139, 1.86 in CN138163, and 1.74 in CN138165. This corresponds to 45 - 86% increased likelihood of response for patients with the addition of aripiprazole to ADT treatment compared to ADT monotherapy.

The percentages of patients who achieved remission were statistically significantly greater for the adjunctive aripiprazole group than the adjunctive placebo group in all 3 studies. At Week 14 (LOCF), the RR for remission (aripiprazole over placebo) was 1.70 in CN138139, 1.66 in CN138163, and 1.95 in CN138165. This corresponds to a 66 - 95% increased likelihood of remission for patients with the addition of aripiprazole to ADT treatment compared to ADT monotherapy.

The adjunctive aripiprazole group had statistically significantly greater improvement than the adjunctive placebo group in the mean CGI-Severity Score at the end of Phase C in all 3 studies (CN138139, $p < 0.001$; CN138163, $p < 0.001$; CN138165, $p < 0.001$).

The adjunctive aripiprazole group had statistically significantly greater improvement than the adjunctive placebo group in the mean CGI-Improvement Score at the end of Phase C in all 3 studies (CN138139, $p = 0.003$; CN138163, $p < 0.001$; CN138165, $p = 0.001$).

The adjunctive aripiprazole group had a statistically significant greater reduction than the adjunctive placebo group in the mean change from end of Phase B to end of Phase C in HAM-D17 Total Score in all 3 studies (all, $p < 0.001$).

Endpoint reductions on the IDS-SR Total Score and QIDS-SR Total score were not statistically significant at the end of Phase C. Nonetheless, results from these instruments are consistent with findings on the MADRS and HAM-D17 insofar as the adjunctive aripiprazole group had numerically greater reductions than the adjunctive placebo group in the mean change from end of Phase B to all timepoints in Phase C on the IDS-SR Total Score and QIDS-SR Total Score in all 3 studies, with the difference being statistically significant at some timepoints.

For the mean change from end of Phase B to end of Phase C (Week 14, LOCF) in SDS Mean Score, results showed a statistically significant difference between the groups in CN138163 ($p = 0.012$), but the difference was not statistically significant in CN138139 ($p = 0.055$) or CN138165 ($p = 0.075$).

2. Long Term Efficacy

Study CN138-164

This was an open-label, 52-week study, designed to provide additional data on long term safety data of aripiprazole and maintenance of the efficacy in patients with diagnosis of Major Depressive Episode (according to DSM-IV-TR) and inadequate response to 1 - 4 historical antidepressant regimens in current episode. Patients entered this study either as de novo patients or after having completed the placebo-controlled studies CN 138-139 or CN 138-163.

METHODS

Inclusion Criteria

De novo patients had a diagnosis of a single or recurrent, non-psychotic episode of MDD, as defined by DSM-IV-TR, with a current depressive episode of at least 8 weeks in duration. De novo patients were currently taking allowable ADT at an adequate dose for a minimum of 6 weeks by the end of the screening phase and reported a history in the current depressive episode of an inadequate response to at least 1 and no more than 4 adequate antidepressant treatments. De novo patients had a MADRS Total Score greater than 10 at the end of screening phase (baseline visit) and, in the opinion of the investigator, had residual symptoms that may have benefited from pharmacologic modification.

Eligible rollover patients were those who completed the randomization phase (Phase C) of either CN138139 or CN138163 as well as those patients who met criteria for a response at the end of the prospective treatment phase (Phase B) but did not meet criteria for remission (MADRS Total Score of ≤ 10) at the Week 14 visit.

Eligible rollover patients continued on the final prescribed dosage of their assigned ADT in the placebo-controlled studies and initiated open-label treatment with 5-mg aripiprazole 1 day after the Week 14 Visit. All rollover patients (prior placebo and prior aripiprazole) started treatment with aripiprazole at a dose of 5 mg, with a subsequent range of 2 to 30 mg/day.

De novo patients entered the study after completing a 7 to 28 day screening phase; the end of this screening phase was considered the baseline visit for these patients. De novo patients continued on their current dose of ADT and initiated treatment with 5-mg aripiprazole.

Efficacy was assessed in the long-term study by the CGI-S scale. A CGI-S score of 2 means “borderline ill” and 3 means “mildly ill”.

RESULTS

Patient Characteristics

Of the 1076 patients enrolled in CN138164, 1002 patients entered the treatment phase and 994 patients received at least 1 dose of aripiprazole in the safety sample. A total of 323 (32.2%) patients completed 52 weeks of treatment. The most frequently reported reason for discontinuation from the study was AE (23.0%).

Patients were predominantly female (66.2%) and white (91.1%), with a mean age of 46 years . The majority of patients (66.0%) had a BMI > 27 kg/m².

Baseline psychiatric evaluations indicated that this population was markedly impaired by depression as based on their status at study entry. For rollover patients, this was assessed prior to entry into the prospective treatment phase (Phase B) of the double-blind study; for de novo patients this was assessed at entry into CN138164. Overall, the patient population had a mean duration of the current episode of depression of 44.2 months and a mean duration of the last period of wellness of 19.9 months.

The majority of patients (78.1%) had recurrent episodes of depression. Presence of atypical features was recorded for 6.6% and presence of melancholic features for 53.1% of patients. The most frequently used ADTs at baseline were escitalopram (27.9%), venlafaxine XR (25.3%), sertraline (17.3%) and fluoxetine (14.8%).

The mean score at baseline on the CGI-S was 3.3 for prior placebo-treated patients and 2.9 for prior aripiprazole-treated patients; the baseline score was higher in de novo patients (4.2) compared with patients who entered from a previous study.

The overall mean change in CGI-S score from baseline to Week 52 (LOCF) was -0.7 points in prior placebo-treated patients and -0.2 points in prior aripiprazole-treated patients, indicating that these patients had reached stability. The mean change in de novo patients was greater (-1.5 points), but the endpoint mean score was the same regardless of prior status (2.7 points for de novo patients, 2.6 points in prior placebo patients, and 2.7 points in prior aripiprazole patients).

Post-Hoc Analysis

A post-hoc analysis examining the long-term efficacy of adjunctive aripiprazole was conducted in those patients who responded ($\geq 50\%$ reduction in MADRS Total Score) to aripiprazole-plus-ADT in the randomization phase of the placebo-controlled studies (CN138139 and CN138163). This analysis (in 101 patients) was conducted to characterize the long-term maintenance of effect, up to 52 weeks, of aripiprazole-plus-ADT that was demonstrated during the 6 weeks of adjunctive treatment. Results of this analysis showed that the mean CGI-S score was maintained between 1.9 and 2.1 through the 52-week open-label study for patients who responded to adjunctive treatment.

- **Choice of the Dose**

In the 3 placebo-controlled trials, dosing of aripiprazole in the randomization phase began at 5 mg/day. The dose could be adjusted in 5-mg increments weekly (through Week 12). The maximum dose of aripiprazole was 20 mg/day when used in combination with escitalopram, sertraline, or venlafaxine XR, and 15 mg/day, in combination with fluoxetine or paroxetine CR (cytochrome P4502D6 [CYP 2D6] inhibitors). If a patient did not tolerate the 5-mg aripiprazole dose, the dose could be decreased to 2 mg/day, and if appropriate, subsequently increased back to 5 mg. Investigators were guided to titrate to at least 10 mg/day, if well tolerated.

The study design employed in CN138139, CN138163, and CN138165, utilizing flexible dosing with guidance to target at least 10 mg/day, does not allow the recommendation of a fixed dose; however, across all ADTs, the mean daily dose of aripiprazole at endpoint was 11.0 mg/day. This dose did not meaningfully differ among the individual ADTs (escitalopram 11.2 mg/day; fluoxetine 9.9 mg/day; paroxetine 9.8 mg/day; sertraline 12.2 mg/day; venlafaxine XR 10.8 mg/day). The dose range of aripiprazole in these studies was associated with statistically significant differences in favor of aripiprazole as well as clinically meaningful improvement of efficacy (eg, 66 - 95% increase in likelihood of remission with aripiprazole compared with placebo) with adequate tolerability (eg, < 4.4% discontinuation rates due to AEs in the pooled database and completion rates similar to placebo).

Given that the majority of patients received 15 mg/day or less in the pivotal studies, regardless of the concomitant ADT, to avoid confusion with regard to CYP interaction and to allow for the generalizability of the dosing recommendation in product labeling, the effective dose range may be considered as 5 to 15 mg with a maximum daily dose of 15 mg.

- **Discussion on clinical efficacy**

In 3 randomised, double blind controlled placebo studies of the same design, the aripiprazole group showed statistically significantly greater improvement than placebo on the primary efficacy measure, the mean change from end of Phase B to end of Phase C (LOCF) in MADRS Total Score. To further evaluate the efficacy in this population, data on how many patients entered the treatment phase B in the phase III studies and went on to achieve a proper response to the anti-depressant medication were provided. The results of each study were re-assessed depending on initial severity degree of MDE for participating patients in order to demonstrate if the initial severity may be predictive of efficacy of treatment and a sensitivity analysis was also provided (counting the drop-outs and withdrawals as failures) in the responders analysis of the placebo-controlled trials. Having considered these further analyses provided by the MAH, the CHMP concluded that the effect size was similar among the 2 categories of initial severity (based on their MADRS score at baseline) and that the requested sensitivity analysis was satisfactory showing consistent results with those reported in the initial analyses.

On the other hand, the CHMP raised a major concern about the studied population which may not have reflected the characteristics (i.e prescription patterns) of the European population, given that these studies were performed in the US. To address this concern, the MAH argued that within the clinical development program, the methods used to diagnose patients, and define incomplete response, the choice of antidepressants and the different strategies such as increasing the dose and switching between and within classes of antidepressants, reflected the common clinical practice in the EU allowing therefore the results to be generalised. This argumentation was accepted by the CHMP.

The CHMP was also concerned about the validity of the ATRQ questionnaire which is used to document the first attempt in the targeted population (i.e. patients failing 2 attempts to treat their current episode of depression). Failure of the second episode was prospectively collected and therefore provided more reliability. Following review and clarifications provided by the MAH on the validity of the ATRQ questionnaire, the CHMP considered that this concern remains.

Overall, the efficacy data obtained in the 3 trials are remarkably consistent. Although the mean MADRS has been used as the primary endpoint despite the Scientific Advice provided in 2005, which recommended the use of the Hamilton HAM-17 as a primary endpoint, all endpoints are congruently statistically relevant, all in the same direction supporting a benefit of aripiprazole. The remission rates are statistically significant in all trials and the absolute risk difference is about 10% being higher in trial 165 where it reaches 18%. In fact, study CN138-165 has a larger effect size in all endpoints.

The CHMP noted that there was no specific study to determine dose in this proposed new indication for aripiprazole. Therefore the posology scheme was empirically proposed using some of the boundaries known from the already approved indication. The CHMP considered that the lowest effective dose has not been adequately defined. Following detailed review of the dose regimens used in the pivotal studies, the CHMP considered that sufficient data were provided by the MAH to justify the proposed dosing recommendation. The 5 mg/day, 10 mg/day and 15mg/day subgroups had comparable sample sizes and mean change from baseline scores. The 2mg/day subgroup had a small number of patients (n=28, 5%) and a large standard error (1.56) to be supportive of a recommended dose, despite showing benefits at this dose level. The 20 mg/day subgroup showed the least improvement in the mean change from baseline in MADRS Total Score as would be expected in a flexible-dose study since this subgroup included patients who did not respond to lower doses of aripiprazole augmentation therapy.

With respect to the long-term data, only one open label study (CN138-164) was performed which makes the results difficult to interpret. Furthermore, in this study, the enrolment strategy allowed a fairly mixed population although separate analyses of the rolling over patients and de novo patients were performed. The CHMP therefore considered that given these limitations, maintenance of the efficacy of aripiprazole in this population remains to be addressed. In light of this major concern, the MAH should also discuss the optimal duration of the treatment, given that the indication relates to the treatment of major depressive episodes as adjunctive treatment.

In light of the major concerns related to the studied population and the proposed indication, the lack of controlled data to establish the duration of treatment and the maintenance of the efficacy and on the basis of the available data to date, the CHMP agreed to convene a Scientific Advisory Group (SAG) Central Nervous System to discuss the clinical requirements for the development of medicinal products in the field of resistant depression, namely the definition of the population, the study design, outcomes and the follow up duration. The SAG CNS was held on 15 June 2009 and the main conclusions were the following:

- The minimum requirements to define resistant depression patients could be defined as follows:
 - Resistance to two different classes of antidepressant treatment;
 - Treatments to be conducted at the maximum tolerated dose for at least 6 weeks before concluding that treatment is ineffective.

- Concomitant conditions and co-morbidities (thyroid disorders, alcohol dependence, severe personality and anxiety disorders) have to be treated with caution concerning the inclusion criteria and the ensuing confounding factors.

In the SAG view, a definition of “resistant depression” that would effectively result in defining a very narrow population of refractory patients (i.e. those who are still depressed after exhausting a full array of treatments, including ECT and TMS) has to be avoided.

It has to be taken into account that co-morbidities (psychiatric and physical- like thyroid disease) could contribute to the clinical manifestations, therefore falsely supporting the impression of resistance. In particular thyroid disease, even if treated, would leave a footprint resulting in higher depression susceptibility for many years. Patients with comorbidities have to be treated with caution for the inclusion in the clinical trials.

The SAG also considered ideal to have two prospective assessments of treatment resistance, but this would set too high a burden to the development of new drugs. One retrospective and one prospective treatment resistances are therefore advised by the SAG. One of the two episodes must have been under the supervision of a psychiatrist, or other specialist, who has explored the full dose range and treatment duration before resistance is inferred.

For the retrospective assessment, patient subjective recollection (as required by the Massachusetts questionnaire) is not advisable, as inaccurate. The retrospective treatment failure should include an assessment tool, and source documentation from the medical records, determining dosage, duration of treatment and treatment response.

For the prospective assessment of treatment resistance, the SAG agreed that is essential that compliance to the prescribed treatment is shown (via blood monitoring) before concluding that treatment failure is due to resistance.

Concerning the severity of the disease, the SAG view was that both moderately and severely ill patients should be included as resistant depression is a serious concern for both classes of patients, who are left with residual untreated symptoms.

Rating scales would be used to measure change in the response from baseline.

Remission rate would be the ideal primary outcome but the SAG recognised that the remission rates are not high and this would entail large patient numbers to be recruited in the study. Therefore, the SAG considered that response rate should be used, defined as a 50% reduction in MADRS or Hamilton rating scale.

- In terms of duration of treatment, the SAG considered that:

- Adequate durations of a double-blind phase of clinical trial in resistant depression to demonstrate short term efficacy and maintenance of the effect would be 6-8 weeks (although for drugs like Lithium effect can be shown in 2 weeks) and 6-9 months, respectively.
- To establish an optimal/minimal duration of treatment, a randomised controlled withdrawal trial would be necessary as currently there are no data from withdrawal studies in any class of drugs and no data on combinations from randomised controlled studies.
- The use of an antipsychotic in augmentation strategy would most probably need to be a chronic treatment (as if a drug used for augmentation strategy makes a patient better, it seems to be needed to maintain the effect as well), unless a randomised controlled withdrawal trial showed otherwise. The optimal study here would be to take patients who had responded to combination and randomly allocate them to antidepressant or to antidepressant plus antipsychotic.

Having considered the above SAG conclusions and the MAH responses to the Request for Supplementary Information (EMA/CHMP/132488/2009), the CHMP considered that the studied population in the clinical program for aripiprazole only fulfilled partially the proposed definition of “resistant depression” according to the Note for Guidance on “Clinical Investigation of Medicinal

Products in the Treatment of Depression” (CPMP/EWP/518/97, revision 1) and the SAG’s recommendation as only 60% of the patients in the pivotal studies, who switched classes of antidepressants in Phase B met the corresponding criteria. Therefore, the CHMP considered that the major concern over the proposed indication remains to be addressed.

Furthermore, the CHMP major concerns over the duration of treatment remain in the absence of adequate long term randomised efficacy data. The MAH considered that the optimal duration of treatment could be based on time to achieve remission, within the context of clinically meaningful treatment phases of depression as defined by Kupfer (1991). The MAH also proposed to conduct a relapse prevention study to address the concerns over the lack of adequate long term data to demonstrate maintenance of the efficacy as a post-authorisation commitment. However, the CHMP is of the opinion that well designed maintenance and relapse and recurrence prevention studies are lacking, making the dossier incomplete. These should be performed as part of the normal clinical development plan instead of post-approval, as both long-term efficacy and long-term safety data are needed before licensing of this indication. The CHMP also considered that the possibility to restrict the use of aripiprazole to specialists in this proposed new population should be discussed by the MAH.

Other additional concern related to the lack of monotherapy data has been raised by the CHMP prior any final conclusions are made.

Clinical safety:

- **Patient exposure**

The 3 placebo controlled studies and the open label study CN138-164 included data from 1267 aripiprazole-treated patients with MDD. A total of 1041 (82.2%) patients with MDD were exposed to aripiprazole for ≥ 42 days, 523 (41.3%) for ≥ 180 days, and 261 (20.6%) for ≥ 360 days.

In a pooled analysis from the 3 placebo controlled studies (CN138-139, CN138-163 and CN138-1265), there were 547 patients who received aripiprazole in the randomization phase (Phase C) of the placebo-controlled studies in MDD and 94.1% of these patients received up to 21 days of study drug.

- **Adverse events**

Placebo-controlled trials

Adverse events that were reported at an incidence of $\geq 5\%$ (including numbers that equaled 5% after rounding) and at least twice the rate of placebo included akathisia, restlessness, fatigue, insomnia, vision blurred, somnolence, and constipation. A slight overlap in patients who reported akathisia versus those who reported restlessness was observed. No treatment-emergent AEs of mania, psychosis, or serotonin syndrome were reported.

All MDD Aripiprazole-Treated Patients

Most (90.4%) aripiprazole-treated patients with MDD reported at least 1 treatment emergent AE. Akathisia (24.9%) was most frequently reported, followed by fatigue (15.8%), weight increased (14.0%), restlessness (14.0%), somnolence (12.1%), insomnia (11.4%), and headache (11.1%).

The incidence of treatment-emergent AEs by time of first onset was highest in the first 42 days of treatment except for weight increase, which increased through 180 days. Incidence of AEs generally decreased over time or remained constant.

The incidence of drug-related treatment-emergent AEs that were assessed by the investigator as related to treatment (definite/certain, probable, or possible causality) and that were reported in $\geq 5\%$ of patients is presented in Table 5.

Table 5: Treatment-Emergent Drug-Related AEs in at Least 5 Percent of Patients: Aripiprazole-Treated Patients in Depressive Disorder (CN138139, CN138163, CN138164, CN138165), Safety Sample

SYSTEM ORGAN CLASS PREFERRED TERM	MDD INCIDENCE (%)
NUMBER OF PATIENTS SCREENED FOR AEs	1267
NUMBER OF MALE PATIENTS	408
NUMBER OF FEMALE PATIENTS	859
NUMBER OF PATIENTS WITH ≥1 AEs	1049 (82.8)
NERVOUS SYSTEM DISORDERS	743 (58.6)
AKATHISIA	314 (24.8)
SOMNOLENCE	151 (11.9)
HEADACHE	103 (8.1)
SEDATION	98 (7.7)
DIZZINESS	87 (6.9)
TREMOR	82 (6.5)
PSYCHIATRIC DISORDERS	449 (35.4)
RESTLESSNESS	174 (13.7)
INSOMNIA	126 (9.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	302 (23.8)
FATIGUE	185 (14.6)
GASTROINTESTINAL DISORDERS	298 (23.5)
NAUSEA	80 (6.3)
CONSTIPATION	65 (5.1)
INVESTIGATIONS	219 (17.3)
WEIGHT INCREASED	172 (13.6)
METABOLISM AND NUTRITION DISORDERS	96 (7.6)
INCREASED APPETITE	70 (5.5)

The incidence of AEs for a particular System Organ Class is the incidence of all AEs in that System Organ Class.
MedDRA Version: 11.0

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- **Serious adverse events and deaths**

No deaths were reported during the MDD studies.

In the safety sample including all MDD aripiprazole treated patients, the overall incidence of treatment-emergent SAEs in patients with MDD was 3.3%. Of the 42 patients who reported at least 1 SAE, 4 (9.5%) patients reported at least 1 SAE that was considered treatment-related. These SAEs included 1 event each of syncope, orthostatic hypotension, chest pain, depression, suicidal ideation, anxiety, and movement disorder.

- **Discontinuation due to TEAEs**

Placebo-controlled trials

The overall incidence of AEs that led to discontinuation of study therapy during the placebo-controlled studies in MDD was 5.9% for the aripiprazole group and 1.7% for the placebo group. The most common reasons for discontinuing from aripiprazole treatment were akathisia (1.3%) and fatigue (0.7%).

All MDD Aripiprazole-treated patients

A total of 247 (19.5%) aripiprazole-treated patients with MDD reported treatment-emergent AEs that led to discontinuation of study therapy (Table 2.1.4.2). The most frequently (>1%) reported AEs were akathisia (3.0%), weight increased (2.6%), somnolence (1.7%), fatigue (1.5%), and anxiety (1.4%).

- **Other safety findings**

Dyskinesia and Tardive Dyskinesia

Among all aripiprazole-treated patients with MDD, 15 (1.2%) patients reported a total of 18 AEs of dyskinesia and 4 (< 1%) patients reported a total of 4 AEs of tardive dyskinesia.

Neuroleptic Malignant Syndrome (NMS)

No aripiprazole treated MDD patient reported NMS.

Seizures

One seizure-related AE was reported by 1 (0.1%) aripiprazole-treated patient in the MDD studies.

Suicide related events

The incidence of suicide-related AEs was 0.017 per patient exposure year (PEY) among aripiprazole treated patients with MDD. This incidence was lower than that reported in the placebo-controlled studies, and compared favorably to the suicide rates reported in the literature.

Somnolence/Sedation Related Adverse Events

In the placebo-controlled studies in MDD, the incidence of somnolence/sedation was 9.9% in the aripiprazole group and 4.6% in the placebo group. In the aripiprazole group, the rate of discontinuation of study therapy because of somnolence or sedation was low (0.4% and 0.2%, respectively)

Prolactin levels

The incidence of potentially clinically relevant serum chemistry measurements in all patients with MDD was low except for the incidence of increased prolactin (10.3%). In placebo-controlled trial, aripiprazole-treated patients reported a median 12.5% decrease in prolactin levels.

Metabolic and Glucose Measurements

In the safety sample including all MDD aripiprazole treated patients, 7 patients treated with aripiprazole in the MDD studies reported hyperglycemia related AEs. No patient had an SAE that was a hyperglycemia related event. Two patients discontinued because of hyperglycemia.

Potentially clinically relevant weight increase was reported for 23.4% of aripiprazole-treated patients in MDD studies. A total of 33 (2.6%) patients discontinued treatment because of increased weight. The rates of clinically relevant weight gain for aripiprazole-treated patients in MDD studies increased over time: 5.5% at ≤ 11 weeks, 28.6% at 12 to 35 weeks, and 36.3% at ≥ 36 weeks. Rates of clinically relevant weight loss also increased over time, reaching 4.4% among patients who had weights recorded at ≥ 36 weeks. Median weight increases were 4.0 kg during this time period. Increases over time were also observed for BMI and waist circumference.

Vital signs

In the safety sample including all MDD aripiprazole treated patients, the incidence of vital sign abnormalities of potential clinical relevance in patients with MDD was low ($\leq 1.5\%$)

Among the aripiprazole-treated patients in the MDD studies, 4 (0.3%) patients discontinued due to hypertension and 1 (0.1%) patient each discontinued due to orthostatic hypotension and shock

ECG Abnormalities

The incidence of ECG abnormalities in aripiprazole treated patients in the MDD studies was low ($\leq 0.7\%$). No patient with MDD demonstrated a QTcE > 500 msec. No patient demonstrated a QTcE greater than 500 msec. Asymptomatic and > 60 msec changes in QTcE interval were reported in 2 patients in the placebo-controlled trials

- **Discussion on clinical safety**

The safety data from this clinical program developed in the context of treatment of depression did not generate any new concerns.

However, the CHMP noted that the frequency of the AEs related to weight gain was higher than previously observed in the other indications where the product is approved. This may also correlate with AEs related to dyslipidaemia. Careful monitoring of these issues should therefore be considered by the MAH, especially since the background of the disease and/or the use of antidepressants may also be contributing to a synergistic AEs profile in this population. To address this concern, the MAH proposed to prospectively evaluate weight and lipid parameters, as well as other safety parameters, as part of the placebo-controlled relapse prevention study proposed to be conducted by the MAH as part of a post-authorisation commitment.

At the SAG CNS meeting held on 15 June 2009, the experts were also requested to discuss identified concerns on assessment of long-term safety for add on antipsychotic treatment considering the risk of extrapyramidal side effects, tardive dyskinesia, and weight gain. The main conclusion was the following:

- The long term side effects of antipsychotics are well known and would need to be balanced against the efficacy.
- The choice of dosage should be justified appropriately by the applicant, and not simply be based on the antipsychotic established dosage in schizophrenia.
- Aspects to which particular attention should be made are: metabolic disease, tardive dyskinesia, extrapyramidal side effects, cognitive function, weight gain (especially in some groups of patients e.g. young women, heart disease patients).

Taking into consideration the SAG conclusion, the MAH should provide an updated RMP to propose measures for the monitoring of the specific risks identified in the unipolar depression if not already present. Safety parameters as discussed by the SAG, should be considered.

Risk Management plan (RMP)

The MAH submitted a revised RMP reflecting the information on MDD. No new safety concerns are identified and therefore the proposed Pharmacovigilance actions and risk minimisation activities are identical to version 4.0 and summarised in Table 6.

Table 6. Safety concerns, proposed Pharmacovigilance (PV) actions, and Proposed Risk Minimisation Activities

Safety Concern	Proposed PV Activities	Proposed Risk Minimization Activities (Routine and Additional)
Important Identified Risks:		
EPS, including tardive dyskinesia	Routine PV as listed in the current RMP	Warnings & Precautions 4.4 of SPC: consider dose reduction or discontinuation if signs and symptoms of tardive dyskinesia appear; symptoms can temporally deteriorate or can even arise after discontinuation of treatment. Undesirable effects 4.8 of the SPC: incidence rates listed for aripiprazole vs active comparators or placebo for bipolar mania program
NMS	Routine PV as listed in the current RMP	Warnings & Precautions 4.4 of SPC: discontinue use if signs and symptoms indicative of NMS or unexplained high fever develops
Important Potential Risks:		
Seizures	Routine PV as listed in the current RMP	Warnings & Precautions 4.4 of SmPC: use with caution.
Hyperglycemia/diabetes	Routine PV as listed in the current RMP	Warnings & Precautions 4.4 of SPC: hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death
Suicide	Routine PV as listed in the current RMP	Warnings & Precautions 4.4 of SmPC: suicidal behavior inherent in psychotic illness and mood disorders, close supervision recommended. Undesirable effects Sect 4.8: Suicide attempt, ideation and completed suicide. Routine PV plus epidemiological claims database study of the association of use of atypical antipsychotics and the incidence of suicide events (CN138458).
Orthostatic Hypotension	Routine PV as listed in the current RMP	Warnings & Precautions 4.4 of SPC: regular monitoring of blood pressure, heart rate, respiratory rate and level of consciousness

Safety Concern	Proposed PV Activities	Proposed Risk Minimization Activities (Routine and Additional)
Dyslipidemia	Routine PV as listed in the current RMP and Proposed clinical data analysis	Will propose risk minimization activities if a causal relationship between aripiprazole and dyslipidemia can be established..
Important Missing Information		
Pregnancy and Lactation	Routine PV as listed in the current RMP	Pregnancy and lactation in section 4.6 of the SPC: potential for developmental toxicity
Pediatrics	Routine PV as listed in the current RMP	Posology 4.2: No experience in children
Other Potential Concerns		
As expected for antipsychotic therapies, onset of clinical improvement may take several days to weeks	Routine PV as listed in the current RMP	Warnings & Precautions 4.4 of SPC: monitor closely
Cardiovascular-related disorders (primarily applies to elderly patients with dementia-related psychosis)	Routine PV as listed in the current RMP	Warnings & Precautions 4.4 of SmPC: use with caution (cardiovascular disease, cerebrovascular disease, conditions predisposing to hypotension or hypertension, including accelerated or malignant.)
Conduction abnormalities (incidence of QT prolongation comparable to placebo)	Routine PV as listed in the current RMP	Warnings & Precautions 4.4 of SPC: use with caution in patients with a family history of QT prolongation.
Weight gain (no statistically significant differences in weight gain/loss in bipolar mania)	Routine PV as listed in the current RMP	Warnings & Precautions 4.4 of SmPC: especially in schizophrenic patients and often due to co-morbidities, especially history of diabetes, thyroid disorder or pituitary adenoma.

Safety Concern	Proposed PV Activities	Proposed Risk Minimization Activities (Routine and Additional)
Dysphagia (primarily applies to schizophrenia population)	Routine PV as listed in the current RMP	Warnings & Precautions 4.4 of SPC: esophageal dysmotility and aspiration; caution in patients at risk for aspiration pneumonia.
Lactose (not new risk for bipolar mania)	Routine PV as listed in the current RMP	Warnings & Precautions 4.4 of SmPC: do not administer if galactose intolerance, lapp lactase deficiency, glucose-galactose malabsorption
Drug interactions (not new risk for bipolar mania)	Routine PV as listed in the current RMP	Drug interaction information in section 4.5 of the SPC: 1.CYP2D6, 3A4 2.Antihypertensives 3.Alcohol or other CNS medications 4. Drugs prolonging QT or causing electrolyte imbalance 5. H2 antagonist
Increased mortality and CVA in elderly patients with dementia	Routine PV as listed in the current RMP	Warnings & Precautions 4.4 of SmPC: drug not approved for treatment of dementia-related psychosis.
Serious Injection Site Reactions (with Solution for Injection only)	Routine PV as listed in the current RMP	Continue monitoring post-marketing Adverse Events reports
Serious Hypersensitivity Reactions to Excipients (with Solution for Injection only)	Routine PV as listed in the current RMP	Continue monitoring post-marketing Adverse Events reports

The CHMP, having considered the data submitted in the application, is of the opinion that the Risk Management Plan should be further developed considering the SAG conclusion on safety.

User Consultation

The MAH referred to the Readability Testing of the aripiprazole tablets Package Leaflet (PL) conducted during the assessment of the initial marketing authorisation application.

The MAH considered that the key safety information differences concerns adverse drug reactions already listed in the PL and that the layout is not significantly changed. This justification was considered acceptable by the CHMP.

IV. OVERALL BENEFIT RISK ASSESSMENT

In 3 randomised, double blind controlled placebo studies of the same design, the aripiprazole group showed statistically significantly greater improvement than placebo on the primary efficacy measure, the mean change from end of Phase B to end of Phase C (LOCF) in MADRS Total Score. To further evaluate the efficacy in this population, data on how many patients entered the treatment phase B in the phase III studies and went on to achieve a proper response to the anti-depressant medication were provided. The results of each study were re-assessed depending on initial severity degree of MDE for participating patients in order to demonstrate if the initial severity may be predictive of efficacy of treatment and a sensitivity analysis was also be provided (counting the drop-outs and withdrawals as failures) in the responders analysis of the placebo-controlled trials. Having considered these further analyses provided by the MAH, the CHMP concluded that the effect size was similar among the 2 categories of initial severity (based on their MADRS score at baseline) and that the requested sensitivity analysis was satisfactory showing consistent results with those reported in the initial analyses.

On the other hand, the CHMP raised a major concern about the studied population which may not have reflected the characteristics (i.e prescription patterns) of the European population, given that these studies were performed in the US. To address this concern, the MAH argued that within the clinical development program, the methods used to diagnose patients, and define incomplete response, the choice of antidepressants and the different strategies such as increasing the dose and switching between and within classes of antidepressants, reflected the common clinical practice in the EU allowing therefore the results to be generalised. This argumentation was accepted by the CHMP.

The CHMP was also concerned about the validity of the ATRQ questionnaire which is used to document the first attempt in the targeted population (i.e.patients failing 2 attempts to treat their current episode of depression). Failure of the second episode was prospectively collected and therefore provided more reliability. Following review and clarifications provided by the MAH on the validity of the ATRQ questionnaire, the CHMP considered that this concern remains.

Overall, the efficacy data obtained in the 3 trials are remarkably consistent. Although the mean MADRS has been used as the primary endpoint despite the Scientific Advice provided in 2005, which recommended the use of the Hamilton HAM-17 as a primary endpoint, all endpoints are congruently statistically relevant, all in the same direction supporting a benefit of aripiprazole. The remission rates are statistically significant in all trials and the absolute risk difference is about 10% being higher in trial 165 where it reaches 18%. In fact, study CN138-165 has a larger effect size in all endpoints.

The CHMP noted that there was no specific study to determine dose in this proposed new indication for aripiprazole. Therefore the posology scheme was empirically proposed using some of the boundaries known from the already approved indication. The CHMP considered that the lowest effective dose has not been adequately defined. Following detailed review of the dose regimens used in the pivotal studies, the CHMP considered that sufficient data were provided by the MAH to justify the proposed dosing recommendation. The 5 mg/day, 10 mg/day and 15mg/day subgroups had comparable sample sizes and mean change from baseline scores. The 2mg/day subgroup had a small number of patients (n=28, 5%) and a large standard error (1.56) to be supportive of a recommended dose, despite showing benefits at this dose level. The 20 mg/day subgroup showed the least improvement in the mean change from baseline in MADRS Total Score as would be expected in a flexible-dose study since this subgroup included patients who did not respond to lower doses of aripiprazole augmentation therapy.

With respect to the long-term data, only one open label study (CN138-164) was performed which makes the results difficult to interpret. Furthermore, in this study, the enrolment strategy allowed a fairly mixed population although separate analyses of the rolling over patients and de novo patients

were performed. The CHMP therefore considered that given these limitations; maintenance of the efficacy of aripiprazole in this population remains to be addressed. In light of this major concern, the MAH should also discuss the optimal duration of the treatment, given that the indication relates to the treatment of major depressive episodes as adjunctive treatment.

In light of the major concerns related to the studied population and the proposed indication, the lack of controlled data to establish the duration of treatment and the maintenance of the efficacy and on the basis of the available data to date, the CHMP agreed to convene a Scientific Advisory Group (SAG) Central Nervous System to discuss the clinical requirements for the development of medicinal products in the field of resistant depression, namely the definition of the population, the study design, outcomes and the follow up duration. The SAG CNS was held on 15 June 2009 and the main conclusions were the following:

- The minimum requirements to define resistant depression patients could be defined as follows:
 - Resistance to two different classes of antidepressant treatment;
 - Treatments to be conducted at the maximum tolerated dose for at least 6 weeks before concluding that treatment is ineffective.
 - Concomitant conditions and co-morbidities (thyroid disorders, alcohol dependence, severe personality and anxiety disorders) have to be treated with caution concerning the inclusion criteria and the ensuing confounding factors.

In the SAG view, a definition of “resistant depression” that would effectively result in defining a very narrow population of refractory patients (i.e. those who are still depressed after exhausting a full array of treatments, including ECT and TMS) has to be avoided.

It has to be taken into account that co-morbidities (psychiatric and physical- like thyroid disease) could contribute to the clinical manifestations, therefore falsely supporting the impression of resistance. In particular thyroid disease, even if treated, would leave a footprint resulting in higher depression susceptibility for many years. Patients with comorbidities have to be treated with caution for the inclusion in the clinical trials.

The SAG also considered ideal to have two prospective assessments of treatment resistance, but this would set too high a burden to the development of new drugs. One retrospective and one prospective treatment resistances are therefore advised by the SAG. One of the two episodes must have been under the supervision of a psychiatrist, or other specialist, who has explored the full dose range and treatment duration before resistance is inferred.

For the retrospective assessment, patient subjective recollection (as required by the Massachusetts questionnaire) is not advisable, as inaccurate. The retrospective treatment failure should include an assessment tool, and source documentation from the medical records, determining dosage, duration of treatment and treatment response.

For the prospective assessment of treatment resistance, the SAG agreed that is essential that compliance to the prescribed treatment is shown (via blood monitoring) before concluding that treatment failure is due to resistance.

Concerning the severity of the disease, the SAG view was that both moderately and severely ill patients should be included as resistant depression is a serious concern for both classes of patients, who are left with residual untreated symptoms.

Rating scales would be used to measure change in the response from baseline.

Remission rate would be the ideal primary outcome but the SAG recognised that the remission rates are not high and this would entail large patient numbers to be recruited in the study. Therefore, the SAG considered that response rate should be used, defined as a 50% reduction in MADRS or Hamilton rating scale.

- In terms of duration of treatment, the SAG considered that:

- Adequate durations of a double-blind phase of clinical trial in resistant depression to demonstrate short term efficacy and maintenance of the effect would be 6-8 weeks (although for drugs like Lithium effect can be shown in 2 weeks) and 6-9 months, respectively.
- To establish an optimal/minimal duration of treatment, a randomised controlled withdrawal trial would be necessary as currently there are no data from withdrawal studies in any class of drugs and no data on combinations from randomised controlled studies.
- The use of an antipsychotic in augmentation strategy would most probably need to be a chronic treatment (as if a drug used for augmentation strategy makes a patient better, it seems to be needed to maintain the effect as well), unless a randomised controlled withdrawal trial showed otherwise. The optimal study here would be to take patients who had responded to combination and randomly allocate them to antidepressant or to antidepressant plus antipsychotic.

Having considered the above SAG conclusions and the MAH responses to the Request for Supplementary Information (EMEA/CHMP/132488/2009), the CHMP considered that the studied population in the clinical program for aripiprazole only fulfilled partially the proposed definition of “resistant depression” according to the Note for Guidance on “Clinical Investigation of Medicinal Products in the Treatment of Depression” (CPMP/EWP/518/97, revision 1) and the SAG’s recommendation as only 60% of the patients in the pivotal studies, who switched classes of antidepressants in Phase B met the corresponding criteria. Therefore, the CHMP considered that the major concern over the proposed indication remains to be addressed.

Furthermore, the CHMP major concerns over the duration of treatment remain in the absence of adequate long term randomised efficacy data. The MAH considered that the optimal duration of treatment could be based on time to achieve remission, within the context of clinically meaningful treatment phases of depression as defined by Kupfer (1991). The MAH also proposed to conduct a relapse prevention study to address the concerns over the lack of adequate long term data to demonstrate maintenance of the efficacy as a post-authorisation commitment. However, the CHMP is of the opinion that well designed maintenance and relapse and recurrence prevention studies are lacking, making the dossier incomplete. These should be performed as part of the normal clinical development plan instead of post-approval, as both long-term efficacy and long-term safety data are needed before licensing of this indication. The CHMP also considered that the possibility to restrict the use of aripiprazole to specialists in this proposed new population should be discussed by the MAH.

Other additional concern related to the lack of monotherapy data has been raised by the CHMP prior any final conclusions are made.

The safety data from this clinical program developed in the context of treatment of depression did not generate any new concerns.

However, the CHMP noted that the frequency of the AEs related to weight gain was higher than previously observed in the other indications where the product is approved. This may also correlate with AEs related to dyslipidaemia. Careful monitoring of these issues should therefore be considered by the MAH, especially since the background of the disease and/or the use of antidepressants may also be contributing to a synergistic AEs profile in this population. To address this concern, the MAH proposed to prospectively evaluate weight and lipid parameters, as well as other safety parameters, as part of the placebo-controlled relapse prevention study proposed to be conducted by the MAH as part of a post-authorisation commitment.

At the SAG CNS meeting held on 15 June 2009, the experts were also requested to discuss identified concerns on assessment of long-term safety for add on antipsychotic treatment considering the risk of extrapyramidal side effects, tardive dyskinesia, and weight gain. The main conclusion was the following:

-The long term side effects of antipsychotics are well known and would need to be balanced against the efficacy.

The choice of dosage should be justified appropriately by the applicant, and not simply be based on the antipsychotic established dosage in schizophrenia.

Aspects to which particular attention should be made are: metabolic disease, tardive dyskinesia, extrapyramidal side effects, cognitive function, weight gain (especially in some groups of patients e.g. young women, heart disease patients).

Taking into consideration the SAG conclusion, the MAH should provide an updated RMP to propose measures for the monitoring of the specific risks identified in the unipolar depression if not already present. Safety parameters as discussed by the SAG should be considered.

Overall, the CHMP considered the benefit risk assessment of Abilify in the proposed indication unfavourable pending to the Request for Supplementary Information.