

London, 04 October 2006

Product name: Abilify

Procedure No. EMEA/H/C/000471/II/0015

SCIENTIFIC DISCUSSION

1.1 Introduction

Acutely agitated patients with neuropsychiatric illness risk harming themselves or others. Psychomotor agitation is defined in the Diagnostics and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) as “excessive motor activity associated with a feeling of inner tension.”

Patients experiencing agitation may manifest a range of disturbed behaviours that interfere with their diagnosis and care (e.g. threatening behaviours, escalating or urgently distressing behaviours, or self-exhausting behaviour) requiring clinicians to use intramuscular antipsychotic medications to achieve immediate control of the agitation.

Treating patients during the first few hours of agitation is most important in emergency and critical care situations. Because such patients may be unable or unwilling to take oral antipsychotic drugs, it may be necessary to use an alternative route of administration to treat them.

Currently, a limited choice of rapid acting intramuscular (IM) formulations of antipsychotics is available for agitated patients with neuropsychiatric illness.

Based on 3 placebo-controlled studies, the Marketing Authorisation Holder (MAH) applied to extend the therapeutic indication to the following:

‘rapid control of agitation and disturbed behaviours in patients with schizophrenia, when oral therapy is not appropriate’.

This extension of indication concerns a new route of administration, Abilify 7.5 mg/ml solution for injection for which an extension application is submitted in parallel (EMA/H/C/471/X/16).

1.2 Clinical aspects

The clinical program to support the extension of indication for IM Abilify included 3 placebo-controlled studies:

- 2 studies (CN138012 and CN138050) were conducted in agitated patients with schizophrenia, schizoaffective, or schizophreniform disorder. Study CN138050 evaluated 4 doses (1 mg, 5 mg, 10 mg, 15 mg) of IM aripiprazole, haloperidol (7.5mg), and placebo in agitated patients with schizophrenia, schizoaffective, or schizophreniform disorder. Based on the results from study CN138050, the second study CN138012 evaluated a dose of 10-mg IM aripiprazole, haloperidol (6.5 mg), and placebo in patients with schizophrenia or schizoaffective disorder, followed by 4 days of the aripiprazole oral-tablet formulation or haloperidol oral capsules
- 1 study (CN138013) was conducted in agitated patients with bipolar I disorder, manic or mixed and evaluated 2 doses of IM aripiprazole (10 mg and 15 mg), lorazepam (2 mg), and placebo

CN138050 and CN138012 are the main clinical studies to support the claimed indication in the treatment of acutely agitated patients with schizophrenia.

Study CN138013 has been provided as a supportive evidence of the use of Abilify 7.5mg/ml solution for injection in acutely agitated patients, irrespective of the cause.

The goal of this program is a normal extension of the role of an antipsychotic in clinical use.

It should be noted that amendments to protocols of the 3 placebo controlled studies were made relative to the doses investigated to enable administration of accurate volume, i.e. 9.75 mg (1.3 ml) and 5.25 mg (0.7 ml) instead of 10 mg (1.33 ml) and 5 mg (0.66 ml).

Although the safety, tolerability, and pharmacokinetics of aripiprazole, administered as tablets and oral solution, have been well characterized, additional pharmacokinetic studies have been conducted to ascertain that the knowledge acquired with oral formulations can be related to the IM formulation.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

- Absorption

Study CN138016

Absolute bioavailability of aripiprazole following IM administration in healthy subjects.

The primary objective of this study was to assess the absolute bioavailability of the 5 mg aripiprazole tablet formulation and 5 mg aripiprazole IM formulation with reference to a 2 mg aripiprazole dose administered by intravenous (IV) infusion. This was an open-label, randomised, three-period, three-treatment crossover study balanced for carryover effects in healthy subjects.

On three occasions separated by a period of at least 21 days, each subject received single doses of aripiprazole administered as a 2 mg IV infusion, a 5 mg oral tablet, and a 5 mg IM injection (of the proposed commercial formulation) according to a computer-generated randomisation schedule. Based on the geometric mean values adjusted for factors in the analysis of variance model, the adjusted estimate of absolute bioavailability was 0.87 for the tablet formulation and 1.01 for the IM formulation. The estimated dose-normalized geometric mean AUC(0-2 hours) of the aripiprazole IM formulation was 90% higher than that of the tablet formulation, indicating faster absorption for the IM formulation than for the tablet formulation.

- Dose proportionality and time dependencies

Study CN138017

Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple intramuscular doses of aripiprazole in patients with schizophrenia or schizoaffective disorder.

The primary objective of this study was to assess the safety and tolerability profile of aripiprazole in subjects with schizophrenia or schizoaffective disorder following either 4 days of once daily IM administration or three IM injections in a single day as compared with three IM injections of haloperidol in a single day. The secondary objectives were to assess the pharmacokinetics and pharmacodynamics of aripiprazole following 4 days of once daily IM administration and to assess the pharmacokinetics of aripiprazole following three IM injections in a single day in subjects with schizophrenia. This was an open-label, sequential group, escalating dose study. Thirty-two (32) subjects were enrolled in the study as groups of four (4) for each treatment. There was a lead-in period of 4 days to washout previous medications before administering aripiprazole. Subjects received daily IM injections of 1, 3, 7.5, 15 or 30 mg aripiprazole for 4 days, respectively.

The pharmacokinetic parameters of aripiprazole obtained following IM administration in this study were comparable to those after oral administration. The single dose geometric mean C_{max}, median T_{max} and geometric mean AUC(0-24 hours) values for aripiprazole following a single 30 mg oral dose of aripiprazole (in the fed state) were 121 ng/mL, 8.0 h and 1989 ng.h/mL, respectively (n = 58). The corresponding values for the 30 mg IM dose in this study were 143 ng/mL, 7 h and 2297 ng.h/mL, respectively (n = 4).

The study shows that C_{max} and AUC are approximately dose proportional at day 1 and day 4 following administration of the IM solution.

- Pharmacokinetic interaction studies

Interaction Study CN138132

A double-blind, randomised study to evaluate pharmacodynamic and pharmacokinetic interactions between intramuscular aripiprazole and intramuscular lorazepam when co-administered in healthy subjects.

The primary objectives of this study were to estimate the effect of lorazepam on the pharmacokinetics of aripiprazole as well as the effect of aripiprazole on the pharmacokinetics of lorazepam, and to estimate the acute pharmacodynamic effect (the degree of sedation) of co-administration of single IM doses of aripiprazole and lorazepam as compared to when each agent was administered alone. This was a double-blind, randomised, 2-group, 2-period crossover study in healthy subjects. In the double-blind portion of the study, 20 subjects in Cohort 1 were randomised to either treatment sequence AC or CA, and 20 subjects in Cohort 2 were randomised to either treatment sequence BC or CB, where

- Treatment A = 15 mg aripiprazole (IM) + placebo matching lorazepam (IM)
- Treatment B = placebo matching aripiprazole (IM) + 2 mg lorazepam (IM)
- Treatment C = 15 mg aripiprazole (IM) + 2 mg lorazepam (IM).

The 90% confidence intervals for the C/B ratios of population geometric means for C_{max}, AUC(INF), and AUC(0-T) of lorazepam concluded that aripiprazole has no effect on the pharmacokinetics of lorazepam.

Co-administration of IM aripiprazole and IM lorazepam had no effect on the pharmacokinetics of either compound. There was an interaction in the pharmacodynamics when aripiprazole and lorazepam were co-administered. The intensity of sedation was greater and the orthostatic hypotension observed was similar with the combination as compared to that with aripiprazole alone. In contrast, the intensity of sedation was similar and the orthostatic hypotension observed was greater with the combination as compared to that with lorazepam alone.

Overall the pharmacokinetic profile of the IM aripiprazole has been appropriately characterised. In studies CN138016 and CN138017, a wide variability in T_{max} values was observed. The CHMP recommended changes to the product information to reflect its impact on the mode of administration of IM aripiprazole.

Clinical Efficacy

- Main studies

Study CN138050:

Randomised, double-blind, dose-ranging study of IM aripiprazole in the treatment of acute agitation in patients with a diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder.

METHODS

Study design

It is a randomised, double-blind, dose-ranging IM study comparing 4 fixed doses of aripiprazole (1, 5, 10 and 15 mg) and 1 dose of haloperidol (7.5 mg) with placebo over 24 hours. It was conducted in patients with schizophrenia, schizoaffective, or schizophreniform disorder in acute agitation (as defined by DSM-IV) and that have PEC: at least 2 components ≥ 4 (moderate) and sum of 5 components ≥ 15 but ≤ 32 .

Primary and Secondary Objectives

The primary objective was to compare the efficacy of intramuscular aripiprazole with placebo in the treatment of acute agitation in patients with a diagnosis of schizophrenia, schizoaffective, or

schizophreniform disorder, as assessed by the mean change from baseline to 2-hours postdose using the PEC scale.

Secondary objectives were:

- to assess the efficacy of IM aripiprazole versus placebo in the treatment of acute agitation in patients with schizophrenia, schizoaffective, or schizophreniform disorder, utilizing the secondary efficacy endpoints
- to measure the effects of IM haloperidol, a known active therapy and standard of care in the treatment of acute agitation in patients with schizophrenia, schizoaffective, or schizophreniform disorder, versus placebo
- to describe the safety and tolerability of IM aripiprazole in the treatment of acute agitation in patients with schizophrenia, schizoaffective, or schizophreniform disorder
- to explore the correlation between post-injection plasma concentrations of aripiprazole/active metabolite and response on the primary efficacy endpoint (change from baseline to 2 hours postdose on the PEC score), and to perform population pharmacokinetic analysis for aripiprazole IM
- to provide data to be used in the selection of 1 of the 3 doses to be taken forward for evaluation in a confirmatory trial in this population

Efficacy Endpoints

The primary efficacy measure was the mean change from baseline to 2 hours post first IM injection in PEC Score. Efficacy rating scales completed during this study included the PEC, ACES, CABS, CGI Severity of Illness and Improvement Scales, PANSS, and the PANSS-derived Brief Psychiatric Rating Scale (BPRS).

Sample size

The planned sample size of 306 evaluable patients (51 per treatment group) was estimated to yield 90% power to differentiate between placebo and at least 1 of the 3 higher-dose aripiprazole treatment groups (5 mg, 10 mg, or 15 mg), when the true difference in the mean changes from baseline in PEC scores was 4.0. This assumed a standard deviation of 5.4 and a 2-sided test at the 0.0167 level of significance (adjusted for 3 comparisons versus placebo to ensure an overall significance level ≤ 0.05).

RESULTS

Three hundred seventy-eight patients were enrolled in the study and 357 patients were randomised to double-blind treatment: 62 to the placebo group, 60 to the haloperidol 7.5-mg group, 57 to the aripiprazole 1-mg group, 63 to the aripiprazole 5-mg group, 57 to the aripiprazole 10-mg group, and 58 to the aripiprazole 15-mg group. Of the 357 patients randomised to treatment, 350 were included in the safety and efficacy samples. Three hundred thirty-eight (95%) of the 357 randomised patients completed the study.

Results showed statistically significant mean changes from baseline to 2 hours post first IM injection versus placebo for the IM haloperidol 7.5-mg group ($p = 0.001$), and for the IM aripiprazole 5-mg ($p = 0.008$), 10-mg ($p < 0.001$), and 15-mg ($p = 0.007$) groups. Statistical separation from placebo was demonstrated as early as 45 minutes ($p = 0.007$) for the 10-mg aripiprazole group, and there was a trend at 30 minutes ($p = 0.051$).

The 1-mg aripiprazole dose did not achieve statistical significance on the PEC ($p = 0.191$), ACES ($p = 0.980$), or CABS ($p = 0.054$) Scores, although it did show efficacy on the CGI Improvement Score ($p = 0.011$).

A statistically significant greater number of patients in the 7.5-mg haloperidol group and 10-mg aripiprazole group than the placebo group were PEC responders at 120 minutes. Furthermore, the mean change from baseline to 2 hours post first IM injection in the BPRS Total Score showed a statistically significant treatment difference between placebo and the 7.5-mg haloperidol group, and 5-mg, 10-mg, and 15-mg aripiprazole groups, but no statistically significant differences were demonstrated on the BPRS Positive Score for these treatment groups.

Statistically significant mean changes from baseline to 2 hours post first IM injection in PEC Score were demonstrated in the schizophrenia subpopulation for the haloperidol 7.5-mg group and for the aripiprazole 5-mg, 10-mg, and 15-mg groups. Similar results were observed in the schizophrenia subpopulation for the mean CGI Improvement Score at the 2-hour timepoint for these same treatment groups.

For nonsedated patients, the mean change from baseline in PEC Total Score (based on the ACES Score and based on AEs related to sedation) showed statistically significant differences versus placebo at 2 hours for the 7.5-mg haloperidol group, and for the 5-mg, 10-mg, and 15-mg aripiprazole groups.

The mean change from predose (prior to second injection) to post second IM injection in the PEC Total Score for patients who were nonresponders was statistically significant different versus placebo for the 7.5-mg haloperidol group, and the 10-mg and 15-mg aripiprazole groups.

The mean CGI Improvement Score relative to a second injection for nonresponders was statistically significantly different versus placebo at 60 minutes and 2 hours post second IM injection for the 7.5-mg haloperidol group and for the 5-mg and 15-mg aripiprazole groups. The 1-mg aripiprazole group was statistically significantly different at 2 hours ($p = 0.037$). The 10-mg aripiprazole group showed a trend ($p = 0.057$) at 2 hours post second IM injection.

Study CN138012

Randomised, double-blind comparison of the efficacy and safety of IM aripiprazole, haloperidol, or placebo in the treatment of acutely agitated patients with a diagnosis of schizophrenia or schizoaffective disorder.

METHODS

Study design

It is a randomised, double-blind, IM study comparing 1 fixed dose of aripiprazole (10 mg) and 1 dose of haloperidol (6.5 mg) with placebo over 24 hours followed by 4 days of oral-tablet aripiprazole or oral-capsule haloperidol. It was conducted in patients with schizophrenia, schizoaffective, or schizophreniform disorder in acute agitation (as defined by DSM-IV) that have PEC: at least 2 components ≥ 4 and sum of 5 components ≥ 15 but ≤ 32 .

Primary and Secondary Objectives

The primary objective was to compare the efficacy of IM aripiprazole versus placebo in the treatment of acute agitation in patients with a diagnosis of schizophrenia or schizoaffective disorder as assessed by the mean change from baseline to 2 hours post IM injection using the PEC scale; and to determine if efficacy of IM aripiprazole is non-inferior to IM haloperidol in the treatment of acute agitation in patients with a diagnosis of schizophrenia or schizoaffective disorder as assessed by the mean change from baseline to 2 hours post IM injection using the PEC scale.

Secondary objectives were:

- to compare the efficacy of IM aripiprazole versus placebo in the treatment of acute agitation in patients with a diagnosis of schizophrenia or schizoaffective disorder as assessed by the Agitation-Calmness Evaluation Scale (ACES), Clinical Global Impressions-Severity of Illness (CGI-S), Clinical Global Impressions-Improvement (CGI-I), Corrigan Agitated Behavior Scale (CABS).
- to compare the effects of IM haloperidol (a known active therapy, and standard of care in the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder) versus placebo.
- to determine the safety and tolerability of IM aripiprazole in the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder. This was assessed by the mean change from baseline to each specified observation time in the Simpson-Angus Scale (SAS) and the Barnes Akathisia Rating Scale. Safety and tolerance was evaluated by reports of adverse events

- (AEs) and clinically significant changes in electrocardiograms (ECGs), vital signs, and laboratory tests.
- to measure the efficacy and safety of transition from IM aripiprazole to oral aripiprazole in the treatment of acute agitation in patients with schizophrenia.

Efficacy Endpoints

The primary efficacy measure was the mean change from baseline to 2 hours post first IM injection in PEC Score. Efficacy rating scales completed during this study included the PEC, ACES, CABS, CGI Severity of Illness and Improvement Scales, PANSS, and the PANSS-derived Brief Psychiatric Rating Scale (BPRS).

Sample size

It was expected that 420 patients would need to be randomised to obtain 400 evaluable patients (160 in each of the IM aripiprazole and IM haloperidol treatment groups, and 80 in the IM placebo group) ie, having a baseline PEC assessment and at least 1 PEC assessment post first IM injection. This sample size would yield 90% power to show non-inferiority of IM aripiprazole 10 mg to IM haloperidol 6.5 mg, when the non-inferiority bound for the difference in the mean changes from baseline in PEC scores was 2.5. This assumed an expected difference in mean changes from baseline of 0.5 (in favour of haloperidol), a standard deviation of 5.5 and a 2-sided test at the 0.05 level of significance.

The planned sample size of 400 evaluable patients would also provide 99% power to differentiate between placebo and the aripiprazole treatment group when the true difference in the mean changes from baseline in PEC score was 3.4, assuming a standard deviation of 5.5 and a 2-sided test at the 0.05 level of significance.

RESULTS

A total of 469 patients were enrolled in the study. Of these, 448 patients were randomised to double-blind treatment: 88 to the placebo group, 185 to the 6.5-mg haloperidol group, and 175 to 10-mg aripiprazole group. A total of 435 (97%) of the 448 patients completed the IM Phase of the double-blind study. A total of 380 (85%) of the 448 patients transitioned from the double-blind IM Phase to the double-blind Oral Phase: 76 from the placebo group, 151 from the 6.5-mg haloperidol group, and 153 from the 10-mg aripiprazole group.

The 10-mg aripiprazole dose group was significantly superior to placebo in the change from baseline to 2-hours post first IM injection in the PEC ($p < 0.001$).

For the schizophrenia subpopulation, the mean change from baseline to 2 hours post first IM injection in PEC Total Score showed statistically significant differences versus placebo for the 10-mg aripiprazole and 6.5-mg haloperidol treatment groups.

For non sedated patients, the mean change from baseline in PEC Total Score (based on the ACES Score and based on AES related to sedation) showed statistically significant differences versus placebo at 2 hours for the 10-mg aripiprazole and 6.5-mg haloperidol treatment groups.

A statistically significant difference at 2 hours post first IM injection for the CGI-I was demonstrated in favour of the 10-mg aripiprazole group ($p < 0.001$) versus the placebo group.

There were statistically significant differences at 2 hours post first IM injection for the 10-mg aripiprazole group in all other secondary outcome measures including CGI-S ($p = 0.004$), ACES ($p = 0.012$), CABS ($p < 0.001$), PEC Responder Analysis ($p = 0.004$), and PEC Individual Item Scores (poor impulse control, tension, hostility, excitement, lack of cooperation). Haloperidol (6.5-mg) was statistically significantly different versus placebo for all secondary outcome measures.

The mean change from predose (prior to second injection) to post second IM injection in the PEC Score for all patients showed statistically significant differences versus placebo at 60 minutes and 2

hours for the 10-mg aripiprazole and 6.5-mg haloperidol groups. For patients who were nonresponders after the first IM injection, statistically significant differences versus placebo were observed at 60 minutes and 2 hours for the 10-mg aripiprazole and 6.5-mg haloperidol groups.

Following the third injection, the 10-mg aripiprazole dose was comparable to haloperidol for all patients in the mean change from baseline to 2 hours in PEC Score.

The mean CGI-I Score for all patients showed statistically significant differences versus placebo at 2 hours post second IM injection for the 10-mg aripiprazole and 6.5-mg haloperidol treatment groups.

For patients who were nonresponders after the first injection, statistically significant differences versus placebo were observed at 2 hours post second IM injection for both the aripiprazole and haloperidol treatment groups.

In the 4-day oral-Tablet Phase, the 15-mg aripiprazole and 10-mg haloperidol treatment groups showed additional small decreases in the mean change from the last evaluation in the IM Phase in PEC Score indicating that switching to oral medication was effective in maintaining the response achieved during the IM phase. Additionally, on the other outcome measures of CGI-I, CGI-S, ACES, and CABS, both the 15-mg aripiprazole and 10-mg haloperidol treatment groups maintained the response achieved during the IM phase.

- Supportive study

Study CN138013

Randomised, double-blind comparison of the efficacy and safety of IM aripiprazole, lorazepam, or placebo in the treatment of acutely agitated patients diagnosed with bipolar I Disorder, manic or mixed.

METHODS

Study design

It is a randomised, double-blind, IM study comparing 2 fixed doses of aripiprazole (10 and 15 mg) and 1 dose of lorazepam (2mg) with placebo over 24 hours in patients with bipolar I disorder, manic or mixed and acute agitation with a PEC: at least 2 components ≥ 4 and sum of 5 components ≥ 15 but ≤ 32 .

Primary and Secondary Objectives

The primary objective was to compare the efficacy of IM aripiprazole versus placebo in the treatment of acutely agitated patients with a diagnosis of Bipolar I Disorder, manic or mixed. This was assessed by the mean change from baseline to 2 hours post first IM injection using the PEC scale.

Secondary objectives were:

- to compare the efficacy of IM aripiprazole versus placebo in the treatment of acute agitation in patients with a diagnosis of Bipolar I Disorder, manic or mixed, as assessed by the Clinical Global Impressions Improvement Scale (CGI-I), Clinical Global Impressions Severity of Illness Scale (CGI-S), Agitation-Calmness Evaluation Scale (ACES), and Corrigan Agitated Behavior Scale (CABS).
- to compare the effects in this study of IM lorazepam, a known active therapy and standard of care in the treatment of acutely agitated patients with Bipolar I Disorder, manic or mixed, versus placebo.
- to determine the safety and tolerability of IM aripiprazole in the treatment of acutely agitated patients with Bipolar I Disorder, manic or mixed. This was assessed by the mean change from baseline to each specified observation time in the Simpson-Angus Scale (SAS) and Barnes Akathisia Rating Scale (Barnes). Safety and tolerance was evaluated by reports of adverse events (AEs) and clinically significant changes in electrocardiograms (ECGs), vital signs, and laboratory tests.

Efficacy Endpoints

The primary efficacy measure was mean change from baseline to 2 hours post first IM injection in PEC Score. Efficacy rating scales completed during this study included PEC, ACES, CGI-I, CGI-S, CABS, PANSS, and Y-MRS.

Sample size

The planned sample size of 260 evaluable patients (65 per treatment group) would yield 90% power to differentiate between placebo and at least 1 of the 2 aripiprazole treatment groups (10 mg or 15 mg), when the true difference in the mean changes from baseline in PEC score was 3.4. This assumed a standard deviation of 5.4 and a 2-sided test at the 0.025 level of significance (adjusted for 2 comparisons versus placebo to ensure an overall probability of type 1 error ≤ 0.05).

RESULTS

Three hundred twenty-nine patients were enrolled in the study and 301 patients were randomised to double-blind treatment: 75 to the placebo group, 70 to the lorazepam group, 78 to the 10-mg aripiprazole group, and 78 to the 15-mg aripiprazole group. Of the 301 patients randomised to treatment, 291 were included in the safety and efficacy Samples. Two hundred eighty-two (94%) of the 301 randomised patients completed the study.

Aripiprazole 10-mg and 15-mg (both $p < 0.001$) were statistically superior to placebo in the primary efficacy measure. Statistical separation from placebo (ie, $p \leq 0.05$) was demonstrated as early as 60 minutes ($p = 0.028$) for the 15-mg aripiprazole group and as early as 90 minutes ($p = 0.008$) for the 10-mg aripiprazole group.

Lorazepam was statistically superior to placebo in the primary efficacy measure ($p < 0.001$) and demonstrated statistical separation from placebo as early as 45 minutes ($p = 0.040$).

For the subgroup of nonsedated patients (defined on the basis of the ACES Score), statistically significant differences versus placebo in the primary efficacy measure were observed in favour of the 10-mg and 15-mg aripiprazole groups, as well as for the lorazepam group.

Aripiprazole 10-mg and 15-mg were statistically superior to placebo on all secondary efficacy measures at 2 hours post first IM injection (LOCF data set).

The mean CGI-I Score, and the mean change from baseline in the CGI-S, ACES, and CABS Score showed statistically significant comparisons versus placebo in favour of the 10-mg and 15-mg aripiprazole groups. Furthermore, statistically significantly higher rates of PEC response were observed for 10-mg and 15-mg aripiprazole than for placebo. Lorazepam was statistically superior to placebo on these secondary outcome measures.

Furthermore, all active treatment groups were statistically superior to placebo on the mean change from baseline in all PEC Individual Item Scores at 2 hours (LOCF).

The repeated measures analysis on the PEC Score through 2 hours post first IM injection showed improvement over time for all treatment groups. The improvement was statistically significantly greater for the 10-mg and 15-mg aripiprazole and lorazepam groups than placebo.

Statistically significantly higher rates in terms of CGI response were observed for all active treatment groups at all timepoints. Patients in the 10-mg and 15-mg aripiprazole groups were more likely to respond and/or to respond sooner in terms of PEC response than patients in the placebo group during the 2-hour period post first IM injection.

Furthermore, patients in the placebo group were more likely to require and/or require sooner a second or third injection than patients in the 10-mg and 15-mg aripiprazole groups, as well as in the lorazepam group.

Aripiprazole 10-mg and 15-mg, as well as lorazepam, were statistically superior to placebo for the mean change in the PEC Score from predose (ie, immediately prior to second IM injection) to 2 hours

post second IM injection. In addition, aripiprazole 10-mg and lorazepam also showed superiority over placebo at the 60 minute time point.

For the subgroup of patients who were non responders to the first IM injection (defined as a patient who received a second injection within 4 hours of the first and who was not a PEC responder in the evaluation just prior to the second injection), statistically significant differences versus placebo were observed in the mean change from predose in favour of the 10-mg and 15-mg aripiprazole and lorazepam groups. In addition, aripiprazole 10-mg and lorazepam also showed superiority over placebo at the 60 minute time point. Following the third IM injection, 10-mg aripiprazole appeared to be similar in effect as lorazepam for the mean change in the PEC Score from baseline (ie, immediately prior to first IM injection).

The mean CGI-I Score for all patients at 1 and 2 hours post second IM injection showed statistically significant differences versus placebo in favour of 10-mg and 15-mg aripiprazole, as well as lorazepam.

For the subgroup of patients who were nonresponders after the first injection, the mean CGI-I Score at 1 and 2 hours post second IM injection showed statistically significant differences versus placebo in favour of 10-mg aripiprazole and lorazepam. The treatment difference versus placebo showed a trend ($p = 0.061$) in favour of 15-mg aripiprazole.

- Discussion on clinical efficacy

The clinical development plan followed closely what has been standard in this field of antipsychotics used for the treatment of agitation in patients with schizophrenia or bipolar I disorder, particularly in term of design, choice of endpoints, number of pivotal trials and populations enrolled.

The results are consistent across endpoints and across trials (Table 3.2A-1).

Table 3.2A-1: Efficacy Results at 2 Hours Post First IM Injection: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), LOCF Data Set, Efficacy Sample

Study/ Treatment	N	PEC Score Mean Change	CGI-I Score Mean	CGI-S Score Mean Change	ACES Score Mean Change	CRES Score Mean Change
Schizophrenia, Schizoaffective						
CN138012 Placebo	88	-4.78	3.10	-0.71	0.83	-4.51
Aripiprazole 10mg	173	-7.27**	2.42**	-1.16**	1.41*	-8.03**
Haloperidol 6.5mg	184	-7.75**	2.37**	-1.17**	1.64**	-8.28**
Schizophrenia, Schizoaffective, Schizophreniform						
CN138050 Placebo	61	-3.28	3.46	-0.42	0.66	-2.95
Aripiprazole 1mg	56	-4.47	3.07*	-0.63	0.65	-5.16
Aripiprazole 5mg	62	-5.65**	2.82**	-0.82*	1.01	-5.97**
Aripiprazole 10mg	56	-6.69**	2.64**	-1.08**	1.50**	-7.08**
Aripiprazole 15mg	58	-5.72**	2.66**	-0.99**	0.99	-7.04**
Haloperidol 7.5mg	57	-6.38**	2.72**	-0.91*	1.50**	-8.13**
Bipolar I Disorder						
CN138013 Placebo	73	-5.76	3.05	-0.94	1.00	-6.37
Aripiprazole 10mg	75	-8.74**	2.17**	-1.48**	1.87**	-9.60**
Aripiprazole 15mg	75	-8.67**	2.33**	-1.34*	2.32**	-9.08**
Lorazepam 2mg	68	-9.57**	2.10**	-1.61**	2.34**	-10.35**

** $p \leq 0.01$, * $p \leq 0.05$

ANOVA model, controlling for treatment, country (CN138-012, CN138-050) or pooled study center (CN138-013), and baseline value, is used for mean change from baseline comparisons.

OM row means score test controlling for treatment, country (CN138-012, CN138-050) or pooled study center (CN138-013), is used for CGI-I score means.

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In particular, the primary efficacy endpoint showed statistical significant difference between 10 mg aripiprazole dose versus placebo ($p < 0.001$) (Table 3.2B-1).

Table 3.2B-1: Mean Change from Baseline to 2 Hours Post First IM Injection in PEC Score: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), LOCF Data Set, Efficacy Sample

Study/ Treatment		N	Baseline	Mean Change from Baseline	Treatment Difference (95% CI) Versus Placebo	P-Value
Schizophrenia, Schizoaffective						
CN138012	Placebo	88	19.32	-4.78		--
	Aripiprazole 10mg	173	19.25	-7.27	-2.48 (-3.77, -1.19)	<0.001
	Haloperidol 6.5mg	184	19.32	-7.75	-2.96 (-4.24, -1.69)	<0.001
Schizophrenia, Schizoaffective, Schizophreniform						
CN138050	Placebo	61	19.21	-3.28		--
	Aripiprazole 1mg	56	19.16	-4.47	-1.19 (-2.96, 0.59)	0.191
	Aripiprazole 5mg	62	19.46	-5.65	-2.37 (-4.10, -0.63)	0.008
	Aripiprazole 10mg	56	19.44	-6.69	-3.40 (-5.18, -1.62)	<0.001
	Aripiprazole 15mg	58	19.34	-5.72	-2.44 (-4.21, -0.68)	0.007
	Haloperidol 7.5mg	57	18.89	-6.38	-3.09 (-4.87, -1.32)	0.001
Bipolar I Disorder						
CN138013	Placebo	73	18.04	-5.76		--
	Aripiprazole 10mg	75	18.84	-8.74	-2.99 (-4.53, -1.44)	<0.001
	Aripiprazole 15mg	75	18.25	-8.67	-2.91 (-4.44, -1.38)	<0.001
	Lorazepam 2mg	68	18.47	-9.57	-3.81 (-5.38, -2.24)	<0.001

ANCOVA model, controlling for treatment, country (CN138-012, CN138-050) or pooled study center (CN138-013), and baseline value, is used for mean change from baseline comparisons.

Subgroup analysis

- Subpopulation

Despite the fact the 3 placebo-controlled studies were not designed to show statistically significant treatment differences in these subpopulations, the following comparisons were performed: age ($\leq$ upper quartile, $>$ upper quartile), gender (men, women), race (white, black, “other”), underlying diagnosis (schizophrenic, schizoaffective, or schizophreniform disorder for CN138012 and CN138050; manic or mixed status, bipolar I disorder for CN138013), and baseline PEC Score ($\leq$ median [≤ 18], $>$ median [> 18]). For the pooled analysis of the 2 schizophrenia studies (CN138012 and CN138050), the upper quartile for age was patients $>$ age 49; for the 1 bipolar I disorder study (CN138013), the upper quartile was patients $>$ age 48.

In studies CN138012 and CN138050, the efficacy of aripiprazole was demonstrated across all subsets, as evidenced by statistically significant treatment comparisons versus placebo, except for patients with age $>$ upper quartile, race of “other,” and patients with an underlying diagnosis of schizophreniform disorder. However, there were greater mean decreases from baseline in the aripiprazole group than the placebo group in these subpopulations.

In study CN138013, aripiprazole was found to be statistically significantly different than placebo on all subset analyses except for patients with race of black or “other,” for patients with an underlying diagnosis of mixed, and for patients with a baseline PEC Score $>$ median. However, the mean decreases from baseline in these subpopulations were greater in the aripiprazole group than the placebo group.

- Non sedated patients based on ACES score

Efficacy was demonstrated to be independent of oversedation, as measured by the ACES Score. The mean change from baseline to 2 hours post first IM injection in PEC Score was analyzed by excluding patients with scores of 8 or 9 on the ACES scale during the first 2 hours. The ACES was scored as follows: 1 = marked agitation, 2 = moderate agitation, 3 = mild agitation, 4 = normal, 5 = mild calmness, 6 = moderate calmness, 7 = marked calmness, 8 (deep sleep) and 9 (unarousable).

Results of this analysis showed that the treatment difference for the 10-mg aripiprazole group versus placebo was statistically significant in the 2 schizophrenia studies (CN138012: $p = 0.001$; CN138050: $p < 0.001$) as well as in the bipolar I disorder study (CN138013: $p < 0.001$). In addition, all other treatment groups, except for the 1-mg aripiprazole group in Study CN138050, were significant versus placebo (Table 3.3B-1).

Table 3.3B-1: Mean Change from Baseline to 2 Hours Post First IM Injection in PEC Score Excluding Patients with Scores of 8 (Deep Sleep) or 9 (Unarousable) on ACES During the First 2 Hours; IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), LOCF Data Set, Efficacy Sample

Study/ Treatment		N	Baseline	Mean Change from Baseline	Treatment Difference (95% CI) Versus Placebo	P-Value
Schizophrenia, Schizoaffective	CN138012					
	Placebo	83	18.75	-4.82	--	--
	Aripiprazole 10mg	152	18.75	-7.20	-2.31 (-3.62, -1.00)	0.001
	Haloperidol 5.5mg	157	18.75	-7.53	-2.64 (-3.95, -1.33)	<0.001
Schizophrenia, Schizoaffective, Schizophreniform	CN138050					
	Placebo	52	12.05	-4.33	--	--
	Aripiprazole 1mg	55	12.15	-5.65	-1.32 (-3.17, 0.53)	0.161
	Aripiprazole 5mg	62	12.45	-7.06	-2.73 (-4.53, -0.93)	0.003
	Aripiprazole 10mg	54	12.37	-7.73	-3.40 (-5.26, -1.54)	<0.001
	Aripiprazole 15mg	57	12.37	-7.23	-2.90 (-4.74, -1.07)	0.002
	Haloperidol 7.5mg	52	18.75	-7.22	-2.89 (-4.77, -1.01)	0.003
	Bipolar I Disorder					
CN138013	Placebo	68	17.91	-5.10	--	--
	Aripiprazole 10mg	70	18.75	-8.44	-3.34 (-4.95, -1.71)	<0.001
	Aripiprazole 15mg	62	18.19	-7.72	-2.62 (-4.29, -0.95)	0.002
	Lorazepam 2mg	55	18.31	-8.70	-3.60 (-5.33, -1.88)	<0.001

ANCOVA model, controlling for treatment and baseline value, is used for mean change from baseline comparisons.

Clinical Safety

- Patient exposure

The safety sample comprised 1214 patients: 795 patients with a diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder (CN138012, CN138050), 291 patients with a diagnosis of bipolar I disorder, manic or mixed (CN138013), and 128 patients with a diagnosis of dementia (additional safety study CN138131 conducted in elderly patients and provided by the applicant). A total of 660 patients received aripiprazole as initial treatment, 240 patients received haloperidol, 69 patients received lorazepam, and 245 patients received placebo. In addition, 62 placebo-treated patients received 10-mg aripiprazole as a third injection and 27 placebo-treated patients received 15-mg aripiprazole as a third injection. Therefore, from the 4 IM placebo-controlled Phase 2/3 studies a total of 749 patients received IM aripiprazole.

- Adverse events

Aside from those events that are associated with the method of administration (e.g. injection site pain), the profile of AEs reported with IM aripiprazole was generally similar to those observed with oral-tablet aripiprazole.

Incidence of Treatment-Emergent Adverse Events That Occurred in at Least 1% of Patients in the Aripiprazole Group: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), Safety Sample

			Number (%) Patients			
System	Organ	Class/	Placebo	Haloperidol	Lorazepam	Aripiprazole
	Preferred Term		N = 220	N = 240	N = 69	N = 501
Cardiac Disorders						
	Tachycardia		1 (0.45)	2 (0.83)	1 (1.45)	8 (1.60)
Gastrointestinal Disorders						
	Nausea		7 (3.18)	3 (1.25)	0	46 (9.18)
	Vomiting		2 (0.91)	2 (0.83)	0	17 (3.39)
	Dyspepsia		1 (0.45)	0	0	7 (1.40)
	Dry Mouth		1 (0.45)	5 (2.08)	1 (1.45)	6 (1.20)
General Disorders and Administration Site Conditions						
	Fatigue		3 (1.36)	6 (2.50)	2 (2.90)	11 (2.20)
	Injection Site Pain		4 (1.82)	2 (0.83)	0	9 (1.80)
	Injection Site Burning		2 (0.91)	0	1 (1.45)	7 (1.40)
Investigations						
	Blood	Pressure	1 (0.45)	3 (1.25)	1 (1.45)	6 (1.20)

Incidence of Treatment-Emergent Adverse Events That Occurred in at Least 1% of Patients in the Aripiprazole Group: IM Placebo-Controlled Studies (CN138012, CN138050, CN138013), Safety Sample

	Number (%) Patients			
Increased				
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal	1 (0.45)	4 (1.67)	0	6 (1.20)
Stiffness				
Nervous System Disorder				
Headache	16 (7.27)	17 (7.08)	3 (4.35)	62 (12.38)
Dizziness	10 (4.55)	11 (4.58)	7 (10.14)	40 (7.98)
Somnolence	8 (3.64)	13 (5.42)	5 (7.25)	34 (6.79)
Sedation	5 (2.27)	7 (2.92)	8 (11.59)	14 (2.79)
Akathisia	0	12 (5.00)	0	10 (2.00)
Psychiatric Disorder				
Insomnia	14 (6.36)	23 (9.58)	1 (1.45)	28 (5.59)
Agitation	6 (2.73)	9 (3.75)	0	14 (2.79)

- Deaths and other serious adverse events

There were 2 reports of death in patients who received study medication in the IM Phase 2/3 clinical program. These were not considered related to study treatment.

There were no SAEs reported in Studies CN138016 and CN138017. One SAE was reported in the Study CN138132: a 40-year old black female, experienced Grade 3 neutropenia that began on Day 27 after aripiprazole 15-mg treatment and lasted for 91 days.

Thirty-two of the 1214 patients in the IM safety Sample (CN138012, CN138050, CN138013, CN138131) experienced SAEs. One SAE for a patient in the placebo group occurred after the third injection, which was 15-mg aripiprazole. Most events were related to patients' underlying psychiatric diseases, and only one report event of dystonia with 6.5 mg haloperidol was considered by the investigators to be related to study medication.

- Other safety findings

In the pooled schizophrenia studies (CN138012, CN138050), a higher incidence of increased fasting serum glucose in aripiprazole- and haloperidol-treated patients than placebo-treated patients following injection with study medication was reported.

When QT intervals were evaluated uncorrected and using other correction methods (QTcB, QTcN, and QTcF), there were no clinically meaningful differences across treatment groups.

Discontinuation due to adverse events

Eight of the 1214 patients discontinued from the studies because of an AE during the IM phase. Five aripiprazole-treated patients discontinued and only 1 of these patients (10-mg) discontinued due to possible drug related events (agitation and musculoskeletal stiffness). None of the 89 placebo-treated patients who received a third IM injection, which was either 10-mg or 15-mg aripiprazole, discontinued from the studies because of an AE.

- Discussion on clinical safety

The safety profile of aripiprazole using the IM formulation was similar to that of the oral-tablet formulation. Based on data collected to date the IM formulation appears favourable. There was only a small number of SAEs, and very few AEs led to discontinuation. There were no important clinical concerns regarding laboratory, vital sign, or ECG findings. Arrhythmias are an obvious concern with this type of product and population. The data about QTc and arrhythmias are reassuring but these AEs should be kept under continuous close monitoring in the future PSURs particularly because orthostatic

hypotension is a clear feature of the safety profile of aripiprazole. In this field, an analysis of the % of patients with systolic blood pressure drop > 20 mmHg including the subpopulation of the indication applied, i.e. schizophrenic patients was provided and showed a higher incidence rate for aripiprazole-treated patients compared to placebo treated patients. The inclusion into the SPC of orthostatic hypotension as a possibly medically relevant adverse event was consequently made. Furthermore, a warning relative to concomitant use of parenteral benzodiazepines associated with excessive sedation and cardiorespiratory depression was also included in the SPC.

1.3 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

Risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
IDENTIFIED RISKS		
1. No important risks identified that require further evaluation 2. Identified common ADRs: somnolence, dizziness, headache, akathisia, tachycardia, nausea, dry mouth, vomiting and fatigue	Routine pharmacovigilance including close monitoring for selected events of interest PSUR submission with oral formulation at 6 monthly intervals unless otherwise decided by CHMP. No specific trials planned	Common ADRs with IM formulation listed in section 4.8

POTENTIAL RISKS		
1. Orthostatic hypotension	Routine pharmacovigilance including close monitoring for selected events of interest. PSUR submission with oral formulation at 6 monthly intervals unless otherwise decided by CHMP. No specific trials planned.	Section 4.4 of SPC <i>Patients receiving aripiprazole solution for injection should be observed for orthostatic hypotension. Blood pressure, pulse, respiratory rate and level of consciousness should be monitored regularly.</i> <i>If parenteral benzodiazepine is deemed necessary in addition to aripiprazole solution for injection, patients should be monitored for excessive sedation and for orthostatic hypotension (see section 4.5)</i> Section 4.5 of SPC <i>Due to its α_1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.</i> Section 4.8 of SPC: event listed as an uncommon ADR*
2. Cardio-respiratory depression (including respiratory distress, failure, arrest)	Routine pharmacovigilance including close monitoring for selected events of interest. PSUR submission with oral formulation at 6 monthly intervals unless otherwise decided by CHMP. No specific trials planned.	Section 4.4 of SPC: <i>Simultaneous administration of injectable antipsychotics and parenteral benzodiazepine may be associated with excessive sedation and cardiorespiratory depression.</i> <i>Patients receiving aripiprazole solution for injection should be observed for orthostatic hypotension. Blood pressure, pulse, respiratory rate and level of consciousness should be monitored regularly.</i> <i>If parenteral benzodiazepine is deemed necessary in addition to aripiprazole solution for injection, patients should be monitored for excessive sedation and for orthostatic hypotension (see section 4.5).</i>
3. Cardiac disorders, including cardiac arrhythmias	See above	No specific information included in the SPC, given the lack of evidence to currently support such events
4. Serious injection site reactions	See above	No specific information included in the SPC, given the lack of evidence to currently support such events
5. Serious hypersensitivity reactions	See above	Section 4.3 of SPC : Contraindications: <i>Hypersensitivity to the active substance or to any of the excipients.</i>

IMPORTANT MISSING INFORMATION		
There was no important missing information identified. Data are lacking in specific populations, not distinctively studied with the IM formulation (e.g. children and adolescents, elderly - except elderly patients with dementia- , pregnant or lactating women, patients with hepatic or renal disorders, patients with disease severity different from those included in clinical trials, sub-populations carrying known and relevant genetic polymorphism, and patients of different racial and/or ethnic origins)	Routine pharmacovigilance including close monitoring for selected events of interest. PSUR submission with oral formulation at 6 monthly intervals unless otherwise decided by CHMP. Submission of study 31-03-239 on adolescents with schizophrenia.	The lack of data for most of these specific patient populations is present in sections 4.1, 4.2 or 4.4. of the SPC, as appropriate

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

1.4 Overall conclusions and benefit/risk assessment

Based on the CHMP review of safety and efficacy, the CHMP considers that the benefit-risk for Abilify 7.5 mg/ml solution for injection in the rapid control of agitation and disturbed behaviours in patients with schizophrenia, when oral therapy is not appropriate, is favourable and recommended the variation to the marketing authorisation.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.

In addition, the MAH committed to submit PSUR at 6-monthly intervals unless otherwise decided by CHMP.