**ASSESSMENT REPORT**
**FOR**
**ABILIFY**

International Nonproprietary Name:
**aripiprazole**

**Procedure No. EMEA/H/C/471/II/0039**

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

## 1.1 Introduction

Bipolar I Disorder is a lifelong episodic illness characterized by manic or depressive episodes followed by symptom-free periods. Psychotic symptoms (delusions, hallucinations, thought disorders) often accompany the manic phase of bipolar disorder. The lifetime prevalence of bipolar disorder is estimated to be 0.4% to 1.6%. The mean age at onset for a first manic episode is the early 20's. Effective treatment of acute mood episodes in Bipolar I Disorder is important. However, preventing or delaying subsequent mood episodes should be a primary objective in effectively treating this illness.

The updated Expert Consensus Guidelines[1] recommend lithium or valproate as first-line therapy for the treatment of manic symptoms associated with Bipolar I Disorder. When monotherapy fails, the guidelines recommend combination therapies.

In addition, antipsychotic drugs are effective as monotherapy for the treatment of manic episodes. Typical antipsychotic drugs such as haloperidol are associated with adverse effects such as extrapyramidal symptoms (EPS), tardive dyskinesia, and neuroleptic malignant syndrome. Atypical antipsychotic drugs such as olanzapine, risperidone, and ziprasidone generally have less EPS but are associated with other safety concerns, such as QT interval prolongation, hyperprolactinemia and weight gain.

In this type II variation, the Marketing Authorisation Holder (MAH) applied for an extension of indication of Abilify:

*'for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in patients whose manic episodes responded to aripiprazole treatment'.*

Consequential changes were made to relevant sections of the Summary of Product Characteristics (SPC). The Package Leaflet (PL) was updated accordingly.

This application does not concern Abilify 7.5 mg/ml solution for injection.

## 1.2 Non clinical aspects

### Environmental risk assessment (ERA)

An ERA according to CHMP guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00, June 2006) was submitted. The physiochemical properties of aripiprazole are: water solubility at 25ºC of 0.00013w/v%; negligible vapour pressure; octanol water distribution coefficient depending of the pH.

In Phase I, based on the highest recommended dose of 30 mg of aripiprazole, a worst-case Predicted Environmental Concentration (PEC) in surface water of 0.150 µg/L was calculated using default values. The calculated PEC in surface water was higher than the action limit of 0.01 µg/L and a Phase II environmental fate and effects analysis was performed based on the available ecotoxicity data studies. The outstanding aquatic ecotoxicity studies are in progress or scheduled.

Essential tier A aquatic ecotoxicity studies are undergoing (Aerobic & anaerobic transformation in aquatic sediment system (OECD 308), Adsorption/desorption to soil and sludge (OECD 106), Chronic toxicity to water flea (*Daphnia magna)* (OECD 211) and Chronic toxicity to Fathead Minnows (*Pimephales promelas)* embryos (OECD 210).

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[1] Keck PE, Perlis RH, Otto MW, et al. Expert Consensus Guideline Series: Treatment of bipolar disorder 2004. Postgrad Med Spec Rep 2004;Dec:4-50.

Having considered that the submitted ERA included a phase II tier A analysis not yet completed, the MAH committed to provide the final results of the studies by 1Q2008 (OECD 106, OECD 211) and 2Q2008 (OECD 308, OECD 210, effect on sediment organism) and further information related to the calculation of the penetration factor (Fpen) refinement as part of follow up measures (FUM).

## 1.3 Clinical aspects

### 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.

### Clinical Efficacy

With reference to the CHMP Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder (CPMP/EWP/567/98, April 2001), the MAH proposed a clinical program that incorporated all elements of the outlined EU requirements for treatment and maintenance of patients with Bipolar I disorder, including the demonstration of efficacy at Week 3 and the maintenance of this effect over an additional 9-week period, as well as the efficacy and safety of aripiprazole as add on therapy to mood stabilizers.

Additionally, the maintenance treatment study **CN138010** provided in this application is supporting the claim '*for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in patients whose manic episodes responded to aripiprazole treatment.'*

### 1. Three-Week Placebo-Controlled Comparisons

METHODS

### Study design

- **CN138007**: A **3-week**, randomized, double-blind, placebo-controlled, **fixed-dose** (3 parallel treatment groups: 15 mg/day aripiprazole, 30 mg/day aripiprazole, and placebo) study in hospitalized patients with Bipolar I Disorder, manic- or mixed-type.

  At the end of Week 2, patients with Clinical Global Impressions-Bipolar (CGI-BP) Change from Preceding Phase (mania) score of 4 to 7 (no change to very much worse) were dropped from the blinded placebo-controlled treatment phase and offered the option to receive open-label aripiprazole (30 mg with dose decreased to 15 mg if needed based on tolerability) for **Week 3**. **These patients and those who completed 3 weeks of double-blind therapy were eligible to enter 1 of 2 long-term studies** (**CN138010** or **CN138037**).
- **CN138009**: A **3-week**, randomized, double-blind, placebo-controlled **flexible-dose** study in hospitalized patients with Bipolar I Disorder, manic- or mixed-type. Patients randomized to aripiprazole were started at a dose of 30 mg/day, with the option to decrease to 15 mg/day based on tolerability, and to subsequently increase to 30 mg/day based on clinical response at any time during the study.

  At the end of Week 2, patients with CGI-BP Change from Preceding Phase (mania) score of 4 to 7 (no change to very much worse) were dropped from the blinded placebo-controlled treatment phase and offered the option to receive open-label aripiprazole (30 mg with dose decreased to 15mg if needed based on tolerability) for Week 3. **These patients and those who completed 3 weeks of double-blind therapy were eligible to enter 1 of 2 long-term studies** (**CN138010** or **CN138037**).
- **CN138074**: Identical design as CN138009 except this study **did not include the open-label treatment option for Week 3**.

This study did not require patients with CGI-BP Change from Preceding Phase (mania) Score 4 to 7 to drop out at the end of Week 2. Patients could continue the study as outpatients during Week 3 if the following criteria were met at the end of Week 2: CGI BP Severity (mania) Score ≤ 3 and CGI-BP Change from Preceding Phase (mania) Score ≤ 2. **All patients who completed 3 weeks of double-blind therapy were eligible to enter 1 of 2 long-term studies** (**CN138010** or **CN138037**).

- **CN138135 and CN138162**: A **12 week**, randomized, double blind, placebo controlled and active controlled flexible dose study**(3 parallel treatment groups: aripiprazole (starting dose of 15 mg/day with an option to increase to 30 mg/day), placebo, or active-control treatment in a 1:1:1 ratio, for 3 weeks)** in hospitalized patients with Bipolar I disorder, manic or mixed type.

  **CN138135** used lithium (starting dose of 900 mg/day with option to increase to 1200 mg/day and 1500 mg/day) and **CN138162** used haloperidol (starting dose of 5 mg/day with an option to increase to 10 mg/day and 15 mg/day) as active controls for assay sensitivity.

  Patients were hospitalized at or before randomization, but could be discharged from the hospital and could continue the study as outpatients at the end of Week 2 if criteria specified in the protocol were met.

**Sample size**

These studies were powered at 90% to detect a difference of 5.5 between placebo and aripiprazole on the mean change from baseline to Week 3, Last Observation Carried Forward (LOCF), in the Young Mania Rating Scale (Y-MRS) Total Score. The assumed standard deviation was 13.4.

**Primary efficacy endpoint**

The primary efficacy measure was the mean change from baseline to Week 3 on the Y-MRS Total Score.

**Secondary and other efficacy endpoints**

The secondary efficacy measures were the mean change from baseline to Week 3 on CGI-BP Severity of Illness (mania) score and the response rate (defined as a decrease of ≥ 50% from baseline on the Y-MRS Total Score).

Other efficacy measures mainly included mean change from baseline in the Positive and Negative Syndrome Scale (PANSS) Hostility Subscale Score and mean CGI-BP Change from Preceding Phase (mania).

In studies CN138007 and CN138009, secondary efficacy measures were also the rate of discontinuation due to lack of efficacy or entry into the open-label aripiprazole phase at Week 2 with a CGI-BP Change from Preceding Phase (mania) score of 4 to 7.

RESULTS

**Patient distribution**

The Efficacy Sample comprised 1900 patients in the 3-week placebo-controlled comparisons (CN138007, CN138009, CN138074, CN138135, and CN138162). Of these 1900 patients, 856 were in the aripiprazole group and 719 were in the placebo group, the remaining 325 were in active control groups. (see Table 1)

**Table 1**

**Table 3.1.1.1: Number of Patients by Study and Treatment Group: 3-Week Placebo-Controlled Comparisons in Acute Bipolar Mania (CN138007, CN138009, CN138074, CN138135, CN138162), Randomized Sample**

| | | | Number of Patients | | | | | |
|---|---|---|---|---|---|---|---|---|
| Treatment Group | | | CN138007 | CN138009 | CN138074 | CN138135 (a) | CN138162 (a) | TOTAL |
| Aripiprazole | Flexible Dose | 30 to 15 mg | | 130 | 137 | | | 267 |
| | | 15 to 30 mg | | | | 155 | 167 | 322 |
| | Fixed Dose | 15 mg | 131 | | | | | 131 |
| | | 30 mg | 136 | | | | | 136 |
| Total Aripiprazole | | | 267 | 130 | 137 | 155 | 167 | 856 |
| Lithium | | | | | | 160 | | 160 |
| Haloperidol | | | | | | | 165 | 165 |
| Placebo | | | 134 | 132 | 135 | 165 | 153 | 719 |

(a) 12-week study with 3-week placebo-controlled phase. Primary efficacy endpoint was at Week 3.

## Baseline Psychiatric Characteristics

At baseline of the placebo-controlled comparisons, the mean age at the start of the current episode was 40.0 years and the number of patients experiencing a manic-type episode was twice (67%) the number of patients experiencing a mixed-type episode (33%).

Ten percent of the total randomized patients were rapid cyclers.
Mean baseline score on the Y-MRS Total Score was 28.4, mean CGI-BP severity of Illness (Mania) was 4.6, and mean PANSS Total Score was 62.6. These scores characterize a moderately to severely ill population. (see Table 2)

**Table 2**



**Table 3.1.1.3: Key Baseline Psychiatric Characteristics: 3-Week Placebo-Controlled Comparisons in Acute Bipolar Mania (CN138007, CN138009, CN138074, CN138135, CN138162), Randomized Sample**

| Variable | | CN138007 N=401 | CN138009 N=262 | CN138074 N=272 | CN138135 (a) N=480 | CN138162 (a) N=485 | Total N=1900 |
|---|---|---|---|---|---|---|---|
| Age Current Episode Began (Years) (b) | MEAN | 40.4 | 40.5 | 38.8 | 39.5 | 40.7 | 40.0 |
| | MEDIAN | 40.5 | 40.5 | 40.0 | 39.9 | 40.9 | 40.8 |
| | MIN - MAX | 18.0- 74.0 | 18.0- 74.0 | 17.0- 72.0 | 17.7- 68.9 | 17.8- 75.7 | 17.0- 75.7 |
| | SE | 0.6 | 0.8 | 0.7 | 0.5 | 0.5 | 0.3 |
| | NOT RECORDED | 1 | 0 | 0 | 0 | 0 | 1 |
| Current Episode N(%) | MIXED | 158 ( 40) | 86 ( 33) | 113 ( 42) | 188 ( 39) | 91 ( 19) | 636 ( 33) |
| | MANIC | 242 ( 61) | 176 ( 67) | 159 ( 58) | 292 ( 61) | 394 ( 81) | 1263 ( 67) |
| | NOT RECORDED | 1 | 0 | 0 | 0 | 0 | 1 |
| Rapid Cycler N(%) (c) | NO | 319 ( 80) | 201 ( 77) | 224 ( 82) | 479 (100) | 479 ( 99) | 1702 ( 90) |
| | YES | 81 ( 20) | 61 ( 23) | 48 ( 18) | 1 ( 0) | 5 ( 1) | 196 ( 10) |
| | NOT RECORDED | 1 | 0 | 0 | 0 | 1 | 2 |
| Y-MRS Total Score | MEAN | 27.9 | 28.4 | 28.7 | 28.9 | 28.0 | 28.4 |
| | MEDIAN | 27.0 | 27.0 | 28.0 | 28.0 | 27.0 | 27.5 |
| | MIN - MAX | 20.0- 49.0 | 20.0- 52.0 | 20.0- 48.0 | 20.0- 51.0 | 10.0- 50.0 | 10.0- 52.0 |
| | SE | 0.3 | 0.4 | 0.3 | 0.3 | 0.3 | 0.1 |
| | NOT RECORDED | 2 | 0 | 0 | 0 | 0 | 2 |
| CGI-BP Severity of Illness (Mania) | MEAN | 4.7 | 4.6 | 4.7 | 4.6 | 4.5 | 4.6 |
| | MEDIAN | 5.0 | 4.0 | 5.0 | 4.0 | 4.0 | 5.0 |
| | MIN - MAX | 3.0- 7.0 | 3.0- 7.0 | 3.0- 7.0 | 2.0- 6.0 | 2.0- 7.0 | 2.0- 7.0 |
| | SE | 0.03 | 0.05 | 0.04 | 0.03 | 0.03 | 0.02 |
| | NOT RECORDED | 6 | 1 | 1 | 2 | 1 | 11 |
| PANSS Total Score | MEAN | 65.0 | 65.2 | 63.0 | 66.8 | 54.9 | 62.6 |
| | MEDIAN | 64.0 | 60.0 | 60.0 | 63.0 | 53.0 | 60.0 |
| | MIN - MAX | 30.0-134.0 | 32.0-153.0 | 34.0-125.0 | 31.0-163.0 | 30.0- 99.0 | 30.0-163.0 |
| | SE | 0.9 | 1.2 | 1.1 | 0.9 | 0.6 | 0.4 |
| | NOT RECORDED | 4 | 0 | 1 | 1 | 0 | 6 |

(a) 12-week study with a 3-week placebo-controlled phase. Primary efficacy endpoint was at Week 3.
(b) Derived from date of onset of episode
(c) Rapid Cyclers were to be excluded from CN138135 and CN138162
PROGRAM SOURCE: /wsbdm/clin/proj/cn/138/bipolar_maint_cse/val/stats/psy_sum.sas RUN DATE: 02APR07 05:18

## Extent of Exposure

In studies CN138009 and CN138074, 261 patients (125 and 136, respectively) received a starting dose of 30 mg/day of aripiprazole with the option to decrease to 15 mg/day, based on tolerability. Sixty-three (50.4%) patients in study CN138009 and 82 (60.3%) patients in study CN138074 remained on study for > 2 weeks.

In studies CN138135 and CN138162, 320 patients (154 and 166, respectively) received a starting dose of 15 mg/day of aripiprazole with an option to increase to 30 mg/day. Ninety-eight (63.6%) patients in study CN138135 and 144 (86.7%) patients in study CN138162 remained on study for >2 weeks.

In study CN138007, 256 patients received fixed doses of aripiprazole (127 patients received 15 mg/day and 129 received 30 mg/day). The retention rate in study CN138007 was similar across all 3 treatment groups (45.7% to 49.6%). (see Tables 3, 4)

**Table 3**

**Table 3.1.1.5A: Disposition of Patients: 3-Week Placebo-Controlled Comparisons in Acute Bipolar Mania (CN138007, CN138009, CN138074), Randomized Sample**

| | Number (%) of Patients | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | CN138007 | | | CN138009 | | CN138074 | | |
| | | Aripiprazole | | | Aripiprazole | | Aripiprazole | |
| Variable / Reason | Placebo | 15 mg | 30 mg | Placebo | 30 mg to 15 mg | Placebo | 30 mg to 15 mg | |
| Randomized Sample | 134 | 131 | 136 | 132 | 130 | 135 | 137 | |
| Total Discontinuations | 80 (60) | 75 (57) | 82 (60) | 104 (79) | 76 (58) | 65 (48) | 62 (45) | |
| Entered open-label treatment phase due to lack of response[a] | 27 (20) | 14 (11) | 26 (19) | 37 (28) | 17 (13) | -- -- | -- -- | |
| AE | 9 (7) | 20 (15) | 9 (7) | 13 (10) | 14 (11) | 10 (7) | 11 (8) | |
| Lack of efficacy | 10 (7) | 9 (7) | 12 (9) | 16 (12) | 13 (10) | 28 (21) | 12 (9) | |
| Patient withdrew consent | 22 (16) | 28 (21) | 29 (21) | 30 (23) | 28 (22) | 25 (19) | 34 (25) | |
| Patient unreliability | 1 (1) | 0 | 1 (1) | 0 | 3 (2) | 1 (1) | 2 (1) | |
| Lost to follow-up | 3 (2) | 3 (2) | 4 (3) | 2 (2) | 1 (1) | 0 | 1 (1) | |
| Other known cause[b] | 8 (6) | 1 (1) | 1 (1) | 6 (5) | 0 | 1 (1) | 1 (1) | |
| Death | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1) | |
| Completed Study[c] | 54 (40) | 56 (43) | 54 (40) | 28 (21) | 54 (42) | 71 (52) | 75 (55) | |

[a] Patients not responding at Week 2, as indicated by CGI-BP Change from Preceding Phase (mania) Score of 4 to 7, were discontinued from the study and offered open-label aripiprazole treatment at Week 3 (CN138007 and CN138009).

[b] Other reasons for discontinuation indicated on the case report form may have included pregnancy, other known cause (other), study terminated by sponsor, protocol violation, patient met withdrawal criteria, patient did not satisfy 1 or more screening criteria, or general inability to continue.

**Table 4**

**Table 3.1.1.5B: Disposition of Patients: 3-Week Placebo-Controlled Comparisons in Acute Bipolar Mania (CN138135, CN138162), Randomized Sample**

| | Number (%) of Patients | | | | | |
|---|---|---|---|---|---|---|
| | CN138135[a] | | | CN138162[a] | | |
| | | | Aripiprazole | | | Aripiprazole |
| Variable / Reason | Placebo | Lithium | 15 mg to 30 mg | Placebo | Haloperidol | 15 mg to 30 mg |
| **Randomized Sample** | 165 | 160 | 155 | 153 | 165 | 167 |
| **Total Discontinuations Prior to End Week 3** | 87 (52.7) | 82 (51.3) | 82 (52.9) | 44 (28.8) | 44 (26.7) | 41 (24.6) |
| Lack of efficacy | 36 (21.8) | 26 (16.3) | 9 (5.8) | 14 (9.2) | 10 (6.1) | 9 (5.4) |
| AE | 13 (7.9) | 20 (12.5) | 23 (14.8) | 16 (10.5) | 8 (4.8) | 14 (8.4) |
| Patient withdrew consent | 25 (15.2) | 28 (17.5) | 32 (20.6) | 11 (7.2) | 19 (11.5) | 14 (8.4) |
| Lost to follow-up | 10 (6.1) | 5 (3.1) | 15 (9.7) | 2 (1.3) | 4 (2.4) | 2 (1.2) |
| Poor/noncompliance | 1 (0.6) | 2 (1.3) | 1 (0.6) | 0 | 1 (0.6) | 1 (0.6) |
| Patient no longer meets study criteria | 1 (0.6) | 1 (0.6) | 1 (0.6) | 1 (0.7) | 2 (1.2) | 1 (0.6) |
| Administrative reason by sponsor | 1 (0.6) | 0 | 0 | 0 | 0 | 0 |
| Other | 0 | 0 | 1 (0.6) | 0 | 0 | 0 |
| **Completed Week 3** | 78 (47.3) | 78 (48.8) | 73 (47.1) | 109 (71.2) | 121 (73.3) | 126 (75.4) |

[a] 12-week study with a 3-week placebo-controlled phase. Primary efficacy endpoint was at Week 3.

**Efficacy endpoints**

**Table 5 Efficacy from the 3 Week Placebo Controlled Comparisons**

***Study CN138007***

| | Placebo | Aripiprazole 15 mg | Aripiprazole 30 mg |
|---|---|---|---|
| **Primary Efficacy Measure** | | | |
| Y-MRS Total Score | N = 130 | N = 127 | N = 129 |
| Mean Baseline | 28.27 | 27.94 | 27.83 |
| Mean Change at Week 3 (LOCF) | -10.12 | -10.01 | -10.80 |
| **Secondary and Other Efficacy Measures** | | | |
| CGI-BP Severity of Illness (mania) Score | N = 129 | N = 125 | N = 128 |
| Mean Baseline | 4.68 | 4.66 | 4.70 |
| Mean Change at Week 3 (LOCF) | -1.17 | -1.29 | -1.33 |
| Response Rate at Week 3 (LOCF) | N = 130 | N = 127 | N = 129 |
| Number of Responders[a] (%) | 49 (38) | 52 (41) | 58 (45) |
| Ratio of Response Rates vs Placebo | -- | 1.06 | 1.21 |
| PANSS Hostility Subscale Score | N = 87 | N = 101 | N = 93 |
| Mean Baseline | 10.58 | 10.71 | 10.89 |
| Mean Change at Week 3 (LOCF) | -2.31 | -1.86 | -2.53 |
| CGI-BP Change from Preceding Phase (mania) Score | N = 130 | N = 127 | N = 129 |
| Mean Score at Week 3 (LOCF) | 3.26 | 3.20 | 3.20 |

***Study CN138009***

| | Placebo | Aripiprazole |
|---|---|---|
| **Primary Efficacy Measure** | | |
| Y-MRS Total Score | N = 122 | N = 123 |
| Mean Baseline | 29.68 | 28.16 |
| Mean Change at Week 3 (LOCF) | -3.35 | -8.15** |
| **Secondary Efficacy Measure** | | |
| CGI-BP Severity of Illness (mania) Score | N = 122 | N = 124 |
| Mean Baseline | 4.74 | 4.56 |
| Mean Change at Week 3 (LOCF) | -0.39 | -1.00** |
| **Other Efficacy Measures** | | |
| Response Rate at Week 3 (LOCF) | N = 122 | N = 123 |
| Number of Responders[a] (%) | 23 (19) | 49 (40) |
| Ratio of Response Rates vs Placebo | | 2.11** |
| PANSS Hostility Subscale Score | N = 78 | N = 99 |
| Mean Baseline | 12.29 | 10.80 |
| Mean Change at Week 3 (LOCF) | 0.49 | -1.61** |
| CGI-BP Change from Preceding Phase (mania) Score | N = 123 | N = 124 |
| Mean Score at Week 3 (LOCF) | 4.09 | 3.31** |

Source: CN138009 CSR. ** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$), compared with placebo. [a]A responder is a patient with at least 50% decrease from baseline on Y-MRS Total Score.

***Study CN138074***

| | Placebo | Aripiprazole |
|---|---|---|
| **Primary Efficacy Measure** | | |
| Y-MRS Total Score | N = 132 | N = 136 |
| Mean Baseline | 28.45 | 28.80 |
| Mean Change at Week 3, LOCF | -7.19 | -12.52** |
| **Key Secondary Efficacy Measures** | | |
| Response Rate at Week 3 (LOCF) | N = 132 | N = 136 |
| Number of Responders[a] (%) | 42 (32) | 72 (53) |
| Ratio of Response Rates vs Placebo | | 1.66** |
| CGI-BP Severity of Illness (mania) Score | N = 129 | N = 135 |
| Mean Baseline | 4.71 | 4.69 |
| Mean Change at Week 3 (LOCF) | -1.12 | -1.59** |
| PANSS Hostility Subscale Score | N = 122 | N = 124 |
| Mean Baseline | 10.74 | 10.60 |
| Mean Change at Week 3 (LOCF) | -0.82 | -2.21** |
| CGI-BP Change from Preceding Phase (mania) Score | N = 129 | N = 135 |
| Mean Score at Week 3 (LOCF) | 3.22 | 2.63** |

Source: CN138074 CSR. ** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$), compared with placebo.
[a]A responder is a patient with at least a 50% decrease from baseline to Week 3 on the Y-MRS Total Score

***Study CN138135***

| | Placebo | Lithium | Aripiprazole |
|---|---|---|---|
| **Primary Efficacy Measure** | | | |
| Y-MRS Total Score | N = 163 | N = 155 | N = 154 |
| Mean Baseline | 28.90 | 29.22 | 28.53 |
| Mean Change at Week 3 (LOCF) | -9.01 | -12.03** | -12.64** |
| **Key Secondary Efficacy Measure** | | | |
| CGI-BP Severity of Illness (mania) Score | N = 162 | N = 154 | N = 153 |
| Mean Baseline | 4.60 | 4.54 | 4.55 |
| Mean Change at Week 3 (LOCF) | -1.06 | -1.34* | -1.48** |
| **Other Secondary Efficacy Measure at Week 3** | | | |
| Response Rate (LOCF) | N = 163 | N = 155 | N = 154 |
| Number of Responders[a] at Week 3 (%) | 56 (34.4) | 71 (45.8) | 72 (46.8) |
| Ratio of Response Rates vs Placebo | -- | 1.33* | 1.31* |

Source: CN138135 CSR. ** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$), compared with placebo.

[a] A responder is a patient with at least a 50% decrease from baseline on the Y-MRS Total Score.

[b] Difference in adjusted treatment means: aripiprazole-lithium.

***Study CN138162***

| | Placebo | Haloperidol | Aripiprazole |
|---|---|---|---|
| **Primary Efficacy Measure** | | | |
| Y-MRS Total Score | N = 152 | N = 161 | N = 166 |
| Mean Baseline | 28.82 | 28.01 | 28.35 |
| Mean Change at Week 3 (LOCF) | -9.70 | -12.83** | -11.98* |
| **Key Secondary Efficacy Measures** | | | |
| CGI-BP Severity of Illness (mania) Score | N = 151 | N = 161 | N = 166 |
| Mean Baseline | 4.60 | 4.46 | 4.50 |
| Mean Change at Week 3 (LOCF) | -1.17 | -1.56** | -1.44* |
| **Other Secondary Efficacy Measure at Week 3** | | | |
| Response Rate (LOCF) | N = 152 | N = 161 | N = 166 |
| Number of Responders[a] at Week 3 (%) | 58 (38.2) | 80 (49.7) | 78 (47.0) |
| Ratio of Response Rates vs Placebo | -- | 1.26 | 1.19 |

Source: CN138135 CSR. ** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$), compared with placebo.

[a] A responder is a patient with at least a 50% decrease from baseline on the Y-MRS Total Score.

[b] Difference in adjusted treatment means: aripiprazole-haloperidol.

## 2. Maintenance of Effect Studies

METHODS

### Study design

- **CN138135**: following the 3 week treatment (either aripiprazole (starting dose of 15 mg/day with an option to increase to 30 mg/day on Day 4 or beyond), placebo, or lithium (starting dose of 900 mg/day with option to increase to 1200 mg/day at Day 4 and 1500 mg/day at Day 7) in a 1:1:1 ratio), patients were receiving either double-blind aripiprazole or lithium for an additional 9 weeks.

  At any time during the study, the patient's aripiprazole or lithium dose could be decreased for tolerability reasons. Patients randomized to placebo were blindly switched to receive aripiprazole treatment at the end of Week 3 (these patients were not included in the maintenance of effect analyses).

  All patients continuing in the study were expected to be discharged from the hospital as of Week 3. Patients completing 12 weeks of double-blind study medication had the option to continue on blinded study medication (aripiprazole or lithium) for an additional extension phase of 40 weeks.
- **CN138162**: Identical design as CN138135 except haloperidol was used as an active control and there was no extension phase. The starting dose of haloperidol was 5 mg/day with an option to increase to 10 mg/day and 15 mg/day.
- **CN138008**: A flexible-dose active-controlled study with a 12-week acute phase and a 14-week extension phase comparing aripiprazole (15 mg/day to 30 mg/day) with haloperidol (10 mg/day to 15 mg/day) in outpatients or inpatients with a diagnosis of Bipolar I Disorder who were experiencing an acute manic episode.

  Patients with a CGI-BP (mania) Change from Preceding Phase Score of ≥ 3 at the end of Weeks 1 or 2 could increase their dose of aripiprazole from 15 mg to 30 mg or haloperidol from 10 mg to 15 mg.

  At the end of the initial 3-week period, patients meeting eligibility criteria (CGI-BP Severity of Illness [mania] Score < 4 and Montgomery Asberg Depression Rating Scale (MADRS) Total Score < 18) continued in the same treatment group at the same dose level for the remainder of the study. The dose of study medication could not be increased during subsequent weeks of the study, but could be decreased to 15 mg of aripiprazole or 10 mg of haloperidol, if necessary, for

tolerability. Patients not tolerating these lower doses were to be discontinued from the study. Anticholinergic medications were not permitted in this study. Patients who completed this 12-week portion of the study and met prespecified criteria could continue treatment in a 14-week, double-blind extension phase.

**Sample size**

CN138008 was powered at 90% to detect a treatment difference of 19% in the proportion of patients in response and on treatment at Week 12, between the aripiprazole group (54%) and the haloperidol group (35%). This assumed a 2-sided test at the 0.05 level. The estimated percentages of patients in response and on treatment at Week 12 were derived from an estimated response rate at the end of Week 3 of 60% in the aripiprazole group versus 50% in the haloperidol group, and the estimated number of patients who either dropped out after the end of Week 3 or were not in response at the end of Week 12 (10% in the aripiprazole group and 30% in the haloperidol group).

**Primary efficacy endpoint (study CN138008)**

The primary efficacy measure was the number of patients who completed Week 12 and were in response at the end of Week 12 (at least 50% improvement from baseline Y-MRS).

**Secondary and other efficacy endpoints**

**CN138008**

The main secondary outcome measures were the response rate at Week 3 and at Week 12 in the subgroup of patients who had a CGI-BP (mania) Severity Score < 4 and a MADRS Total Score < 18 at Week 3; the remission rate at Week 12 (safety sample), defined as the proportion of patients who completed Week 12 with a Y-MRS Total Score < 12; time to discontinuation for any reason (safety sample) and proportion of patients with at least 70% improvement from baseline in Y-MRS Total Score at Week 3.

Other efficacy analyses included the mean changes from baseline to each specified visit in the Y-MRS Total Score, the CGI-BP Severity of Illness (mania, depression, and overall) Scores, the PANSS Total Score, the PANSS Cognitive Subscale Score, the PANSS Hostility Subscale Score, and the MADRS Total Score.

**CN138135 and CN138162**

The main secondary efficacy measures were the mean change from baseline to Week 12 on the Y-MRS Total Score, on CGI-BP Severity of Illness (mania) score and the response rate (defined as a decrease of ≥ 50% from baseline on the Y-MRS Total Score).

RESULTS

For studies CN138135 and CN138162, patient distribution and baseline psychiatric characteristics are described under the section for the 3 week placebo controlled comparisons.

**Patient distribution**

In study CN138008, 347 patients randomized to double-blind treatment: 175 patients to the aripiprazole group and 172 patients to the haloperidol group. Nine of the 347 patients randomized to treatment were excluded from the Efficacy Sample, resulting in a total of 338 patients in the Efficacy Sample (174 aripiprazole-treated and 164 haloperidol-treated).

**Baseline Psychiatric Characteristics**

More patients experienced a manic-type episode than a mixed-type episode at baseline. The treatment groups were similar on the baseline ratings scales.

**Extent of Exposure**

In study CN138135, the mean daily dose of aripiprazole in the first week of the double-blind treatment phase was 17.1 mg/day. Thereafter through Day 91 of treatment, the weekly mean daily dose was between 23.2 and 26.6 mg/day. During Week 12 (Days 78-84), 26.6% of patients in the aripiprazole group and 35.5% patients in the lithium group were still on treatment. At Week 3 (LOCF), 44.2% of aripiprazole patients were receiving a dosage of 15 mg/day.

In study CN138162, the mean daily dose of aripiprazole in the first week of the double-blind treatment phase was 17.8 mg/day and the weekly mean daily dose through Day 91 was between 22.0 and 23.7 mg/day. During Week 12 (Days 78-84), approximately 58% of patients in the aripiprazole and the haloperidol group were still on treatment. At Week 3 (LOCF), 41.6% of aripiprazole patients were receiving a dosage of 15 mg/day.

In study CN138008, the mean daily dose of aripiprazole was 21.5 mg and of haloperidol was 10.7 mg.at endpoint. At Week 12 (Days 78-84), 52.6% of aripiprazole-treated patients and 30.2% of haloperidol-treated patients were still on treatment.

**Efficacy endpoints**

**Table 6 Efficacy from the Maintenance of effect studies**

***Study CN138135***

| | Placebo | Lithium | Aripiprazole |
|---|---|---|---|
| **Secondary Efficacy Measures at Week 12** | | | |
| Y-MRS Total Score | -- | N = 155 | N = 154 |
| Mean Baseline | -- | 29.22 | 28.53 |
| Mean Change at Week 12 (LOCF) | -- | -12.71 | -14.48 |
| Treatment Difference[b] (95% CI) | | -1.78 (-4.02, 0.47) | |
| CGI-BP Severity of Illness (mania) Score | | N = 154 | N = 153 |
| Mean Baseline | -- | 4.54 | 4.55 |
| Mean Change at Week 12 (LOCF) | -- | -1.53 | -1.70 |
| Treatment Difference[b] (95% CI) | | -0.18 (-0.47, 0.12) | |
| Response Rate (LOCF) | | N = 155 | N = 154 |
| Number of Responders[a] at Week 12 (%) | -- | 76 (49.0) | 87 (56.5) |
| Ratio of Response Rates vs lithium (95% CI) | | | 1.13 (0.92, 1.39) |

Source: CN138135 CSR. ** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$), compared with placebo.

[a] A responder is a patient with at least a 50% decrease from baseline on the Y-MRS Total Score.

[b] Difference in adjusted treatment means: aripiprazole-lithium.

***Study CN138162***

| | Placebo | Haloperidol | Aripiprazole |
|---|---|---|---|
| **Secondary Efficacy Measures at Week 12** | | | |
| Y-MRS Total Score | | N = 161 | N = 166 |
| Mean Baseline | -- | 28.01 | 28.35 |
| Mean Change at Week 12 (LOCF) | -- | -17.84 | -17.16 |
| Treatment Difference[b] (95% CI) | | 0.68 (-1.64, 3.00) | |
| CGI-BP Severity of Illness (mania) Score | | N = 161 | N = 166 |
| Mean Baseline | | 4.46 | 4.50 |
| Mean Change at Week 12 (LOCF) | -- | -2.19 | -2.11 |
| Treatment Difference[b] (95% CI) | | 0.08 (-0.22, 0.37) | |
| Response Rate | | N = 161 | N = 166 |
| Number of Responders[a] at Week 12 (%) | -- | 119 (73.9) | 120 (72.3) |
| Ratio of Response Rates vs haloperidol (95%CI) | | | 1.01 (0.89, 1.14) |

Source: CN138135 CSR. ** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$), compared with placebo.

[a] A responder is a patient with at least a 50% decrease from baseline on the Y-MRS Total Score.

[b] Difference in adjusted treatment means: aripiprazole-haloperidol.

***Study CN138008***

| | Haloperidol | Aripiprazole |
|---|---|---|
| **Primary Efficacy Measure** | | |
| Response Rate (Safety Sample) | N = 169 | N = 175 |
| Number of Responders[a] at Week 12 (%) | 48 (28.4) | 87 (49.7) |
| Ratio of Response Rates vs Haloperidol (95% CI) | 1.75 (1.33, 2.30)** | |
| **Secondary Efficacy Measures** | | |
| Response Rate (Safety Sample) | N = 169 | N = 175 |
| Number of Responders[b] at Week 3 (%) | 72 (42.6) | 89 (50.9) |
| Ratio of Response Rates vs Haloperidol (95% CI) | 1.19 (0.95, 1.50) | |
| Responders at Week 12 in the Subset of Patients who Completed Week 3 with a CGI-BP Severity (mania) Score of < 4 and a MADRS Total Score < 18 | N = 77 | N = 112 |
| Number of Responders[a] (%) | 42 (54.6) | 77 (68.8) |
| Ratio of Response Rates vs Haloperidol (95% CI) | 1.26 (1.00, 1.58)* | |
| **Other Secondary Efficacy Measures** | | |
| Remission Rate (Safety Sample) | N = 169 | N = 175 |
| Number in Remission[c] at Week 12 (%) | 45 (27) | 87 (50)** |
| Ratio of Remission Rates vs Haloperidol (95% CI) | 1.87 (1.41, 2.47)** | |
| Time to discontinuation for any reason (Safety Sample) | N = 169 | N = 175 |
| Hazard Ratio | 1.94 (1.47, 2.57)** | |
| Y-MRS Total Score (Efficacy Sample, LOCF) | N = 162 | N = 174 |
| Mean Baseline | 31.39 | 31.07 |
| Mean Change at Week 12 (LOCF) | -18.22 | -19.93 |

Source: CN138008 Week 12 CSR. ** ($P \leq 0.01$), * ($0.01 < P \leq 0.05$), compared with haloperidol

[a] A responder was a patient who had at least a 50% decrease from baseline on the Y-MRS Total Score and who did not discontinue at or before Week 12.

[b] A responder was a patient who had at least a 50% decrease from baseline on the Y-MRS Total Score and who did not discontinue at or before Week 3.

[c] A patient with remission in a specific study week was a patient with a Y-MRS Total Score < 12 who did not discontinue in, or prior to, that study week.

## 3. Maintenance Treatment Studies for the Prevention of Recurrence

METHODS

### Study design

- **CN138010**: This was a randomized, double-blind, multicenter, flexible-dose, placebo-controlled study of aripiprazole in the maintenance treatment for the prevention of recurrence of Bipolar I Disorder.

There were 2 routes of entry into this study. Patients who had experienced a manic-or mixed-type episode and had recently completed an acute mania study of aripiprazole were eligible to enter and also patients who had recently experienced a manic or mixed-type episode but had not participated in an aripiprazole study were eligible to enter this study.

The study consisted of 3 phases : Stabilization phase: Open-label treatment with aripiprazole at a starting dose of 30 mg/day; could be decreased to 15 mg/day at any time, if necessary, for tolerability. Duration was from 6 to 18 weeks with visits every 2 weeks. Patients continued in this phase until their manic symptoms were stable as defined by prespecified criteria (Y-MRS Total Score ≤ 10 and a MADRS Total Score ≤ 13 during 4 consecutive visits) over a minimum of 6 weeks. Maintenance phase: Once stabilized, eligible patients were then randomized to aripiprazole or placebo. Patients assigned to aripiprazole started this phase at the same dose they were taking at the end of the Stabilization phase. The dose of aripiprazole was 15 mg/day or 30 mg/day and could be changed at any time during the study, as necessary, based on therapeutic effect and tolerability.

Patients were discontinued from the study because of lack of efficacy if they were hospitalized for manic or depressive symptoms, or required an addition to or increase in their psychotropic medications other than study medication (ie, predefined criteria for relapse). Benzodiazepines (lorazepam unless not locally available) were the only psychotrophic medications allowed in the maintenance phase, and only in small doses and limited frequency. Patients continued in this phase of the study for up to 26 weeks.

Eligible patients continued on the blinded study drug treatment they were receiving at the end of the maintenance phase, either aripiprazole (15 or 30 mg/day) or placebo, and their dose could be adjusted at any time during the study, as necessary, to enhance therapeutic effect or tolerability. Patients continued in the extension phase of the study for up to 74 weeks. Criteria for relapse in this extension phase were the same as in the maintenance phase. Patients unable to tolerate the lowest dose of study medication or who relapsed at any time during the phase were discontinued.

### Sample size

It was expected that the 6-month placebo relapse rate would be 45% and that the aripiprazole relapse rate would be 20%. A total of 45 events would be required to yield 87% power to detect the expected 25% difference in the percentage of patients relapsing between placebo and the aripiprazole treatment groups, assuming these relapse rates, a drop-out rate for reasons other than relapse of 18%, and a 2-sided test at the 0.05 level. One hundred and fifty two patients were expected to be randomized to obtain 150 evaluable patients (75 per treatment group) to yield 45 events (total number of patients who relapsed). The hazard ratio for these relapse rates and sample size was 2.7 based on a ratio of placebo/aripiprazole.

### Primary efficacy endpoint

The primary efficacy outcome measure was the time to relapse (as defined by discontinuation due to lack of efficacy) from randomization into the Maintenance Phase.

Other efficacy measures mainly included the mean change from randomization to endpoint in the Y-MRS Total Score, the MADRS Total Score, the Positive and Negative Symptom Scale (PANSS)

Total Score, the PANSS Cognitive Subscale Score, the PANSS Hostility Subscale Score, the Clinical Global Impressions-Bipolar Version (CGI-BP) Severity Scores, and the mean at endpoint in the CGI-BP Change from Preceding Phase Scores. In addition, time from randomization to relapse during the combined Maintenance and Extension Phases was assessed.

RESULTS

**Baseline Psychiatric Characteristics**

Within the Randomized Sample, the treatment groups were balanced for all variables except for the proportion of patients experiencing a manic-type episode which was 78% in the placebo group and 62% in the aripiprazole group. More patients experienced a manic-type episode (70%) than a mixed-type episode (30%) at baseline.

Patients entered the maintenance phase when they were determined to be stable over a period of 6 consecutive weeks (in the stabilization phase) as defined by prespecified criteria (Y-MRS Total Score ≤ 10 and a MADRS Total Score ≤ 13 during 4 consecutive visits).

**Extent of Exposure**

The mean daily dose for aripiprazole-treated patients at the endpoint of the maintenance phase was 24.29 mg/day. Overall, the mean daily dose of aripiprazole remained constant throughout the 26-week maintenance phase.

**Efficacy endpoints**

**Table 7 Efficacy from Study CN138010**

| | Placebo N = 83 | Aripiprazole N = 77 |
|---|---|---|
| **Maintenance Phase** | | |
| **Primary Efficacy Measure** | | |
| Time to Relapse[a] for Any Event | | |
| Number of Relapses (%) | 36 (43) | 19 (25) |
| Hazard Ratio[b] (95% CI) | 0.523* (0.300, 0.913) | |
| **Key Secondary Efficacy Measures** | | |
| Time to Manic Relapse | | |
| Number of Manic Relapses (%) | 19 (23) | 6 (8) |
| Hazard Ratio[b](95% CI) | 0.309**(0.123, 0.774) | |
| Time to Depressive Relapse | | |
| Number of Depressive Relapses (%) | 11 (13) | 9 (12) |
| Hazard Ratio[b](95% CI) | 0.833 (0.345, 2.011) | |
| **Combined Maintenance and Extension Phase** | | |
| Time to Relapse[c] for Any Event | | |
| Number of Relapses (%) | 43(52) | 25 (32) |
| Hazard Ratio[b](95% CI) | 0.531 (0.324 , 0.871)* | |

Source: CN138010 CSR. ** ($p \leq 0.01$), * ($0.01 < p \leq 0.05$), compared with placebo.

[a] Defined as discontinuation due to lack of efficacy. Patients were discontinued from the study because of lack of efficacy if they were hospitalized and/or required an addition to or increase in their allowed psychotropic medications, other than study medication, for manic or depressive symptoms.

[b] Cox's Proportional Hazards model, aripiprazole: placebo. A hazard ratio < 1 favors aripiprazole.

The proportion of relapses was lower in the aripiprazole group (25%) than the placebo group (43%) in the maintenance phase. Aripiprazole treatment significantly reduced the risk of relapse compared to

placebo by approximately half as indicated by the hazard ratio: 0.523, 95% Confidence Interval CI:0.300, 0.913.

The results showed a statistically significant difference, in favour of aripiprazole, in time to manic relapse (P = 0.008), but no significant difference in time to depressive relapse (P = 0.684) during the maintenance phase. The number of patients who had a manic-type relapse was approximately 3 times less in the aripiprazole group than the placebo group (8% in aripiprazole versus 23% in placebo). See Table 8.

**Table 8 By Relapse Type, Analysis of Time to Relapse During the Maintenance Phase: Maintenance Treatment for Prevention of Recurrence Study (CN138010), Maintenance Safety Sample**

| | Analysis of Time to Relapse[a] | |
|---|---|---|
| **Relapse Type[b]** | **Placebo (N = 83)** | **Aripiprazole (N = 77)** |
| **Manic: Number Relapsed (%)** | 19 (23) | 6 (8) |
| **Time to Manic Relapse** | | |
| Hazard Ratio[c] (Aripiprazole : Placebo), 95% CI | 0.309 (0.123, 0.774) | |
| Log-rank test P-value for equality of 2 survival curves | 0.008 | |
| **Depressive: Number Relapsed (%)** | 11 (13) | 9 (12) |
| **Time to Depressive Relapse** | | |
| Hazard Ratio[c] (Aripiprazole : Placebo), 95% CI | 0.833 (0.345, 2.011) | |
| Log-rank test P-value for equality of 2 survival curves | 0.684 | |

**Extension phase : Maintenance of Treatment Greater than 1 Year**

A total of 67 patients completed the maintenance phase, 66 of these patients entered the extension phase. These patients were followed for relapse during the extension phase for an additional period of up to 17 months or a total of up to 23 months from randomization in the maintenance phase. The prespecified analysis of time from randomization to relapse (as defined by discontinuation due to lack of efficacy) for a period greater than 1 year was evaluated during the combined maintenance and extension phases.

Consistent with findings in the maintenance phase, aripiprazole was superior to placebo in delaying the time to relapse during the combined maintenance and extension phases, further supporting the efficacy of aripiprazole in maintaining the effect in prevention of relapse in patients with Bipolar I Disorder. The proportion of relapses was lower in the aripiprazole group (32%) than the placebo group (52%). Aripiprazole treatment reduced the risk of relapse compared to placebo by nearly half as indicated by the hazard ratio: 0.531, 95% CI (0.324, 0.871).

### 4. 6-Week Combination Therapy Study

**Study design**

- **CN138134:** This was a multicenter, randomized, double-blind, flexible-dose, placebo-controlled study with 2 parallel treatment groups.

Patients who were partially nonresponsive to lithium or valproate monotherapy were randomly assigned to receive either aripiprazole or placebo in a 2:1 ratio, in combination with lithium or valproate for 6 weeks.

Patients considered appropriate by the investigator (ie, able to be treatment compliant; might benefit from longer-term treatment) could continue in the study for an additional 46 weeks on open-label aripiprazole in combination with lithium or valproate.

The study consisted of four phases. Phase 1: It was a 3-day to 4-week phase to achieve the therapeutic levels of lithium or valproate as well as screening and psychotropic washout phase. Patients who were receiving lithium or valproate, just prior to entering the study as well as those not receiving these treatments prior to entering the study, were eligible to participate. All patients received lithium or valproate during this phase. A Y-MRS total score of ≥ 16 was required for patients to enter Phase 2. Phase 2: This phase lasted 2 weeks and was used to confirm that patients were partially nonresponsive to mood stabilizers (defined by a Y-MRS Total Score ≥ 16 during Phase 1 and at the end of Phase 2, with a decrease of ≤ 25% between Phases 1 and 2). Phase 3: Patients who met partial nonresponse criteria were randomized to receive either aripiprazole or placebo in combination with lithium or valproate in a 6-week, double-blind phase. Patients were randomized in a 2:1 ratio (aripiprazole:placebo), stratified by mood stabilizer treatment and study center, and started treatment with either placebo or with aripiprazole at 15 mg/day with the option to increase to 30 mg/day at Day 7 (Week 1) or beyond for clinical response. Phase 4: This was a 46-week open-label extension phase. Patients who completed the double-blind treatment phase could enter this phase with aripiprazole and either lithium or valproate.

**Sample size**

Study CN138134 was powered at 90% to detect a difference of 3.23 in the mean change from baseline in Y-MRS at Week 6 between aripiprazole combined with lithium or valproate and placebo combined with lithium or valproate. This assumed a standard deviation of 8.82 and a 2-sided t-test for the difference between aripiprazole and placebo at the 0.05 significance level.

**Primary efficacy endpoint**

The primary efficacy endpoint was the mean change from baseline to Week 6 (LOCF) in the Y-MRS Total Score.

**Secondary efficacy endpoints**

The key secondary efficacy endpoint was the mean change from baseline to Week 6 (LOCF) in the CGI-BP Severity of Illness Score (Mania).

## RESULTS

**Patient distribution**

There were 384 patients randomized according to 2:1 (aripiprazole: placebo) ratio to the 6-week combination treatment phase (Phase 3): 131 to the placebo group and 253 to the aripiprazole group. Seven of the 384 patients were excluded from the Efficacy Sample, resulting in a total of 377 patients in the Efficacy Sample.

**Baseline Psychiatric Characteristics**

The mean age at the start of manic or mixed symptoms was 27.0 years; 75% of patients were experiencing a manic-type episode and 25% were mixed-type episode at baseline. Therapeutic levels of lithium and valproate were confirmed at the end of medication washout Phase 1, prior to entering the mood stabilizer monotherapy Phase 2. In addition, only patients with a Y-MRS ≥ 16 were eligible to enter Phase 2.

The mean Y-MRS Total Score was 23.9 at the end of Phase 1. The mean duration of Phase 1 mood stabilizer dosing was 18.9 days. The treatment groups were similar with respect to the baseline psychiatric evaluations.

The mean baseline (end of Phase 2) Y-MRS Total Score of the Randomized Sample was 23.1. The mean baseline CGI-BP Severity of Illness Score (mania) for all randomized patients was 4.2. Baseline assessment scores of psychiatric rating scales were similar for the aripiprazole and placebo groups. Patients who were partially nonresponsive to lithium or valproate monotherapy were randomly assigned in a 2:1 ratio (aripiprazole:placebo) for 6 weeks in combination with lithium or valproate, stratified by mood stabilizer treatment; 41% of the randomized patients were on lithium and 59% were on valproate.

**Extent of Exposure**

For the aripiprazole-treated patients, the mean daily dose in the first week of treatment was 15.5 mg/day. Thereafter to end of treatment in the double-blind phase the weekly mean daily dose was between 17.3 and 19.0 mg/day. At Week 6 (Days 36-42), 77.9 % of aripiprazole-treated and 88.5% placebo-treated patients were still on treatment.

**Efficacy endpoints**

For the primary efficacy endpoint, the mean change from baseline to Week 6 (Phase 3) in the Y-MRS Total Score (LOCF), aripiprazole added to lithium or valproate showed statistically significantly greater improvement than placebo; the treatment difference was -2.62 (P = 0.002).

For the key secondary efficacy endpoint, the mean change from baseline to Week 6 in CGI-BP Severity of Illness score (Mania) (LOCF), the aripiprazole group showed statistically significantly greater improvement than the placebo group (treatment difference -0.33, P = 0.014).

The aripiprazole group (aripiprazole in combination with either lithium or valproate was superior to the placebo group (placebo in combination with either lithium or valproate) on the primary efficacy endpoint, the mean change from baseline to Week 6 (Phase 3) in the Y-MRS Total Score (LOCF) and on the key secondary efficacy endpoint, the CGI-BP Severity of Illness (mania) Score (LOCF).

There was a statistically significant difference between treatment groups in the mean CGI-BP Change from Preceding Phase (Mania) Score favoring aripiprazole at Week 6 (P = 0.037). The aripiprazole group was superior to the placebo group in PANSS hostility Subscale scores (P = 0.001). The mean changes from baseline to Week 6 in CGI-BP Severity of Illness (Depression) Score and in MADRS Total Score were similar between the aripiprazole group and the placebo group.

The treatment-by-mood stabilizer interactions assessed at Week 6 for both the primary and secondary efficacy endpoints were not statistically significant (P = 0.332, and P = 0.203, respectively).

**5. Sensitivity analysis on patients without use of specified central nervous system (CNS) medications**

The agents included antiepileptics, anxiolytics, opioids, other analgesics/antipyretics, hypnotics/sedatives, and antipsychotics. For each study, an analysis of the primary endpoint (mean change from baseline to endpoint in Y-MRS Total Score) was conducted excluding patients who took any of these medications concomitantly with study medication.

The subset of patients who did not use these concomitant medications showed statistically significant improvement on the mean Y-MRS Total Score from baseline to Week 3, in favour of aripiprazole versus placebo in studies CN138074 and CN138162 (P = 0.003, and P = 0.011, respectively). In studies CN138009 and CN138135, the aripiprazole group showed greater improvement in the mean Y-MRS Total Score from baseline to Week 3 than the placebo group; however, the difference was not statistically significant (P = 0.086 and P = 0.104, respectively). Study CN138007 was not included in this analysis because the purpose of this sensitivity analysis was to test the robustness of the results from positive studies when excluding patients who used these concomitant medications.

## 6. Discussion on Clinical Efficacy

***1. Three-Week Placebo Controlled Comparisons***

There are 5 completed clinical studies directly relevant for the demonstration of efficacy at 3 weeks. Two of them included active comparators i.e lithium (CN138135) or haloperidol (CN138162). and were also designed to provide data for the 12 week endpoint. The primary endpoint in all the trial was the Young-Mania Rating Scale (YMRS) scale and responders defined as improvement of 50% in that scale were also analysed.

Study **CN1380007** failed to discriminate from placebo. In this clinical study, the treated arm improved from baseline around 12 points which is in the range of the effect expected but the placebo results were similar in this respect.

All the other clinical studies showed consistently efficacy in the expected range and aripiprazole effect was similar to the one obtained with lithium and haloperidol.

In all trials drop-outs rates were high in the range of 50 to 60% and about half of those were due to lack of response or lack of efficacy.

Rates of responders in the positive studies were placebo 19% vs aripiprazole 40% (CN138009); placebo 32% vs aripiprazole 53% (CN138074); placebo 34.4% vs lithium 45.8% vs aripiprazole 46.8%(CN138135); placebo 38.2% vs haloperidol 49.8% vs aripiprazole 47% (CN138162). The secondary endpoints were consistent with the effect seen in the YMRS and responders.

***2. Maintenance of Effect Studies***

- **CN138135**

In the aripiprazole group, 20.0% of patients discontinued beyond end of Week 3 and 27.1% patients completed the 12-week double-blind phase. In the lithium group, 15.0% discontinued beyond end of Week 3 and 33.8% patients completed the 12-week double-blind phase.

The treatment effect of aripiprazole observed at the end of Week 3 was maintained at Week 12, the same was true for the lithium group.

The improvement in mean change from baseline to the end of Week 3 in Y-MRS Total Score was maintained at Week 12 in the aripiprazole group (Week 3: -12.64, Week 12: -14.48) and the lithium group (Week 3: -12.03, Week 12: -12.71).

The mean changes from baseline in Y-MRS Total Score were similar between the aripiprazole and the lithium group at Week 12.

The proportion of responders (patients with ≥ 50% improvement from baseline in Y-MRS Total score) increased from Week 3 to Week 12 for both the aripiprazole group (Week 3: 46.8%, Week 12: 56.5%) and the lithium group (Week 3: 45.8%, Week 12: 49.0%). The response rate was higher in the aripiprazole than the lithium group at Week 12.

The percentages of patients in remission (defined as a Y-MRS Total score ≤ 12) increased between Week 3 and Week 12, in the aripiprazole group (40.3% and 49.4%, respectively) and remained stable the lithium group (40.0% and 39.4%, respectively).

- **CN138162**

In study CN138162, 18.6% patients from the aripiprazole and 15.8% from the haloperidol group discontinued beyond end of Week 3. The number of patients who completed the 12-week double-blind

phase was similar for the aripiprazole and haloperidol group (aripiprazole, 56.9% and haloperidol, 57.6%). In both studies CN138135 and CN138162, the most frequently reported reason for discontinuation from treatment beyond end of Week 3 across the treatment groups was adverse event (AE).

The aripiprazole and the haloperidol groups continued to show improvement at all timepoints from Week 3 to Week 12.

The effect observed at Week 3 was maintained at Week 12 in the aripiprazole group (Week 3: -11.98, Week 12: -17.16) and the haloperidol group (Week 3: -12.83, Week 12: -17.84).
The mean changes from baseline in Y-MRS Total Score at Week 12 were similar between the aripiprazole and the haloperidol group.

The response rate was increased from Week 3 to Week 12 in both aripiprazole (Week 3: 47.0%, Week 12: 72.3%) and the haloperidol groups (Week 3: 49.7%, Week 12: 73.9%). The response rates were similar between the aripiprazole and the haloperidol groups at Week 12.

Remission rates were higher at Week 12 than Week 3 in both the aripiprazole (69.9% vs 44.0%) and the haloperidol group (71.4% vs 45.3%) and were similar between the treatment groups.
Both studies CN138135 and CN138162 showed minimal improvement in MADRS Total Score from baseline to the end of Week 12 in the aripiprazole and the active control groups

- **CN138008**

In study CN138008, aripiprazole was superior to haloperidol on the primary efficacy endpoint, percentage of patients on-treatment and in response at Week 12 ($P < 0.001$).

For the secondary efficacy measure of percentage of patients on-treatment and in response at the end of Week 3, the aripiprazole group showed a higher response (51%) compared to the haloperidol group (43%); however; the difference was not statistically significant.

For the cohort of patients who continued in the study by meeting eligibility criteria at Week 3 (CGI-BP Severity of Illness [mania] Score < 4 and MADRS Total Score < 18), the aripiprazole group (69%) was superior to the haloperidol group (55%) at the end of Week 12 ($P = 0.048$).

The proportion of patients on-treatment and remission (Y-MRS Total Score < 12) was greater in the aripiprazole group (50%) than in the haloperidol group (28%) at Week 12 ($P < 0.001$). Furthermore, aripiprazole was superior to haloperidol ($P < 0.001$) in time to discontinuation for any reason.

The mean change from baseline to Week 12 in the Y-MRS Total Score (LOCF) was similar between the aripiprazole and the haloperidol group.

Overall, the CHMP considered that the data provided are supportive of the efficacy of aripiprazole in the treatment of the acute maniac episode.

***3. Maintenance Treatment Studies for the Prevention of Recurrence***

Although the combined maintenance and extension phases provided a period of evaluation that is more than a year, the primary analysis of CN138010 evaluated relapses during the 6 month double-blind phase. The maintenance phase was 6 months in duration and was followed by a double-blind extension phase that continued for up to an additional 74 weeks (patients continued on the same drug and dose as in the maintenance phase).

Given the results on the first 6 months and the 74 weeks double blind data, the CHMP considered that the overall study duration of CN138010 was acceptable.

Additionally, the CHMP acknowledged that the use of an active comparator in recurrence prevention studies can be of methodologically concern due to possible switch or use of combination treatment

during the stabilisation phase. The MAH performed a literature review to further support the efficacy of aripiprazole as compared to other antipsychotics (lithium, lamotrigine, olanzapine, and valproate) in the treatment of any phase of Bipolar I disorder. Based on these data which included a meta analysis of 14 long term studies conducted with other antipsychotics, the CHMP was of the opinion that the overall data provided were acceptable.

***4. Six-Week Combination Therapy Study (CN138134)***

Study CN138134 evaluated aripiprazole in association with classical non neuroleptic mood-stabilizers as observed in clinical practice. Results showed a benefit favouring aripiprazole 15 to 30 mg. The extension phase is currently ongoing.

### 3.3.2 Clinical Safety

A total of 2626 patients received aripiprazole tablets in the acute bipolar mania clinical trial program; 13543 patients received aripiprazole tablets across all Phase 2/3/4 studies.Patients in the bipolar mania clinical program received substantial exposure to aripiprazole. A total of 2626 patients received at least one dose of aripiprazole treatment; 1895 received aripiprazole for at least 3 weeks; and 1446 received aripiprazole for at least 6 weeks. The number of patient exposure years was 546.8.

In the bipolar mania studies, most aripiprazole-treated patients were distributed evenly in overall mean dose categories of >12.5 to ≤ 17.5 mg/day (36.3%) and >25.0 to ≤ 32.5 mg/day (39.2%), reflecting 15 mg/day and 30 mg/day dose regimens, respectively.

**Patient exposure**

All aripiprazole dataset included data from a total of 13543 patients: bipolar mania (N = 2626), bipolar depression (N = 593), adjunctive treatment in major depressive disorder (N = 1055), schizophrenia (N = 8215), and other disorders (N=1054).

Overall, patient exposure years (PEY) totaled 7618.9, with 546.8 years for patients with bipolar mania. A total of 1895 bipolar mania patients received aripiprazole for at least 3 weeks, and 1446 received aripiprazole for at least 6 weeks.

**Adverse events (AEs)**

**1. Three-Week Placebo-Controlled Comparisons**

Data from all available 3-week placebo-controlled comparisons in bipolar mania were derived from 917 patients treated with aripiprazole and 753 treated with placebo.

The incidence of treatment-emergent AEs was 82.2% in the aripiprazole group and 71.7% in the placebo group. Events of akathisia, sedation, extrapyramidal disorder, and restlessness were reported at an incidence of ≥ 5% (including numbers that equaled or were greater than 5% after rounding) and twice that of placebo.

In these pooled studies, the adverse drug reaction (ADR) profile of Abilify was similar to that reported in the schizophrenia placebo-controlled studies. When results from the bipolar mania and schizophrenia placebo-controlled trials are combined, 3 new ADR terms not currently in the SPC meet criteria (≥ 1% the rate in the placebo group): anxiety, salivary hypersecretion, and extrapyramidal disorder.

**2. Twelve-Week Active-Controlled Studies**

In the 12-week lithium-controlled study (CN138135), the aripiprazole group reported lower incidences than the lithium group of tremor, but higher incidences of akathisia, sedation, insomnia, agitation, restlessness, dry mouth, musculoskeletal stiffness, and fatigue.

In the 12-week haloperidol-controlled studies (CN138162 and CN138008), the aripiprazole group reported lower incidences relative to the haloperidol group of akathisia, extrapyramidal disorder, tremor, and parkinsonism, with the latter 2 primarily reported in CN138008. The aripiprazole group reported higher incidences of nausea (primarily in CN138008) and mania (primarily in CN138162).

**3. Maintenance Treatment Study**

Data from the maintenance treatment study were derived from 77 patients treated with aripiprazole and 83 treated with placebo during the maintenance phase.

The incidence of treatment-emergent AEs during the maintenance phase of CN138010 was similar for the aripiprazole (74.0%) and placebo (69.9%) groups. There was a higher incidence of ADRs in the aripiprazole group than the placebo group, which was largely accounted for by the higher incidence of tremor (aripiprazole 7.8%, placebo 1.2%) and musculoskeletal stiffness (aripiprazole 6.5%, placebo 1.2%). During the combined maintenance and extension phases, the incidences of ADRs were similar to those reported in the maintenance phase.

**4. Six-Week Combination Therapy Study**

Data from the 6-week combination therapy study were derived from 253 patients treated adjunctively with aripiprazole and lithium or valproate, and 130 treated adjunctively with placebo and lithium or valproate.

In the combination therapy study of aripiprazole or placebo co-administered with lithium or valproate, the overall incidence of treatment-emergent AEs was 62.1% for aripiprazole and 53.8% for placebo. AEs reported for patients in the aripiprazole group at ≥ 5% (including numbers that equaled or were greater than 5% after rounding) and twice that of placebo included akathisia, insomnia, and extrapyramidal disorder.

**Serious adverse events (SAEs) and deaths, discontinuation due to adverse events**

**1. Three-Week Placebo-Controlled Comparisons**

There was 1 death reported in an aripiprazole-treated patient (hydrocodone intoxication, unrelated to therapy).

The incidence of treatment-emergent SAEs was similar between treatment groups (6.0% aripiprazole, 4.4% placebo), with the majority of events occurring in the system organ class of psychiatric disorders.

The rates of treatment-emergent AEs that led to discontinuation of study therapy were also similar between treatment groups: 11.0% for the aripiprazole group and 9.6% for the placebo group. Mania and akathisia were the most frequently reported AEs leading to discontinuation of study therapy in the aripiprazole group.

**2. Twelve-Week Active-Controlled Studies**

In study CN138135, no deaths were reported during the 12-week phase.

In study CN138162, two deaths (pulmonary necrosis and lung abscess) were reported after patients were randomized to placebo in the placebo-controlled phase and switched to aripiprazole after Week 3 of the 12-week double-blind phase.

The rates of SAEs were higher in the aripiprazole groups than the active-control groups in study CN138162 (11.4% vs 3.0% haloperidol, respectively) and study CN138135 (12.3% vs 8.2% lithium, respectively), but lower than the haloperidol group in study CN138008 (2.3% vs 7.1%, respectively). Most events were reported in the system organ class of psychiatric disorders.

The incidence of treatment-emergent AEs leading to discontinuation of study therapy in CN138008 was lower in the aripiprazole group than the haloperidol group (18.9% vs 49.1%), and higher than the haloperidol group in CN138162 (14.5% vs 10.9%).

The most frequently reported AEs leading to discontinuation of aripiprazole treatment were akathisia and depression (primarily in study CN138008), and mania (primarily in studyCN138162).

In the 12-week lithium-controlled study (CN138135), the incidence of treatment-emergent AEs leading to discontinuation of study therapy was 20.1% for the aripiprazole group and 17.6% for the lithium group. The most frequently reported AE leading to discontinuation of aripiprazole treatment was akathisia (3.2%).

**3. Maintenance Treatment Study**

There was one death for an aripiprazole-treated patient due to heroin intoxication during the stabilization phase of CN138010.

The incidence of SAEs was lower in the aripiprazole group (7.8%) than the placebo group (13.3%) during the maintenance phase, with most events reported in the system organ class of psychiatric disorders.

The incidence of discontinuation of study therapy was also lower in the aripiprazole group (10.4%) than the placebo group (19.3%), with mania the most frequently reported event leading to discontinuation in both groups.

**4. Six-Week Combination Therapy Study**

No deaths were reported in the 6-week placebo-controlled phase of CN138134, and the incidence of SAEs was low (aripiprazole 3.2%, placebo 2.3%).

More aripiprazole-treated (11.9%) than placebo-treated (6.2%) patients discontinued from study therapy because of an AE, with most of this treatment difference accounted for by the higher incidence in the aripiprazole group of akathisia (aripiprazole 5.1%, placebo 0.8%) and tremor (aripiprazole 2.0%, placebo 0.8%).

**Laboratory findings**

In the 3-week placebo-controlled comparisons, 4 patients discontinued aripiprazole treatment because of events of syncope, hypotension, orthostatic hypotension, and heart rate increased.

In the maintenance treatment study, no aripiprazole-treated patient discontinued the maintenance phase because of a laboratory or electrocardiogram (ECG) abnormality; 1 aripiprazole-treated patient discontinued study therapy due to mild hypertension.

In the six-week combination therapy study, One aripiprazole-treated patient discontinued study therapy because of increased creatine phosphokinase (CPK); no aripiprazole-treated patients discontinued because of vital sign or ECG abnormalities.

**Discussion on clinical safety**

The safety profile of aripiprazole in the bipolar mania clinical program was described comprehensively. The MAH also performed an analysis using all aripiprazole safety database to compare the profile across the reported indications, more particularly between schizophrenia and bipolar mania. Furthermore EPS, neuroleptic malignant syndrome (NMS), seizures, orthostatic hypotension and related AEs, suicide-related AEs, metabolic abnormalities AEs were specifically reviewed.

Among all aripiprazole-treated patients in bipolar mania studies, the incidence of treatment-emergent AEs that led to discontinuation of study therapy was 17.6%. The incidences of discontinuation of aripiprazole treatment due to depression, mania, and akathisia were higher for patients with bipolar mania than those reported for patients with schizophrenia.

The incidence of akathisia was higher for patients with bipolar mania (16.3%) than patients with schizophrenia (7.3%).

Among aripiprazole-treated patients in the acute bipolar mania studies, the incidence of clinically relevant weight gain increased over time, regardless of whether aripiprazole was given as monotherapy or given in combination with mood stabilizers . Furthermore, the mean percent changes from baseline to endpoint in body weight, body mass index (BMI), and waist circumference also increased through Week 26 and beyond. However, among all aripiprazole-treated patients in Phase 2/3/4 studies, the incidence of clinically relevant weight increase for patients with acute bipolar mania was lower than for patients with schizophrenia or overall.

Of the 1663 patients with bipolar mania who began aripiprazole treatment with a normal baseline CPK level, 43 (2.6%) had a potentially clinically relevant elevated CPK level during the study. The incidence was lower than seen with the schizophrenia indication and slightly higher than seen in other indications. Of the 43 events, 13 reported concurrent SAEs (1 convulsion, 1 neuroleptic malignant syndrome, 1 [non-cardiac] chest pain, 1 hypomania and loss of consciousness, 1 pancreatitis, 2 bipolar disorder exacerbated and 7 mania aggravated or exacerbated).

The overall incidence of treatment-emergent SAEs for patients with acute bipolar mania was lower than that reported for patients with schizophrenia (8.8% and 17.7%, respectively).

The incidence of QTc with an increase of ≥ 30 msec was 7.9% for patients with bipolar mania was lower than that reported for schizophrenia (14.8%) or overall (12.3%).

In overall, although there were some differences identified in the frequencies of the most common AEs as compared with the schizophrenia population, the safety profile of aripiprazole appeared to remain unchanged and no new safety concerns were raised in the bipolar mania clinical program.

Nevertheless, the CHMP raised some concerns related to the occurrence of depression as treatment-emergent AEs that led to discontinuation from study therapy which was observed more frequently in patients with bipolar-mania than in patients with schizophrenia (respectively, 2.7% versus 0.3%).The CHMP therefore recommended to reflect this information into the SPC.

## 1.4 Pharmacovigilance

The MAH submitted two updates of the risk management plan during the period of the assessment of this extension of indication.

The latest version of the RMP is summarised in Table 9:

**Table 9**

**Safety Concerns, Proposed Pharmacovigilance (PV) Actions, and Proposed Risk Minimization 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.<br>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 SPC: 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 SPC: suicidal behavior inherent in psychotic illness and mood disorders, close supervision recommended.<br>Undesirable effects Sect 4.8: Suicide attempt, ideation and completed suicide.<br>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 |
| **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** | | |

**Table 9**

**Safety Concerns, Proposed Pharmacovigilance (PV) Actions, and Proposed Risk Minimization Activities**

| Safety Concern | Proposed PV Activities | Proposed Risk Minimization Activities (Routine and Additional) |
|---|---|---|
| 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 SPC: 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 SPC: especially in schizophrenic patients and often due to co-morbidities, especially history of diabetes, thyroid disorder or pituitary adenoma. |
| 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 SPC: 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:<br>1) CYP2D6, 3A4<br>2) Antihypertensives<br>3) Alcohol or other CNS medications<br>4) Drugs prolonging QT or causing electrolyte imbalance<br>5) H2 antagonist |

**Table 9**

**Safety Concerns, Proposed Pharmacovigilance (PV) Actions, and Proposed Risk Minimization Activities**

| Safety Concern | Proposed PV Activities | Proposed Risk Minimization Activities (Routine and Additional) |
|---|---|---|
| Increased mortality and CVA in elderly patients with dementia | Routine PV as listed in the current RMP | Warnings & Precautions 4.4 of SPC: 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 no additional risk minimisation activities are required beyond those included in the product information.

## 1.5 Overall conclusions and benefit-risk assessment

Acute efficacy of manic episodes was demonstrated in 4 short-term monotherapy trials, 2 of which showed maintenance of effect similar to lithium or haloperidol up to 12 weeks, and 1 adjunctive therapy trial with lithium or valproate demonstrated the safe and effective use of aripiprazole in combination with mood stabilizers. The majority of these trials included patients with moderate to severe manic episodes, some of whom also had psychotic symptoms.

The supportive study for the recurrence prevention (CN138010) used "time to relapse" as primary outcome measure. However, the result was only driven by effects on the recurrence of new manic episodes, no effect was seen on recurrence prevention of new depressive episodes based on the key secondary endpoints. Nevertheless, taking into account the first 6 months and the 74 weeks double blind data, the CHMP was of the opinion that the proposed indication could be acceptable, provided that the target population is further defined. The CHMP recommended the following wording:

*'Abilify is 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 (see section 5.1).''*

Furthermore, the CHMP recommended to reflect the negative results concerning the prevention of depressive episodes into section 5.1 of the SPC.

The MAH also committed to further investigate in clinical trials the efficacy of aripiprazole in combination with mood stabilizers (lithium and valproate) or lamotrigine in the prevention of recurrence in patients with Bipolar I Disorder.

With regards to safety, aripiprazole was safe and well-tolerated in the bipolar mania clinical program. The adverse effects of aripiprazole were generally mild to moderate and similar to those previously observed in the schizophrenia population treated with aripiprazole. No unexpected safety concerns were identified.

Importantly, the adverse effect profile of aripiprazole was different from that of other atypical antipsychotic drugs that are commonly used to treat mania. Aripiprazole did not show any safety concerns on QT prolongation, hyperprolactinemia, or weight gain. EPS was more frequently reported in aripiprazole-treated than in placebo-treated patients, but at a rate of approximately half that of haloperidol-treated patients.

Nevertheless, the CHMP raised some concerns on the occurrence of depression as treatment-emergent AEs that led to discontinuation from study therapy and therefore recommended to reflect this information into the SPC.

Overall, the CHMP considered the benefit risk assessment of Abilify *'in 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'* positive and recommended the variation to the Marketing Authorisation.