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APPLICATION NUMBER:

NDA 202-971/S003

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	202971 S-003
Priority or Standard	Standard
Submit Date(s)	February 7, 2014
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Division / Office	Division of Psychiatry Products Office of Drug Evaluation I
Reviewer Name(s)	Phillip Kronstein, M.D.
Review Completion Date	November 12, 2014
Established Name	Aripiprazole for extended release injectable suspension
(Proposed) Trade Name	Abilify Maintena
Therapeutic Class	Antipsychotic
Applicant	Otsuka Pharmaceutical
Formulation(s)	Powder for suspension
Dosing Regimen	300 or 400mg IM q4 weeks
Indication	Schizophrenia
Intended Population(s)	Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical standpoint, it is recommended that this sNDA be approved, pending the successful outcome of labeling negotiations.

1.2 Risk-Benefit Assessment

At the time of the approval of the original NDA for ABILIFY MAINTENA, which was based on one longer-term, double-blind, placebo-controlled, randomized-withdrawal (maintenance) study in adults with schizophrenia, the clinical reviewer made the following risk-benefit assessment:

> The risks associated with ABILIFY MAINTENA treatment appear to be the same as those with the marketed oral formulations of aripiprazole. The therapeutic efficacy is expected to be comparable as well. ABILIFY MAINTENA offers the added benefits of convenience of administration and assured delivery of drug. Therefore, for patients with schizophrenia being treated with aripiprazole and especially for patients with poor compliance, the benefits of Abilify Maintena therapy outweigh the risks.

In this sNDA, we now have the results of one short-term (12-week), randomized, double-blind, placebo-controlled trial in acutely relapsed adults with schizophrenia. With this information, a new signal for generally mild neutropenia has been identified, which, in the opinion of this reviewer, does not significantly change the original risk-benefit assessment but requires some changes to labeling [see "Hematology" under Section 7.4.2 of this review].

In addition, the current labeling states, under Section 2.1 "Dosage Overview for the Treatment of Schizophrenia":

> For patients who have never taken aripiprazole, establish tolerability with oral aripiprazole prior to initiating treatment with ABILIFY MAINTENA.

This reviewer considers it important to inform clinicians that "due to the (b) (4) half-life of oral aripiprazole, it may take up to 2 weeks to fully assess tolerability" [see "Additional Comments/Concerns" under Section 6.1 of this review].

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The sponsor does not believe that there is any risk that requires a Risk Evaluation and Mitigation Strategy (REMS). The sponsor states that the following steps will be adequate to monitor the safety of aripiprazole IM depot:

- an ongoing pharmacovigilance plan that includes systematic collection of adverse event information, real time and periodic assessment of single and aggregate safety reports to identify potential signals, and submission of aggregate reports as required by regulations.

- the sponsor recommends that the Medication Guide be distributed to outpatients at the time of first injection, upon request at subsequent injections, and after any material change to the document. There would be no requirement for distribution to inpatients, in accordance with draft guidance from the Agency.[1] However, the Medication Guide would be distributed to any inpatient who requests it.

The reviewer for the original NDA agreed that there appears to be no significant safety concerns with ABILIFY MAINTENA that would require a REMS. There is no new information in this sNDA to change this assessment.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for Postmarketing Requirements or Commitments at this time. A full pediatric waiver has already been granted.

2 Introduction and Regulatory Background

2.1 Product Information

Aripiprazole is a second generation antipsychotic that has been widely used since its initial approval in 2002 for the treatment of schizophrenia. The current approved indications for oral formulations of aripiprazole include: treatment of schizophrenia; acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate; maintenance treatment of bipolar I disorder, both as monotherapy and as an adjunct to lithium or valproate; adjunctive treatment of major depressive disorder; and treatment of irritability associated with autistic disorder. The current approved indication for the immediate-release injectable formulation of aripiprazole is treatment of acute agitation associated with schizophrenia or bipolar I disorder. The original NDA 202971 led to the approval of the IM depot formulation of aripiprazole in Feb. 2013 for the treatment of schizophrenia.

1 U.S. Food and Drug Administration. Draft Guidance for Industry: Medication Guides - Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS), February 2011.

2.2 Currently Available Treatments for Proposed Indications

Both first and second generation antipsychotics may be used in the treatment of schizophrenia. Several of these agents are available in an IM depot formulation in the U.S.:

- haloperidol decanoate (Haldol Decanoate) (NDA 18-701)
- fluphenazine decanoate (ANDA 71-413)
- risperidone (Risperdal Consta) (NDA 21-346)
- paliperidone palmitate (Invega Sustenna) (NDA 22-264)
- olanzapine pamoate (Zyprexa Relprevv) (NDA 22-173)

2.3 Availability of Proposed Active Ingredient in the United States

Aripiprazole is currently available as a tablet (NDA 21-436), an oral solution (NDA 21-713), an orally disintegrating tablet (NDA 21-729), an immediate-release injectable formulation (NDA 21-866), and an IM depot formulation (NDA 202971).

2.4 Important Safety Issues with Consideration to Related Drugs

Other second generation antipsychotic drugs carry a risk of metabolic effects, such as weight gain, hyperglycemia, and hyperlipidemia. In addition, Zyprexa Relprevv may cause severe sedation or delirium after injection, and patients receiving this drug must be observed for 3 hours post-injection in a registered facility with emergency response capabilities.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

For a detailed history of pre-submission regulatory activity for the original NDA, please see the clinical review by Gregory Dubitsky, M.D., dated May 29, 2012.

The pivotal efficacy study for the original NDA 202971 (Study 31-07-246) was a double-blind, placebo-controlled, randomized-withdrawal (maintenance) trial in adults with schizophrenia. Although Study 31-07-246 entailed a randomized, placebo-controlled phase, Dr. Dubitsky noted that the analyses based on this phase were problematic because they included only patients who had tolerated and experienced a response to several weeks of treatment with both oral and IM depot aripiprazole. In addition, there was a substantial difference in follow-up times between the drug and placebo treatment groups during this phase, making a comparison of safety between the two groups unreliable. Therefore, Dr. Dubitsky considered the safety analyses that used these data misleading for the purposes of labeling. Nonetheless, with the exception of injection site reactions, he noted that the nature, frequency, and severity of adverse events associated with aripiprazole IM depot would be expected to be very similar to those observed with oral aripiprazole. Therefore, the majority of the safety data in the final

ABILIFY MAINTENA labeling was revised to be based on the information contained in the ABILIFY (oral tablet) labeling.

A Type B Pre-sNDA Meeting was scheduled for July 16, 2013 to "discuss and receive Agency feedback on the clinical development program and the proposed sNDA for ABILIFY MAINTENA for the treatment of (b) (4) schizophrenia." Of note, the sponsor was satisfied with our preliminary responses, so the meeting was cancelled. In the background package for the meeting, the sponsor stated:

> OTSUKA believes that the clinical trials to be presented in the sNDA are sufficient to support filing and subsequent approval of a sNDA for the treatment of (b) (4) schizophrenia in adults. This is based on FDA comments provided in their review of Protocol 31-12-291 (submitted to IND 67380, Serial Number 210 on 10 August 2012).
>
> On 11 September 2012, in an email from Sonny Saini [the RPM] to David Goldberger, FDA commented that "Trial 31-12-291, as described in the submitted protocol, is adequately designed to evaluate the efficacy and safety of ABILIFY MAINTENA in the treatment of (b) (4) schizophrenic patients. This single trial could support a claim for ABILIFY MAINTENA in the treatment of schizophrenia."
>
> In addition to Trial 31-12-291, the sNDA will contain information from an ongoing open-label trial (Protocol 31-12-297) enrolling patients that have completed Protocol 31-12-291….

We indicated our agreement but added: "However, please be advised (b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

On 16 April 2014, OSI/DGCPC was formally consulted to conduct inspections at the following two sites for Study 31-12-291:

- Site #907 (Tram K. Tran-Johnson, PharmD; San Diego, CA)
- Site #926 (David P. Walling, PhD; Long Beach, CA)

The two sites were selected for inspection based on high subject enrollment and large contributions to the overall treatment effect for the primary efficacy endpoint. According

to the Clinical Inspection Summary, dated 14 August 2014, no significant GCP deviations were found at either site.

3.2 Compliance with Good Clinical Practices

Each Clinical Study Report in Module 5 contains a statement of compliance:

> This trial was conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research subjects, no trial procedures were performed on trial candidates until written consent had been obtained from them. The informed consent form (ICF), protocol, and amendments for this trial were submitted to and approved by the institutional review board (IRB) or independent ethics committee (IEC) for each respective trial site or country.

In addition, the sponsor submitted a memo signed 6 January 2014 by David Goldberger (Vice-President, Regulatory Affairs) stating that "Otsuka Pharmaceutical Development & Commercialization, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."

3.3 Financial Disclosures

The sponsor submitted a "Financial Certification and Disclosure for Protocol 31-12-291", which included the details of the process for collecting financial disclosures and listed all the clinical investigators/sub-investigators. Four were found to have disclosable information. A Form FDA 3455 was submitted for each of them. For all four, the only disclosure box checked was "any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria." No further details were provided.

The sponsor also provided a Form FDA 3454, signed 9 January 2014 by David Goldberger, in which the box was checked stating:

> As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not

disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new CMC data.

4.2 Clinical Microbiology

No new microbiology data.

4.3 Preclinical Pharmacology/Toxicology

No new preclinical pharmacology/toxicology data.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The efficacy of this second generation antipsychotic has been hypothesized to be mediated through a combination of partial agonism at dopamine D_2 and serotonin 5-HT_{1A} receptors as well as antagonism at serotonin 5-HT_{2A} receptors.

4.4.2 Pharmacodynamics

The pharmacodynamics of aripiprazole IM depot was evaluated at the time of the original NDA submission by the review team (including DPP and OCP) and is described in the currently approved labeling.

4.4.3 Pharmacokinetics

The pharmacokinetics of aripiprazole IM depot was evaluated at the time of the original NDA submission by the review team (including DPP and OCP) and is described in the currently approved labeling.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1 and Table 2 list the clinical studies included in this submission that were reviewed in order to determine efficacy and/or safety. Of note, Study 31-12-297 was completed on 17 February 2014, with the study report being issued on 10 May 2014. Also, although Study 31-12-297 was an open-label extension study, it was conducted in such a way as to maintain the blind for Study 31-12-291.

Table 1 Tabular Listing of Study 31-12-291

Type of Study Clinical Phase	Protocol Number Location of Study (Number of Study Sites)	Study Report Location	Study Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Treatment Duration	Study Status; Type of Report
Efficacy, Safety Phase 3	31-12-291 Multinational (55 sites)	Section 5.3.5.1.4	Evaluate the efficacy of aripiprazole IM depot as treatment of acute episodes of schizophrenia Evaluate the safety and tolerability of aripiprazole IM depot administered every 4 weeks for 12 weeks	Randomized (1:1), double-blind, placebo-controlled	Screening Phase: oral aripiprazole, 10 mg (10-mg tablets) for 3 days for tolerability, if applicable Acute Treatment Phase: aripiprazole IM depot 400 mg or 300 mg (400 mg lyophilized powder for injection) or matching IM placebo monthly. For the first 2 weeks concomitant oral aripiprazole (10-20 mg/day) for IM depot subjects and concomitant oral matching placebo for placebo subjects	506 340 (168 to aripipra-zole [167 treated] and 172 to placebo)	Schizo-phrenia, must have an acute psychotic episode	Screening phase up to 13 days Acute treatment phase 12 weeks	Completed; full

Table 2 Tabular Listing of Study 31-12-297

Safety Phase 3	31-12-297 Multinational (38 sites as of 30Jun2013) (approximately 150 sites planned)	Section 5.3.5.2.3	Evaluate the safety and tolerability of aripiprazole IM depot administered for 26 weeks	Open-label, extension	Aripiprazole IM depot 400 mg or 300 mg (400 mg lyophilized powder for injection) once monthly	42 (as of 30Jun 2013)	Schizo-phrenia; Subjects completing Trial 31-12-291	Open-label treatment: 24 weeks	Ongoing, synoptic report

5.2 Review Strategy

Both studies were reviewed in terms of safety, though not to the same extent, due to differences in study design (see Section 7.1.1). Study 31-12-291 was the only study in this supplement reviewed to determine the efficacy of aripiprazole IM depot as a treatment for schizophrenia in adult patients. However, as mentioned above, the pivotal efficacy trial for the original NDA 202971 (Study 31-07-246) was a placebo-controlled, randomized-withdrawal (maintenance) study.

6 Review of Efficacy

6.1 Treatment of Schizophrenia

Study 31-12-291 was titled "A 12-week, Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Aripiprazole Intramuscular Depot (OPC-14597, Lu AF41155) in the Acute Treatment of Adults with Schizophrenia." A total of 41 trial sites (37 in the US, 2 in Croatia, and 2 in Latvia) enrolled subjects.

Objectives

- The primary objective of this trial was to evaluate the overall *efficacy* of aripiprazole IM depot as an acute treatment in adult subjects with schizophrenia.

- The secondary objective of this trial was to evaluate the *safety and tolerability* of aripiprazole IM depot as an acute treatment in adult subjects with schizophrenia

Inclusion Criteria

- The trial population included male and female subjects between 18 and 65 years of age, inclusive, with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnosis of schizophrenia for at least 1 year prior to screening who would benefit from hospitalization or continued hospitalization for the treatment of a current acute relapse of schizophrenia. Of note, the screening visit (i.e., signing of the informed consent) must have occurred no more than 5 days after the date of hospital admission.

- Subjects had to be experiencing an acute exacerbation of psychotic symptoms as demonstrated by meeting BOTH of the following criteria at screening and baseline:

    - Currently experiencing an acute exacerbation of psychotic symptoms accompanied by significant deterioration in the subject's clinical and/or

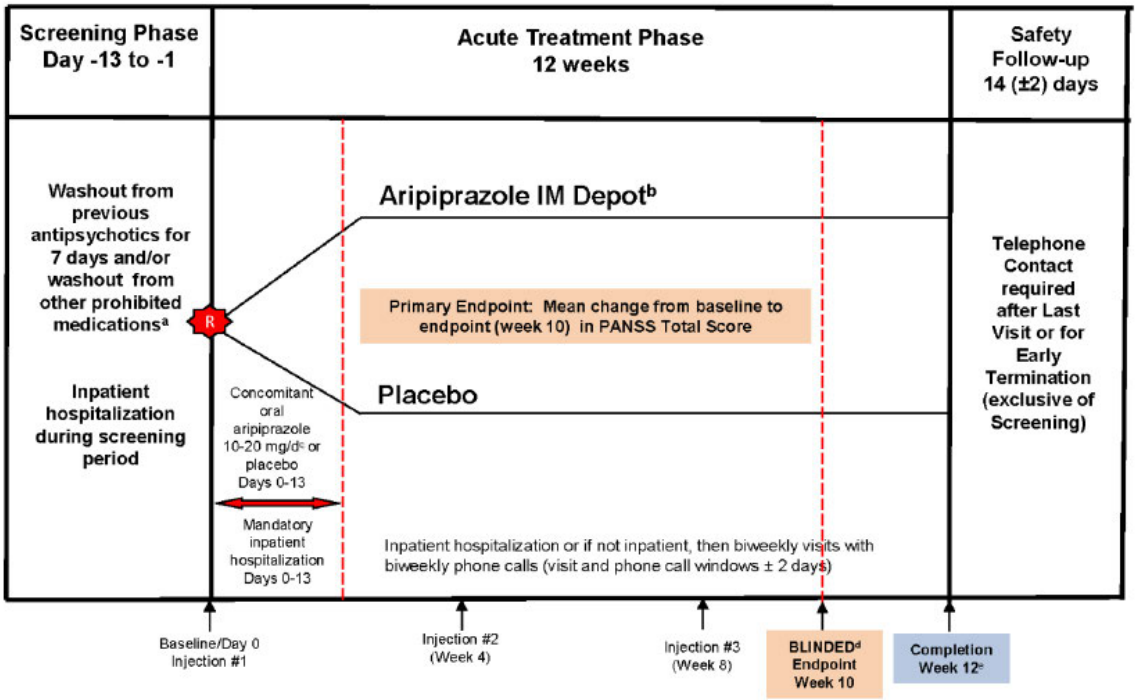
functional status from their baseline clinical presentation with a PANSS total score ≥80 AND

- Specific psychotic symptoms on the PANSS as measured by a score of >4 on each of the following items (possible scores of 1 to 7 for each item)
  - Conceptual disorganization (P2)
  - Hallucinatory behavior (P3)
  - Suspiciousness/persecution (P6)
  - Unusual thought content (G9)

Overall Design

This was a short-term (12-week), randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of aripiprazole IM depot as treatment for an acute episode of schizophrenia in adult subjects. The dose of aripiprazole IM depot was 400 mg q4 weeks with allowed decrease to 300 mg for safety and return to 400 mg for efficacy if needed; this is consistent with the current labeling. Completers of the acute treatment phase were able to enter the 6-month open-label extension trial (Study 31-12-297) at the Investigator's discretion. A schematic of the trial design (Screening Phase, Acute Treatment Phase, and Safety Follow-up) is provided in Figure 1.

Figure 1 Trial Design for Study 31-12-291



Subjects entered a pretreatment Screening Phase of up to 13 days to assess eligibility criteria. If subjects had been exposed to aripiprazole in the past (i.e., tolerability had been established), then subjects entered a washout period for 7 days from prior antipsychotic and other prohibited concomitant medications. If the investigator could reasonably verify that the subject had been off antipsychotics for at least 7 days and had a history of tolerating aripiprazole, then the subject was allowed a Screening Phase of <7 days. If subjects had not been exposed to aripiprazole in the past, oral aripiprazole 10 mg daily was given for 3 days "to establish tolerability" prior to the 7-day washout period. Subjects were required to be hospitalized during the entire Screening Phase. If not already hospitalized, the subject was to be hospitalized from the time of the signing of the informed consent onward during the Screening Phase.

At baseline, eligible subjects were randomized in a 1:1 ratio to either aripiprazole IM depot or placebo. Subjects received either aripiprazole IM depot 400 mg/300 mg or matching placebo injected into a gluteal muscle every 4 weeks (i.e., at baseline/Day 0, Week 4, and Week 8) during the 12-week Acute Treatment Phase for a total of three injections. For 14 days, beginning with the first injection, subjects randomized to aripiprazole IM depot received concomitant oral aripiprazole, while subjects randomized to placebo received concomitant oral placebo. During the first 2 weeks of the Acute Treatment Phase, all subjects were required to remain as inpatients. However, during the remainder of the Acute Treatment Phase, a subject could have been either an inpatient or outpatient, based on the investigator's judgment of the subject's clinical status.

To minimize any potential bias, the investigator and subject were blinded to the timing of the primary efficacy endpoint evaluation (i.e., Week 10). Although the pre-planned endpoint for the primary analysis was defined as Week 10 in the statistical analysis plan (SAP), this information was not included in the protocol or communicated to site staff during the trial.

Efficacy Endpoints and Analysis

- The primary efficacy endpoint was the change from baseline to Week 10 in the PANSS total score.

- The key secondary efficacy endpoint was the change from baseline to Week 10 in the Clinical Global Impression - Severity (CGI-S) scale.

- For the other secondary endpoints, please see the Statistical Review.

The primary statistical comparison was performed using the Mixed Model Repeated Measure (MMRM) approach. Analyses included the categorically fixed effects of treatment, region (pooled sites), trial week, and treatment-by-week interaction, as well as the continuously fixed covariates of baseline score-by-week interaction. An

unstructured covariance structure was used to model the within-subject errors and Kenward-Rodger degree of freedom was used to test the fixed effects.

Demographics and Other Baseline Characteristics[2]

The demographic characteristics for randomized subjects were similar between the two treatment groups. Most subjects randomized were male (79.1%), Black/African American (65.6%), and non-Hispanic/Latino (90.3%). The mean age was 42.4 years and mean BMI was 28.5 kg/m^2. Most subjects (96.2%) were enrolled in the US. (Please see the Statistical Review for more details).

Baseline disease characteristics were comparable between the 2 treatment groups. As expected based on entry criteria, these subjects were markedly ill. In the enrolled population, mean overall PANSS total scores were 103 (range 82-144), and mean P2, P3, P6, and G9 scores were all >5. Mean CGI-S scores were 5.2 (range 4-7). All subjects had been diagnosed with schizophrenia for ≥1 year and less than half (42.6%) had been previously exposed to oral aripiprazole.

Disposition

The patient disposition in the 12-week Acute Treatment Phase is summarized in Table 3. Three hundred forty subjects were randomized from 41 trial sites, where 168 subjects were randomly assigned to treatment with aripiprazole IM depot 400 mg/300 mg and 172 subjects to placebo. However, only 162 patients in the aripiprazole IM depot and 167 patients in the placebo group had post-randomization measurements, meaning that only a total of 329 patients belonged to the modified Intent to Treat (mITT) population, i.e., the primary efficacy sample.

The reasons for discontinuation by Week 10 are summarized in Table 4. Overall, 64.3% and 49.4% of subjects completed Week 10 in the aripiprazole IM depot and placebo groups, respectively. The most frequent cause of discontinuation by Week 10 in the placebo group was lack of efficacy (as determined by the investigator), which was 29.1% (50/172) vs. only 7.1% (12/168) in the aripiprazole IM depot group. In the aripiprazole IM depot group, the most common cause of discontinuation by Week 10 was subject withdrawal of consent, which was 19.0% vs. 8.7% for placebo.

[2] For this and the following sections of the Review of Efficacy, a majority has been excerpted from the Statistical Review by Yeh-Fong Chen, Ph.D.

Table 3 Patient Disposition for Study 31-12-291

n (%)	Aripiprazole IM Depot 400/300 mg (N=168)	Placebo (N=172)	Total (N=340)
Screened			506
Screen Failure			166
Randomized	168 (100.0)	172 (100.0)	340 (100.0)
Modified Intent to Treat (ITT) Population	162 (96)	167 (97)	329 (97)
Completed	94 (56.0)	65 (37.8)	159 (46.8)
Discontinued	74 (44.0)	107 (62.2)	181 (53.2)
Analyzed for Safety	167 (99.4)	172 (100.0)	339 (99.7)
Analyzed for Efficacy	167 (99.4)	172 (100.0)	339 (99.7)

Source: Sponsor's Table 10.1-1 of clinical study report

Table 4 Reasons for Discontinuation by Week 10 for Study 31-12-291

n (%)	Aripiprazole IM Depot 400/300 mg (N=168)	Placebo (N=172)	Total (N=340)
Randomized	168 (100.0)	172 (100.0)	340 (100.0)
Completed Trial Week 10	108 (64.3)	85 (49.4)	193 (56.8)
Discontinued Prior to Trial Week 10	60 (35.7)	87 (50.6)	147 (43.2)
Lost to Follow-up	3 (1.8)	4 (2.3)	7 (2.1)
Adverse Events	7 (4.2)	13 (7.6)	20 (5.9)
Sponsor Discontinued Study	0 (0)	0 (0)	0 (0)
Subject Met Withdrawal Criteria	5 (3.0)	5 (2.9)	10 (2.9)
Investigator Withdrawal Subject	1 (0.6)	0 (0)	1 (0.3)
Subject Withdrawal Consent	32 (19)	15 (8.7)	47 (13.8)
Protocol Deviation	0 (0)	0 (0)	0 (0)
Lack of Efficacy as Determined by Investigator	12 (7.1)	50 (29.1)	62 (18.2)

Source: Sponsor's Table 10.1-2 of clinical study report

Sponsor's Results for Primary Efficacy Endpoint

The sponsor's results for the change from baseline to each study week in PANSS total score by the MMRM method are presented in Table 5. For the primary efficacy endpoint, the treatment difference between the aripiprazole IM depot group (mean change -26.8) and the placebo group (mean change -11.7) at Week 10 was -15.1, which is statistically significant with a p-value of <0.0001. The treatment difference at Week 12 was -14.6, which was also statistically significant with a p-value of <0.0001.

Table 5 Sponsor's Results by MMRM for Change from Baseline in PANSS Total Score for Study 31-12-291

		Baseline Value		Change from Baseline		Comparisons	
Trial Week	Treatment Group	N	Mean (SD)	N	LS Mean (SE)	Difference	P-Value
Baseline	ARIP IMD	162	102.4 (11.4)				
	Placebo	167	103.4 (11.1)				
Week 1	ARIP IMD	162	93.8 (14.2)	162	-8.9 (0.9)	-3.9	0.0005
	Placebo	167	98.9 (15.9)	167	-5.0 (0.9)		
Week 2	ARIP IMD	144	87.2 (16.1)	144	-15.2 (1.2)	-7.0	<0.0001
	Placebo	157	94.8 (17.0)	157	-8.3 (1.2)		
Week 4	ARIP IMD	134	82.6 (16.8)	134	-19.0 (1.4)	-9.2	<0.0001
	Placebo	140	91.9 (18.1)	140	-9.8 (1.3)		
Week 6	ARIP IMD	126	78.3 (16.3)	126	-21.5 (1.5)	-11.1	<0.0001
	Placebo	117	89.8 (18.2)	117	-10.3 (1.5)		
Week 8	ARIP IMD	108	74.1 (15.3)	108	-23.7 (1.6)	-14.0	<0.0001
	Placebo	96	88.3 (19.9)	96	-9.7 (1.6)		
Week 10	ARIP IMD	99	70.6 (15.2)	99	-26.8 (1.6)	-15.1	<0.0001
	Placebo	81	85.6 (18.4)	81	-11.7 (1.6)		
Week 12	ARIP IMD	99	70.6 (16.4)	99	-27.2 (1.7)	-14.6	<0.0001
	Placebo	68	83.7 (18.4)	68	-12.6 (1.8)		

Source: Table 11.4.1.1-1 of CSR
Note: LS Mean, SE and p-value were derived from an MMRM analysis with fixed effects of treatment, region (pooled sites), week, treatment by week interaction and baseline by week interaction as covariate. Unstructured covariance structure for observations within a subject was used.

The sponsor also performed sensitivity analyses by ANCOVA for the last observed carried forward data (ANCOVA-LOCF) and for observed cases data (ANCOVA-OC). Both analysis results were very similar to those by MMRM; the p-values were less than 0.05 for all weeks.

Sponsor's Results for Key Secondary Efficacy Endpoint

Table 6 presents the sponsor's results for change from baseline to each study week in CGI-S score. As can be seen, the differences between the aripiprazole IM depot and placebo groups (including at Week 10, the pre-specified endpoint) are all statistically significant, with a p-value ≤0.0001.

Table 6 Sponsor's Results by MMRM for Change from Baseline in CGI-Severity Score for Study 31-12-291

		Baseline Value		Change from Baseline		Comparisons	
Trial Week	Treatment Group	N	Mean (SD)	N	LS Mean (SE)	Difference	P-Value
Baseline	ARIP IMD	162	5.2 (0.5)				
	Placebo	168	5.2 (0.5)				
Week 1	ARIP IMD	162	4.8 (0.7)	162	-0.4 (0.1)	-0.3	0.0001
	Placebo	168	5.1 (0.6)	168	-0.2 (0.1)		
Week 2	ARIP IMD	144	4.4 (0.9)	144	-0.8 (0.1)	-0.4	<0.0001
	Placebo	157	4.9 (0.7)	157	-0.4 (0.1)		
Week 4	ARIP IMD	134	4.2 (0.9)	134	-1.0 (0.1)	-0.6	<0.0001
	Placebo	140	4.8 (0.8)	140	-0.4 (0.1)		
Week 6	ARIP IMD	126	4.0 (0.9)	126	-1.2 (0.1)	-0.7	<0.0001
	Placebo	117	4.6 (0.9)	117	-0.5 (0.1)		
Week 8	ARIP IMD	108	3.8 (0.9)	108	-1.3 (0.1)	-0.7	<0.0001
	Placebo	96	4.5 (1.0)	96	-0.6 (0.1)		
Week 10	ARIP IMD	99	3.6 (0.8)	99	-1.4 (0.1)	-0.8	<0.0001
	Placebo	81	4.4 (1.0)	81	-0.6 (0.1)		
Week 12	ARIP IMD	99	3.6 (0.9)	99	-1.4 (0.1)	-0.8	<0.0001
	Placebo	68	4.3 (1.0)	68	-0.6 (0.1)		

Source: Table 11.4.1.2.1-1 of CSR

For the analyses of the other secondary endpoints, please see the Statistical Review.

The sponsor also performed subgroup analyses for gender (male, female), race (Caucasian, non-Caucasian), age (<45 years, ≥45 years), ethnicity (Hispanic/Latino, Not Hispanic/ Latino), and BMI (≤28 kg/m^2, >28 kg/m^2) at baseline for the change from baseline to endpoint (Week 10) in PANSS total score (primary efficacy endpoint) and for the change from baseline to Week 10 in CGI-S (key secondary efficacy endpoint). The statistical reviewer confirmed the sponsor's results. As she notes in her review, none of the subgroup analyses were prospectively planned in terms of study-wise type I error rate control; they were all performed for the purpose of exploration.

Sponsor's Conclusions

The sponsor concluded that aripiprazole IM depot 400 mg/300 mg administered monthly was efficacious for the treatment of schizophrenia in acutely relapsed adult subjects as demonstrated by superiority to placebo in the primary efficacy endpoint, change from baseline to Week 10 in PANSS total score, and in the key secondary endpoint, change from baseline to Week 10 in CGI-S score, as well as in various other secondary endpoints.

Conclusions

1. The statistical reviewer confirmed most of the sponsor's analysis results and agreed that the data from Study 31-12-291 support the efficacy of aripiprazole IM depot 400 mg/300 mg in treating patients with schizophrenia, based on the prospectively specified efficacy endpoints. Nevertheless, one should note that although the overall discontinuation rate in the aripiprazole IM depot group was lower than placebo (35.7% vs. 50.6%), which is not unusual for schizophrenia trials, those in the aripiprazole IM depot group who dropped out due to withdrawal of consent was much higher than placebo (19% vs. 8.7%).

2. Regarding the efficacy of aripiprazole IM depot, the statistical reviewer found the following statement in Section 14 of the proposed labeling to be inappropriate:

(b) (4)

(b) (4)

Of note, this clinical reviewer is in complete agreement regarding the recommendations in comment #2, (b) (4)

Additional Comments/Concerns

As noted above, the overall discontinuation rate in the aripiprazole IM depot group was lower than in placebo (35.7% vs. 50.6%), which is not unusual for schizophrenia trials. However, the percentage of patients in the aripiprazole IM depot group who dropped out due to withdrawal of consent was much higher than placebo (19% vs. 8.7%). To better understand the causes as well as the impact on the efficacy and safety results, the review team asked the sponsor to perform some exploratory analyses. Our information request is shown below:

- **FDA Question about subjects dropping out due to withdrawal consent :**
  We are concerned about the number of discontinuations due to "subject withdrew consent" in Study 31-12-291 and the fact that they occurred in the drug group at twice the rate of the placebo group (19% for Arip. IMD; 8.7% for placebo). To help us understand the possible causes, please submit the following information:

  a. For all discontinuations due to "subject withdrew consent", please indicate the number and percent of subjects (by treatment group) who were aripiprazole naïve (meaning those who had not previously been treated with aripiprazole prior to entry into Study 31-12-291). In addition, please indicate the total number and percent of subjects (by treatment group) in the intent-to-treat population who were aripiprazole naïve.

  b. Please indicate the ID number of all subjects in the intent-to-treat population who were aripiprazole naïve, and submit a revised panss0.xpt data set by adding a variable to indicate aripiprazole naïve patients.

  c. Refer to Table 10.1-2 entitled "*Reasons for Discontinuation by Week 10 – Primary Efficacy Endpoint (Randomized Sample)*" of your study report. Please provide a similar table but for the subgroups of aripiprazole naïve and non-naïve patients.

  d. Refer to the pre-specified primary analysis of the primary endpoint. Please perform exploratory subgroup analysis by whether patients were aripirpazole naïve or not.

From the sponsor's response, we found out that 58% of subjects randomized to the aripiprazole IM depot group and 56% randomized to placebo were aripiprazole naïve. We further determined that aripiprazole IM depot had a larger treatment effect in aripiprazole naïve patients than in those who had been previously treated with aripiprazole. However, aripiprazole IM depot appeared to be effective in both subgroups. Please see the Statistical Review for the detailed exploratory analysis results for the two subgroups.

In addition, we noted that among the 35 dropouts due to withdrawal of consent in the aripiprazole IM depot group, 63% of them did not have any previous aripiprazole exposure. In contrast, among the 17 placebo dropouts due to withdrawal of consent, only 41% were aripiprazole naïve.

In summary, there was a higher than normal percentage of dropouts due to withdrawal of consent in the aripiprazole IM depot group (19%; twice the rate of placebo), and of the subjects in the aripiprazole IM depot group who withdrew consent, 63% were aripiprazole naïve (the proportion being reversed in the placebo group). From these results, one could hypothesize that a significant number of dropouts due to withdrawal of consent in the aripiprazole IM depot group were due to a lack of tolerability that was

not properly captured under adverse events (e.g. the subject gave a false, vague, or no reason for withdrawal of consent, and no further information could be obtained).

This hypothesis is made more plausible by the fact that in Study 31-12-291, tolerability in aripiprazole naïve patients was established by giving aripiprazole 10 mg po QD for only 3 days (in the Screening Phase, prior to the 7-day washout period). Clinically significant adverse events, such as akathisia (which is more common with aripiprazole than other second generation antipsychotics), can take significantly longer than 3 days to appear, especially considering the PK of oral aripiprazole. According to the current ABILIFY labeling (Section 2.1), "dosage increases should generally not be made before 2 weeks, the time needed to achieve steady-state."

In Study 31-12-291, no serious consequences can be directly linked to the way the sponsor established tolerability in aripiprazole naïve patents. However, this reviewer recommends adding the following sentence to Section 2.1 of the proposed ABILIFY MAINTENA labeling:

> Due to the (b) (4) half-life of oral aripiprazole, it may take up to 2 weeks to fully assess tolerability.

This reviewer considers it important for the clinician to have this information. Three days of oral dosing (as in Study 31-12-291) is enough if one is just trying to rule out an allergy to aripiprazole. However, in a patient at higher risk for a TEAE, blood levels will need to be closer to steady state in order to ascertain true tolerability. This is of particular concern for the TEAE of akathisia, which in more severe cases is difficult to treat (especially while waiting 4+ weeks for the IM depot to leave the patient's system) and may be associated with suicidal ideation and/or behavior.

7 Review of Safety

Safety Summary

This review, with one exception, reveals no significant new information regarding the safety profile of ABILFY MAINTENA. The exception is a new safety signal for generally mild neutropenia (see Section 7.4.2). As planned, the placebo-controlled safety data from Study 31-12-291 will now replace the oral aripiprazole safety data in the current ABILIFY MAINTENA labeling (see Section 2.5).

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

For this sNDA, the studies used to evaluate safety are the pivotal efficacy study (31-12-291) and the open-label extension of that study (31-12-297). The design of Study 31-12-297 makes it difficult to assess adverse events. Therefore, only serious adverse events (SAEs) and adverse events that led to premature termination (AE dropouts) will be considered for Study 31-12-297.

7.1.2 Categorization of Adverse Events

Adverse events for both studies were coded using MedDRA version 15.0. For Study 31-12-291, the JMP tables of adverse events were examined by this reviewer, comparing the investigator verbatim terms to the preferred terms. No gross errors were found.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data from Study 31-12-291, which is a double-blind, placebo-controlled trial, cannot be pooled with data from Study 31-12-297, which is an open-label extension of 31-12-291. For this reason, the Division agreed that an ISS would not be indicated for this sNDA.

7.2 Adequacy of Safety Assessments

7.2.1 Exposure at Appropriate Doses/Durations and Demographics of Target Populations

<u>Overall Exposure</u>

The ICH E1 exposure requirements were met as part of the original NDA. According to the sponsor, as of the cut-off date of 30 June 2013:

> ABILIFY MAINTENA has been evaluated for safety in 2,188 adult patients in clinical trials in schizophrenia, with approximately 2,646 patient-years of exposure. A total of 1,230 patients were treated with ABILIFY MAINTENA for at least 180 days (at least 7 consecutive injections) and 935 patients treated with ABILIFY MAINTENA had at least 1 year of exposure (at least 13 consecutive injections).

Of note, clinical studies of ABILIFY (oral and MAINTENA) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Extent of Exposure for Study 31-12-291

Of the 340 subjects randomized, 195 received oral aripiprazole (10 mg/day for 3 days) during the screening period to "establish tolerability."

Subjects randomized to aripiprazole IM depot 400 mg/300 mg received oral aripiprazole tablets (10-20 mg/day) during Weeks 1 and 2 of the Acute Treatment Phase. They took a mean daily dose of 12.8±3.2 mg oral aripiprazole tablets during this time.

All subjects randomized to aripiprazole IM depot who received a first injection (n=167) were started on the 400 mg dose. Keeping in mind that only 104 (61.9%) of the 168 subjects randomized to aripiprazole IM depot received all three injections, a vast majority of the subjects who received a first injection did not have subsequent doses decreased to 300 mg. For more details, see the table below.

Table 7 Extent of Exposure to IMP - Aripiprazole IM Depot/Placebo Injection (Randomized Sample) in Study 31-12-291

	Aripiprazole IM Depot 400/300mg (N=168)						Placebo (N=172)					
	INJECTION DOSE LEVEL						INJECTION DOSE LEVEL					
	300 MG		400 MG		TOTAL		300 MG		400 MG		TOTAL	
INJECTION	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
1ST INJECTION	0	(0.0)	167	(100.0)	167	(99.4)	0	(0.0)	172	(100.0)	172	(100.0)
2ND INJECTION	4	(3.2)	122	(96.8)	126	(75.0)	4	(3.2)	120	(96.8)	124	(72.1)
3RD INJECTION	3	(2.9)	101	(97.1)	104	(61.9)	0	(0.0)	83	(100.0)	83	(48.3)
LAST INJECTION	3	(1.8)	164	(98.2)	167	(99.4)	3	(1.7)	169	(98.3)	172	(100.0)

Note: Last injection is the last IMP injection during the Acute Treatment Phase whether a subject completed or discontinued the trial.
Source: CT-7.2.1.

7.2.2 Explorations for Dose Response

Study 31-12-291 had flexible dosing as per the drug label (400 mg q4 weeks with allowed decrease to 300 mg for safety and return to 400 mg for efficacy if needed), so it was not possible to conduct explorations for dose response. Also, a vast majority of subjects received only the 400 mg dose.

7.2.3 Special Animal and/or In Vitro Testing

No new animal or in vitro data.

7.2.4 Routine Clinical Testing

For Studies 31-12-291 and 31-12-297, the type and frequency of vital sign, clinical laboratory, and ECG monitoring seems adequate given the known safety profile of aripiprazole (IM depot and oral).

7.2.5 Metabolic, Clearance, and Interaction Workup

No new metabolic or clearance data.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Potential adverse effects based on those for similar drugs in the drug class are outlined in Section 2.4. These were evaluated as part of the original clinical NDA review and/or this review. The currently approved labeling also includes class warnings as appropriate.

7.3 Major Safety Results

7.3.1 Deaths

No subjects died during Study 31-12-291 or 31-12-297.

7.3.2 Nonfatal Serious Adverse Events

Study 31-12-291

Fourteen (4.1%) of 339 subjects had serious adverse events, including 8/167 (4.8%) of aripiprazole IM depot subjects and 6/172 (3.5%) of placebo subjects. Serious adverse events reported for ≥1% of aripiprazole IM depot subjects were schizophrenia (3/167 [1.8%] subjects) and psychotic disorder (2/167 [1.2%] subjects); these events were considered serious as the subject required psychiatric hospitalization. All serious adverse events reported during this trial are summarized in Table 8. Also, the narrative summaries for all the serious adverse events were reviewed by the undersigned. None of the SAEs appeared to represent a clinically significant new event attributable to aripiprazole IM depot therapy. Of note, the case of “arthralgia” was in fact knee pain due to a basketball injury (requiring hospitalization).

Table 8 Incidence of Serious Adverse Events by System Organ Class (SOC) and MedDRA Preferred Term (Safety Sample) for Study 31-12-291

		Aripiprazole IM Depot 400/300mg (N=167)	Placebo (N=172)
SYSTEM ORGAN CLASS	**MEDDRA PREFERRED TERM**	**n (%)**	**n (%)**
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ARTHRALGIA	1 (0.6)	0 (0.0)
PSYCHIATRIC DISORDERS	AGITATION	1 (0.6)	0 (0.0)
	PSYCHOTIC DISORDER	2 (1.2)	2 (1.2)
	SCHIZOPHRENIA	3 (1.8)	3 (1.7)
	SUBSTANCE ABUSE	1 (0.6)	0 (0.0)
	SUICIDAL IDEATION	1 (0.6)	0 (0.0)
VASCULAR DISORDERS	HYPOTENSION	0 (0.0)	1 (0.6)
TOTAL		8 (4.8)	6 (3.5)

Note: A TEAE was defined as an AE that began after start of IMP treatment; or if the event was continuous from baseline and was serious, IMP-related, or resulted in death, discontinuation, interruption or reduction of IMP. Multiple occurrences of TEAE were counted once per specific MedDRA (version 15.0) preferred term. Subjects with TEAEs in multiple SOCs were counted only once towards the total.
Note: Except for hypotension, which was considered a medically significant condition, all serious TEAEs were considered serious due to requiring hospitalization (initial or prolonged).
Source: CT-8.5.2 and CT-9.2.

Study 31-12-297

A total of 5/74 (6.8%) subjects had 6 serious adverse events during this open-label extension trial. One subject had a spontaneous abortion, 2 subjects had depression, one subject had worsening of schizophrenia, and one subject had an exacerbation of schizophrenia and suicidal ideation. The narrative summaries for all the serious adverse events were reviewed by the undersigned. None of the SAEs appeared to represent a clinically significant new event attributable to aripiprazole IM depot therapy.

Of note, the spontaneous abortion occurred in the first trimester, which is not that uncommon in the general population. According to the narrative, “the factors that may have contributed to the ‘abortion spontaneous’ were the subject's history of spontaneous abortion at age 18 (in the second trimester) due to reported unspecified uterus problems, recent personal stresses including financial strain, physical battery/assault by boyfriend, strained relationship, recent break-up, and living situation problems (she was recently evicted from her apartment).”

7.3.3 Dropouts and/or Discontinuations

Study 31-12-291

Treatment-emergent adverse events (TEAEs) resulting in discontinuation of the investigational medicinal product (IMP) were experienced by 20/339 (5.9%) subjects: 7/167 (4.2%) subjects in the aripiprazole IM depot group and 13/172 (7.6%) for placebo. TEAEs resulting in IMP discontinuation reported for ≥1% of subjects in any treatment group were schizophrenia (1.8% of aripiprazole IM depot subjects and 4.7% for placebo) and psychotic disorder (1.2% of aripiprazole IM depot subjects and 1.7% for placebo). All TEAEs leading to discontinuation of IMP are summarized in Table 9. The SAEs that led to discontinuation appear again in this listing.

Table 9 Incidence of TEAEs Resulting in Discontinuation from IMP by SOC and MedDRA Preferred Term (Safety Sample) for Study 31-12-291

		Aripiprazole IM Depot 400/300mg (N=167)	Placebo (N=172)
SYSTEM ORGAN CLASS	**MEDDRA PREFERRED TERM**	**n (%)**	**n (%)**
GASTROINTESTINAL DISORDERS	DYSPHAGIA	0 (0.0)	1 (0.6)
PSYCHIATRIC DISORDERS	ANXIETY	1 (0.6)	0 (0.0)
	PSYCHOTIC DISORDER	2 (1.2)	3 (1.7)
	SCHIZOPHRENIA	3 (1.8)	8 (4.7)
	SUICIDAL IDEATION	1 (0.6)	0 (0.0)
VASCULAR DISORDERS	HYPERTENSION	0 (0.0)	1 (0.6)
TOTAL		7 (4.2)	13 (7.6)

A TEAE was defined as an AE that began after start of IMP treatment; or if the event was continuous from baseline and was serious, IMP-related, or resulted in death, discontinuation, interruption or reduction of IMP. Multiple occurrences of TEAE were counted once per specific MedDRA (version 15.0) preferred term. Subjects with TEAEs in multiple SOCs were counted only once towards the total.
Source: CT-8.6.2.

Study 31-12-297

A total of 6/74 (8.1%) subjects were discontinued from IMP due to TEAEs. One subject had a moderate TEAE of “hepatic enzyme increased” and one subject had a moderate TEAE of “weight increased.” The other TEAEs leading to discontinuation are already discussed as SAEs.

Of note, the subject with the elevated liver enzymes (ALT 156 U/L, AST 72 U/L, and GGT 111 U/L) experienced this TEAE on the same day as his first aripiprazole IM depot injection (this means that he was in the placebo group for Study 31-12-291). Therefore,

the most likely explanation for the elevated liver enzymes is the subject's history of alpha-1-antitrypsin deficiency.

7.3.4 Significant Adverse Events

For Studies 31-12-291 and 31-12-297, a review of the adverse event line listings did not reveal any events of particular concern that were not included under serious adverse events or adverse events leading to discontinuation (except for several cases of neutropenia, which are discussed in Section 7.4.2).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In Study 31-12-291, TEAEs reported at a rate of ≥5% in the aripiprazole IM depot group and at least twice the rate of placebo were the following: increased weight (16.8% vs. 7.0%), akathisia (11.4% vs 3.5%), injection site pain (5.4% vs. 0.6%), and sedation (5.4% vs 1.2%). None of these events were considered to be serious adverse events or were associated with discontinuation of treatment.

Table 10 presents TEAEs reported for ≥2% of aripiprazole IM depot subjects and at a greater incidence than placebo during the Active Treatment Phase.

Table 10 Incidence of TEAEs Occurring in ≥2% Aripiprazole IM Depot Subjects and at a Greater Incidence than Placebo by SOC and MedDRA Preferred Term (Safety Sample) for Study 31-12-291

		Aripiprazole IM Depot 400/300mg (N=167)	Placebo (N=172)
SYSTEM ORGAN CLASS	**MEDDRA PREFERRED TERM**	**n (%)**	**n (%)**
GASTROINTESTINAL DISORDERS	ABDOMINAL DISCOMFORT	4 (2.4)	2 (1.2)
	CONSTIPATION	16 (9.6)	12 (7.0)
	DIARRHOEA	5 (3.0)	4 (2.3)
	DRY MOUTH	6 (3.6)	4 (2.3)
	TOOTHACHE	9 (5.4)	8 (4.7)
	VOMITING	5 (3.0)	2 (1.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	FATIGUE	4 (2.4)	3 (1.7)
	INJECTION SITE PAIN	9 (5.4)	1 (0.6)
INFECTIONS AND INFESTATIONS	UPPER RESPIRATORY TRACT INFECTION	6 (3.6)	3 (1.7)
INVESTIGATIONS	WEIGHT DECREASED	6 (3.6)	4 (2.3)
	WEIGHT INCREASED	28 (16.8)	12 (7.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ARTHRALGIA	6 (3.6)	2 (1.2)
	BACK PAIN	7 (4.2)	4 (2.3)
	MUSCULOSKELETAL PAIN	5 (3.0)	2 (1.2)
	MYALGIA	6 (3.6)	1 (0.6)
NERVOUS SYSTEM DISORDERS	AKATHISIA	19 (11.4)	6 (3.5)
	DIZZINESS	6 (3.6)	3 (1.7)
	SEDATION	9 (5.4)	2 (1.2)
	TREMOR	5 (3.0)	1 (0.6)
PSYCHIATRIC DISORDERS	INSOMNIA	8 (4.8)	8 (4.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	COUGH	10 (6.0)	10 (5.8)
	NASAL CONGESTION	4 (2.4)	2 (1.2)

Note: A TEAE was defined as an AE that began after start of IMP treatment; or if the event was continuous from baseline and was serious, IMP-related, or resulted in death, discontinuation, interruption or reduction of IMP. Multiple occurrences of TEAE were counted once per specific MedDRA (version 15.0) preferred term. Subjects with TEAEs in multiple SOCs were counted only once towards the total.
Source: CT-8.2.4.3.

7.4.2 Laboratory Findings

In Study 31-12-291, samples for serum chemistry, hematology, and urinalysis were obtained at Screening and Week 12/ET. Additional urine and blood samples were collected for further evaluation of safety as warranted by the investigator's judgment. Subjects were instructed to fast for a minimum of 10 hours prior to the blood draws for assessment of safety, including at Screening. If non-fasting blood samples were obtained initially after the informed consent for determining trial eligibility, a fasting blood sample was to be drawn prior to randomization. The protocol specified the following laboratory assessments:

Hematology: White blood cell count with differential Red blood cell count Hematocrit Hemoglobin Platelet count	Serum Chemistry: ALT Alkaline phosphatase AST Bilirubin, total Blood urea nitrogen Calcium Cholesterol (total, LDL, and HDL) Chloride CPK Creatinine Gamma glutamyl transferase Glucose Hemoglobin A1c Insulin Lactate dehydrogenase Potassium Blinded Prolactin Protein, Total Sodium Triglycerides Uric acid
Urinalysis Specific gravity pH Glucose Protein Ketones Blood Microscopic exam (performed only if any part of the urinalysis is not negative)	Additional Tests: Urine pregnancy (WOCBP) Serum pregnancy (WOCBP) Urine drug screen Blood alcohol

HDL = high density lipoprotein; LDL = low density lipoprotein.

Of note, the criteria for laboratory values of potential clinical significance were reportedly reviewed by DPP and found to be acceptable except those for potassium and neutrophils. Based on our feedback, the original protocol specified values of potential clinical significance for potassium (standard unit mEq/L) were revised from ≤2.5 or ≥6.5 to ≤3.0 or ≥5.5. Those for neutrophils were revised from <15% to absolute neutrophils of ≤1.5 thous/µL.

Serum Chemistry

The sponsor reports that no clinically relevant mean changes from baseline in serum chemistry test results were observed during the Acute Treatment Phase. Also, no subjects met criteria for Hy's Law.

Serum chemistry test abnormalities reported as TEAEs were increased ammonia (1/172 [0.6%] placebo subjects), increased blood CPK (1/167 [0.6%] aripiprazole IM depot subjects and 1/172 [0.6%] placebo subjects), increased blood lactate dehydrogenase (LDH; 1/167 [0.6%] aripiprazole IM depot subjects), and increased hepatic enzyme (1/167 [0.6%] aripiprazole IM depot subject). The TEAE of increased blood CPK in the subject randomized to aripiprazole IM depot is described below:

- Subject 926S3038, a 45-year-old African-American male with schizophrenia, was randomized to treatment with aripiprazole IM depot. On Day 85 (Week 12), increased blood CPK was reported as a TEAE based on a total CPK of 1,035 U/L (normal range 24-250 U/L). This subject also had a high total CPK value at Screening (722 U/L). Two weeks after his Week 12 assessment, the subject's total CPK value increased to 1,769 U/L. Although his total CPK remained elevated, the value decreased to 1,241 U/L approximately 2 weeks after that (which was apparently his last visit). The subject did receive all 3 injections of aripiprazole IM depot 400 mg and completed the trial.

Clinically relevant serum chemistry values reported for ≥5% of aripiprazole IM depot subjects and at an incidence greater than placebo were high fasting triglycerides (33.6% vs. 30.8%), high fasting glucose (12.2% vs. 11.7%), high non-fasting glucose (9.1% vs. 0%), high potassium (5.6% vs. 3.5%), and high total CPK (5.6% vs. 4.9%). The incidence of potentially clinically relevant serum chemistry values is summarized in Table 11.

Table 11 Incidence of Serum Chemistry Values of Potential Clinical Relevance Based on High or Low (Safety Sample) for Study 31-12-291

			Aripiprazole IM Depot 400/300mg (N=167)			Placebo (N=172)		
	TEST		Ne	n	(%)	Ne	n	(%)
CHEMISTRY	ALKALINE PHOSPHATASE (U/L)	HIGH	142	0	(0.0)	142	0	(0.0)
	ALT (SGPT) (U/L)	HIGH	142	2	(1.4)	142	1	(0.7)
	AST (SGOT) (U/L)	HIGH	141	1	(0.7)	142	1	(0.7)
	BILIRUBIN, TOTAL (mg/dL)	HIGH	142	0	(0.0)	141	0	(0.0)
	CALCIUM (mg/dL)	LOW	142	0	(0.0)	142	0	(0.0)
		HIGH	142	0	(0.0)	142	0	(0.0)
	CHLORIDE (mEq/L)	LOW	142	1	(0.7)	142	0	(0.0)
		HIGH	142	0	(0.0)	142	0	(0.0)
	CHOLESTEROL, TOTAL, FASTING (mg/dL)	HIGH	131	12	(9.2)	120	15	(12.5)
	CPK, TOTAL (U/L)	HIGH	142	8	(5.6)	142	7	(4.9)
	CREATININE (mg/dL)	HIGH	142	0	(0.0)	142	1	(0.7)
	GLUCOSE (mg/dL)	HIGH	22	2	(9.1)	28	0	(0.0)
	GLUCOSE, FASTING (mg/dL)	HIGH	131	16	(12.2)	120	14	(11.7)
	HDL CHOLESTEROL, FASTING (mg/dL)	LOW	131	6	(4.6)	120	4	(3.3)
	LACTIC DEHYDROGENASE (U/L)	HIGH	135	0	(0.0)	139	0	(0.0)
	LDL-CHOL CALCULATION, FASTING (mg/dL)	HIGH	129	8	(6.2)	116	10	(8.6)
	POTASSIUM (mEq/L)	LOW	142	0	(0.0)	142	0	(0.0)
		HIGH	142	8	(5.6)	142	5	(3.5)
	SODIUM (mEq/L)	LOW	142	1	(0.7)	142	0	(0.0)
		HIGH	142	0	(0.0)	142	0	(0.0)
	TRIGLYCERIDES, FASTING (mg/dL)	HIGH	131	44	(33.6)	120	37	(30.8)
	UREA NITROGEN (mg/dL)	HIGH	142	1	(0.7)	142	1	(0.7)
	URIC ACID (mg/dL)	HIGH	142	1	(0.7)	142	0	(0.0)

Hematology

The sponsor states that no clinically relevant mean changes from baseline in hematology test results were observed during the Acute Treatment Phase. Hematology test abnormalities reported as TEAEs were neutropenia (1/167 [0.6%] aripiprazole IM depot subjects and 1/172 [0.6%] placebo subjects). The TEAE of neutropenia in the subject randomized to aripiprazole IM depot is described below:

- Subject 953S3250, a 59-year-old African-American male with schizophrenia, was randomized to treatment with aripiprazole IM depot. Prior medical history included athlete's foot, headaches, hepatitis C, hypertension, insomnia, periodontal disease, and poor dentition. Concomitant medications included clotrimazole, lorazepam, paracetamol, and zolpidem. On Day 87, mild neutropenia was reported based on the Week 12 laboratory result; the event was considered to be possibly related to IMP. The event was noted to be resolving at the end of the trial. The only other TEAE reported for this subject was agitation. He received all 3 injections of aripiprazole IM depot 400 mg and completed the study. He then entered the open-label continuation trial (Study 31-12-297). At Screening for Study 31-12-291, he had an absolute neutrophil count (ANC) of 2.09 thous/µL, which decreased to 1.23 thous/µL at Week 12. His WBC at Screening was 4.2 thous/µL, which decreased to 3.4 thous/µL at Week 12.

    - According to the report for Study 31-12-297, his ANC increased to 1.49 thous/µL on Day 29 (unscheduled visit), to 1.53 thous/µL at Week 12, and to 2.06 thous/µL at Week 24 (last observed value). The subject completed the open-label extension study, and the neutropenia was considered resolved at the subject's last visit. Of note, there were no other cases of neutropenia (based on lab values) in Study 31-12-297.

However, the only clinically relevant hematology value reported for ≥5% of aripiprazole IM depot subjects and at an incidence greater than placebo was in fact low absolute neutrophil count (5.7% vs 2.1%), defined as absolute neutrophils of ≤1.5 thous/µL. The incidence of potentially clinically relevant hematology values is summarized in Table 12.

Table 12 Incidence of Hematology Values of Potential Clinical Relevance Based on High or Low (Safety Sample) for Study 31-12-291

			Aripiprazole IM Depot 400/300mg (N=167)			Placebo (N=172)		
	TEST		Ne	n	(%)	Ne	n	(%)
HEMATOLOGY	EOSINOPHILS (%)	HIGH	140	1	(0.7)	141	1	(0.7)
	HEMATOCRIT (%)	LOW	139	1	(0.7)	140	0	(0.0)
	HEMOGLOBIN (g/dL)	LOW	140	2	(1.4)	141	1	(0.7)
	NEUTROPHILS, ABSOLUTE (THOUS/uL)	LOW	140	8	(5.7)	141	3	(2.1)
	PLATELET COUNT (cells/uL)	LOW	140	0	(0.0)	138	0	(0.0)
		HIGH	140	0	(0.0)	138	0	(0.0)
	WHITE BLOOD COUNT (THOUS/uL)	LOW	140	0	(0.0)	141	0	(0.0)
		HIGH	140	2	(1.4)	141	2	(1.4)

We requested the narratives for the 8 subjects in the aripiprazole IM depot group with absolute neutrophils of ≤1.5 thous/µL (this meets the generally accepted definition of neutropenia). The narrative for Subject 953S3250 is described above, as the investigator reported the low neutrophils as a TEAE. That subject's neutropenia began to resolve while continuing to receive aripiprazole IM depot every 4 weeks in the open-label extension study (31-21-297) and had completely resolved by Week 24. It is the opinion of this reviewer that his neutropenia was unlikely related to aripiprazole IM depot.

This reviewer examined the narratives for the other 7 subjects with neutropenia on aripiprazole IM depot in Study 31-12-291:

- Subject 913S3054: At Screening, this subject already was neutropenic (1.45 thous/µL). He received all three doses of aripiprazole IM depot over the 12-week double-blind treatment phase. During those 12 weeks, a number of unscheduled blood draws revealed an absolute neutrophil count (ANC) ranging from 1.24 to 1.67 thous/µL, with an ANC at Week 12 of 1.5 thous/µL. It is the opinion of this reviewer that the subject's neutropenia was unlikely related to aripiprazole IM depot.

- Subject 953S3433: At Screening, this subject was also already neutropenic (1.03 thous/µL). He received all three doses of aripiprazole IM depot over the 12-week double-blind treatment phase. At Week 12, his ANC was 1.23 thous/µL. He continued on to the open-label extension trial, at the end of which (Week 24) his ANC was 1.58 thous/µL. It is the opinion of this reviewer that the subject's neutropenia was unlikely related to aripiprazole IM depot.

- Subject 957S3407: No Screening ANC was available for this subject. He received all three doses of aripiprazole IM depot over the 12-week double-blind treatment phase. At Week 12, his ANC was 1.42 thous/µL. He continued on to the open-label extension trial (Study 31-12-297). At Week 12 of that trial, his ANC was 3.86 thous/µL, and at Week 24 it was 1.81 thous/µL. Even in light of this insufficient information, it is the opinion of this reviewer that the subject's neutropenia was unlikely related to aripiprazole IM depot.

- Subject 920S3076: At Screening, this subject had low neutrophils (but was, by definition, not neutropenic), with an ANC of 1.60 thous/µL. He received all three doses of aripiprazole IM depot over the 12-week double-blind treatment phase. At Week 12, he had an ANC of 1.29 thous/µL. An unscheduled blood draw one week later revealed an ANC of 1.15 thous/µL (with low platelets of 125,000 cells/µL and low WBCs of 3.2 thous/µL). There was apparently no further study follow-up. It is the opinion of this reviewer that the subject's neutropenia was probably related to aripiprazole IM depot.

- Subject 927S3237: At Screening, this subject had low neutrophils (but was, by definition, not neutropenic), with an ANC of 1.83 thous/µL. He received two of the three doses of aripiprazole IM depot over the double-blind treatment phase. At an early termination visit (due to "lack of efficacy"), he had an ANC of 0.95 thous/µL (with slightly low WBCs of 3.9 thous/µL). An unscheduled blood draw four days later revealed an ANC of 1.38 thous/µL. There was apparently no further study follow-up. The subject did receive a dose of haloperidol 20 mg at the early termination visit, but it is not clear if the dose was given before or after the blood draw. Even if the haloperidol had been given shortly before the blood draw, it could not have had an effect on white blood cells so quickly. It is therefore the opinion of this reviewer that the subject's neutropenia was probably related to aripiprazole IM depot.

- Subject 903S3468: At Screening, this subject had low neutrophils (but was, by definition, not neutropenic), with an ANC of 1.84 thous/µL. He received all three doses of aripiprazole IM depot over the 12-week double-blind treatment phase. At Week 12, he had an ANC of 1.09 thous/µL (with low WBCs of 3.0 thous/µL). An unscheduled blood draw five days later revealed an ANC of 1.56 thous/µL (with low WBCs of 3.6 thous/µL). Of note, on day 64 of the trial, the subject had an AE of "otitis externa", rated by the investigator as moderate. It is the opinion of this reviewer that the subject's neutropenia was probably related to aripiprazole IM depot.

- Subject 907S3016: At Screening, this subject had a normal ANC of 2.34 thous/µL. He received all three doses of aripiprazole IM depot over the 12-week double-blind treatment phase. At Week 12, he was neutropenic, with an ANC of 1.24 thous/µL. An unscheduled blood draw seven days later revealed an ANC of 2.31 thous/µL. It is the opinion of this reviewer that the subject's neutropenia was probably related to aripiprazole IM depot.

In summary, it is the opinion of this reviewer that 4 of the 8 cases of neutropenia were probably related to aripiprazole IM depot. This opinion is also based on the fact that, according to the sponsor, none of the subjects had a documented history of neutropenia. Also, looking at the narratives for the 4 cases, there are no previous medical conditions listed or adverse events reported that could explain the neutropenia.

This reviewer does not agree with the sponsor's inference that concomitant medications could have contributed to the neutropenia in these 4 subjects. Their concomitant medications during the 12-week double-blind treatment phase (as listed in the narratives) were only lorazepam and ibuprofen, which are both unlikely to cause neutropenia. Subject 907S3016 did receive quetiapine (which he had been taking at a dose of 200-800 mg daily for 6 years) until three days after Screening, but he is the only one of the 4 subjects who had an ANC at Screening in the normal range (albeit on the

lower end). Also, his neutropenia was detected at Week 12, meaning he had been off the quetiapine for at least three months at the time of that blood draw.

As far as we know, none of the cases of neutropenia were fatal, serious, caused a related disease, or led to discontinuation from the study. However, 2 of the 4 cases lacked further study follow-up visits to ensure that the neutropenia had resolved. Subject 920S3076 is particularly concerning, as his ANC continued to fall and reached 1.15 thous/µL as of the last measurement. However, this is balanced by the fact that all but one of the cases met the definition for mild neutropenia (ANC <1.5 but ≥1 thous/µL). Also, Subject 927S3237, the only one to go below 1 thous/µL (at 0.95 thous/µL) recovered to 1.38 thous/µL only four days later (at which point it had been 18 days since his second and last injection).

It is also encouraging that Subjects 903S3468 and 907S3016, who were newly neutropenic at Week 12, demonstrated ANCs >1.5 thous/µL at unscheduled blood draws 5-7 days later. The Week 12 visit is when these subjects, if they had been real world patients, would have been due for their next injection. So, one can infer that as their blood levels of aripiprazole started to slowly decline in the 7 days following the Week 12 visit, the ANCs quickly recovered.

Finally, it should be noted that although none of the subjects had a documented history of neutropenia, 3 of these 4 subjects had a low ANC at Screening (between 1.60 and 1.84 thous/µL, which is below normal but above the cut off for neutropenia). The other subject had a low normal baseline ANC of 2.35 thous/µL.

After evaluating all of the above information on these cases of neutropenia, this reviewer recommends making the following changes to the ABILIFY MAINTENA labeling:

- Edits to Section 5.7:

5.7 Leukopenia, Neutropenia, and Agranulocytosis

~~*Class Effect:*~~ In clinical trials and post-marketing experience, leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including ~~oral aripiprazole~~ABILIFY MAINTENA. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and a history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC / ANC or drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of ABILIFY MAINTENA at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue ABILIFY MAINTENA in patients with severe neutropenia (absolute neutrophil count $<1000/mm^3$) and follow their WBC counts until recovery.

- Under Section 6.1, adding a paragraph stating:

Laboratory Test Abnormalities

In the short-term, placebo-controlled trial in schizophrenia in adults taking ABILIFY MAINTENA, the incidence of neutropenia (absolute neutrophil count ≤1.5 thous/µL) for aripiprazole-treated patients was 5.7% vs. 2.1% for placebo. An absolute neutrophil count of <1 thous/µL (i.e. 0.95 thous/µL) was observed in only one aripiprazole-treated patient and resolved spontaneously without any associated adverse events [*see* Leukopenia, Neutropenia, and Agranulocytosis *(5.7)*].

Urinalysis

According to the sponsor, no clinically relevant mean change from baseline in urinalysis test results was observed during the Acute Treatment Phase. Abnormal urinalysis laboratory results reported as TEAEs were urinary tract infection (1/167 [0.6%]

aripiprazole IM depot subjects and 1/172 [0.6%] for placebo) and pollakiuria[3] (2/172 [1.2%] aripiprazole IM depot subjects and 0/172 [0.0%] for placebo).

The TEAEs of pollakiuria (Subjects 926S3022 and 944S3191) were further evaluated to assess for concomitant conditions (e.g., prostate enlargement [males] or overactive bladder [females]). Both subjects were African-American men who received 3 injections of aripiprazole IM depot 400 mg and completed the trial. Neither subject had a medical history or physical examination findings related to pollakiuria.

- Mild pollakiuria considered by the investigator to be unrelated to IMP was reported for Subject 926S3022 on Day 26. Other TEAEs reported for this subject included increased weight, flatulence, and musculoskeletal stiffness.
- Moderate pollakiuria was reported for Subject 944S3191 on Day 3; the event was considered by the investigator to be possibly related to IMP. The only other TEAE reported for this subject was fatigue.

The pollakiuria in both subjects resolved. Although the timeframe is unclear, this TEAE was clearly not bothersome enough for either subject to drop out of the trial.

Metabolic Parameters

(see Section 7.4.3 below for weight)

Effects on Lipids

In Study 31-12-291, no subject in either treatment group had a TEAE related to lipid parameters.

There was a higher incidence of clinically relevant increases from baseline for the aripiprazole IM depot group vs. placebo in:

- fasting total cholesterol (≥40 mg/dL), 12.3% vs. 5.5%
- fasting calculated LDL cholesterol (≥30 mg/dL), 14.2% vs. 8.7%
- fasting triglycerides (≥50 mg/dL), 19.7% vs. 18.2%

A lower incidence of clinically relevant decreases from baseline in fasting HDL (≥20 mg/dL) occurred in the aripiprazole IM depot group (7/122 [5.7%]) compared to placebo (12/110 [10.9%]).

The incidence of all the potentially clinically relevant shifts in lipids is summarized in Table 13. Note that for the borderline to high shifts in fasting total cholesterol and in

[3] Abnormally frequent urination

LDL, there is a significant signal. This is relevant as borderline baseline lipids are likely found in much of the real world patient population.

Table 13 Incidence of Treatment-emergent Clinically Relevant Changes in Lipids (Safety Sample) in Study 31-12-291

			Aripiprazole IM Depot 400/300mg (N=167)			Placebo (N=172)		
TEST	**BASELINE**	**POST BASELINE**	**Ne**	**n**	**(%)**	**Ne**	**n**	**(%)**
CHOLESTEROL, TOTAL, FASTING (mg/dL)	NORMAL <200	HIGH >=240	83	3	(3.6)	73	2	(2.7)
	BORDERLINE 200-<240	HIGH >=240	27	6	(22.2)	19	2	(10.5)
	NORMAL/BORDERLINE <240	HIGH >=240	110	9	(8.2)	92	4	(4.3)
	NORMAL <200	BORDERLINE/HIGH >=200	83	14	(16.9)	73	9	(12.3)
	ANY VALUE	INCREASED >=40	122	15	(12.3)	110	6	(5.5)
LDL-CHOL CALCULATION, FASTING (mg/dL)	NORMAL <100	HIGH >=160	59	1	(1.7)	51	1	(2.0)
	BORDERLINE 100-<160	HIGH >=160	52	5	(9.6)	41	1	(2.4)
	NORMAL/BORDERLINE <160	HIGH >=160	111	6	(5.4)	92	2	(2.2)
	NORMAL <100	BORDERLINE/HIGH >=100	59	14	(23.7)	51	12	(23.5)
	ANY VALUE	INCREASED >=30	120	17	(14.2)	103	9	(8.7)
HDL CHOLESTEROL, FASTING (mg/dL)	NORMAL >=40	LOW <40	104	14	(13.5)	87	11	(12.6)
	ANY VALUE	DECREASED >=20	122	7	(5.7)	110	12	(10.9)
TRIGLYCERIDES, FASTING (mg/dL)	NORMAL <150	HIGH >=200	98	7	(7.1)	78	4	(5.1)
	NORMAL <150	VERY HIGH >=500	98	1	(1.0)	78	0	(0.0)
	BORDERLINE 150-<200	HIGH >=200	11	3	(27.3)	15	4	(26.7)
	BORDERLINE 150-<200	VERY HIGH >=500	11	0	(0.0)	15	0	(0.0)
	NORMAL/BORDERLINE <200	HIGH >=200	109	10	(9.2)	93	8	(8.6)
	NORMAL/BORDERLINE <200	VERY HIGH >=500	109	1	(0.9)	93	0	(0.0)
	NORMAL <150	BORDERLINE/HIGH/VERY HIGH >=150	98	18	(18.4)	78	13	(16.7)
	NORMAL/BORDERLINE/HIGH <500	VERY HIGH >=500	121	1	(0.8)	109	2	(1.8)
	ANY VALUE	INCREASED >=50	122	24	(19.7)	110	20	(18.2)

Note: Ne is the total number of subjects with a specified baseline at least one postbaseline numeric result for the given laboratory test; n is the number of subjects with a potentially clinically relevant shift. The denominator for percentage calculation is Ne.
Source: CT-13.1.3.

Also, mean changes in fasting lipid values at Week 12 and at last visit are summarized in Table 14.

Table 14 Mean Change From Baseline in Fasting Lipid Parameters at Week 12 and at the Last Visit (Safety Sample) for Study 31-12-291

Parameter Treatment	n[a]	Baseline Mean[b]	Mean Change (SD) from Baseline at Week 12[b]
Cholesterol, total fasting (mg/dL)			
Aripiprazole IM depot 400 mg/300 mg	88	182.69	3.34 (31.46)
Placebo	59	190.56	−6.75 (33.51)
HDL cholesterol, fasting (mg/dL)			
Aripiprazole IM depot 400 mg/300 mg	88	53.39	−1.90 (10.09)
Placebo	59	54.14	−4.81 (12.56)
LDL cholesterol, fasting, calculated (mg/dL)			
Aripiprazole IM depot 400 mg/300 mg	87	103.43	4.13 (26.90)
Placebo	55	107.45	−1.56 (26.50)
Triglycerides, fasting (mg/dL)			
Aripiprazole IM depot 400 mg/300 mg	88	127.75	8.97 (61.57)
Placebo	59	139.10	6.73 (67.95)

Parameter Treatment	n[a]	Baseline Mean[b]	Mean Change (SD) from Baseline at Last Visit[b]
Cholesterol, total fasting (mg/dL)			
Aripiprazole IM depot 400 mg/300 mg	122	183.25	1.52 (31.00)
Placebo	110	189.11	−6.75 (33.88)
HDL cholesterol, fasting (mg/dL)			
Aripiprazole IM depot 400 mg/300 mg	122	54.75	−1.77 (9.64)
Placebo	110	53.65	−4.53 (14.02)
LDL cholesterol, fasting, calculated (mg/dL)			
Aripiprazole IM depot 400 mg/300 mg	120	103.63	1.53 (27.83)
Placebo	103	107.17	−2.95 (26.66)
Triglycerides, fasting (mg/dL)			
Aripiprazole IM depot 400 mg/300 mg	122	120.91	14.15 (73.47)
Placebo	110	140.54	9.65 (92.51)

[a] n = total number of randomized and treated subjects with both a baseline value and evaluation of the given parameter at the specific trial week.

[b] Baseline = the last evaluation prior to first injection; last visit = the last available post-baseline evaluation including early termination.

Source: CT-13.2.1

Effect on Glucose

No subject in either treatment group had a TEAE related to glucose metabolism. Diabetes mellitus (1/172 [0.6%] placebo subjects) and type 2 diabetes mellitus (1/167 [0.6%] aripiprazole IM depot subjects) were reported as TEAEs during the trial. The AE of diabetes mellitus was considered to be not likely related to IMP, while the AE of type 2 diabetes mellitus was considered to be possibly related to IMP. The incidence of potentially clinically relevant shifts in fasting glucose is summarized in Table 15.

Table 15 Incidence of Treatment-emergent Clinically Relevant Changes in Glucose (Safety Sample) in Study 31-12-291

			Aripiprazole IM Depot 400/300mg (N=167)			Placebo (N=172)		
TEST	BASELINE	POST BASELINE	Ne	n	(%)	Ne	n	(%)
GLUCOSE, FASTING (mg/dL)	NORMAL <100	HIGH >=126	88	7	(8.0)	75	0	(0.0)
	IMPAIRED 100-<126	HIGH >=126	33	1	(3.0)	33	3	(9.1)
	NORMAL/IMPAIRED <126	HIGH >=126	121	8	(6.6)	108	3	(2.8)
	ANY VALUE	INCREASED >=10	122	29	(23.8)	110	32	(29.1)

Note: Ne is the total number of subjects with a specified baseline and at least one postbaseline numeric result for the given laboratory test; n is the number of subjects with a potentially clinically relevant shift. The denominator for percentage calculation is Ne.
Source: CT-13.1.4.

At Week 12, there was a mean±SD increase from baseline in fasting glucose values in the aripiprazole IM depot group (9.82±41.97 mg/dL; n=88) and in the placebo group (0.69±19.59 mg/dL; n=59). At the last visit, there was a mean±SD increase from baseline in fasting glucose values in the aripiprazole IM depot group (7.10±36.99 mg/dL; n=122) and in the placebo group (1.03±20.88 mg/dL; n=110).

Of note, the sponsor does not appear to have peformed a categorical analysis (i.e. incidence of treatment-emergent clinically relevant changes) for the Hemoglobin A1c measurements.

7.4.3 Vital Signs

In Study 31-12-291, vital signs were taken at screening, randomization, and at each weekly study visit thereafter; they included body temperature, systolic and diastolic blood pressure, and heart rate. Orthostatic assessments of blood pressure and heart rate were made after the subject had been supine for at least 5 minutes and again after the subject had been sitting for 2 minutes. Body weight was measured at the screening, randomization, and Week 12 visits.

According to the sponsor, no clinically relevant mean changes from baseline were observed in vital sign parameters (excluding weight) during the Acute Treatment Phase. The mean changes in weight from baseline for the aripiprazole IM depot group were 3.5 kg at Week 12 and 2.8 kg at the last visit, compared to 0.8 kg at both Week 12 and at the last visit for the placebo group.

Except for the incidence of weight gain ≥7% (21.5% for the aripiprazole IM depot group vs. 8.5% for placebo), the incidences of potentially clinically relevant shifts in vital signs at any time during the study were similar between treatment groups. These results are summarized in Table 16.

Table 16 Incidence of Potentially Clinically Relevant Shifts in Vital Signs (Safety Sample) in Study 31-12-291

		Aripiprazole IM Depot 400/300mg (N=167)			Placebo (N=172)		
VITAL SIGN PARAMETER	ABNORMALITY	Ne	n	(%)	Ne	n	(%)
HEART RATE SUPINE (BEATS/MIN)	INCREASE >= 15 BPM	162	1	(0.6)	168	1	(0.6)
	DECREASE >= 15 BPM	162	1	(0.6)	168	0	(0.0)
HEART RATE SITTING (BEATS/MIN)	INCREASE >= 15 BPM	162	1	(0.6)	168	1	(0.6)
	DECREASE >= 15 BPM	162	1	(0.6)	168	0	(0.0)
SYSTOLIC SUPINE BP (mmHg)	INCREASE >= 20 mmHg	162	2	(1.2)	168	0	(0.0)
	DECREASE >= 20 mmHg	162	0	(0.0)	168	0	(0.0)
SYSTOLIC SITTING BP (mmHg)	INCREASE >= 20 mmHg	162	2	(1.2)	168	0	(0.0)
	DECREASE >= 20 mmHg	162	0	(0.0)	168	0	(0.0)
DIASTOLIC SUPINE BP (mmHg)	INCREASE >= 15 mmHg	162	0	(0.0)	168	2	(1.2)
	DECREASE >= 15 mmHg	162	0	(0.0)	168	0	(0.0)
DIASTOLIC SITTING BP (mmHg)	INCREASE >= 15 mmHg	162	1	(0.6)	168	2	(1.2)
	DECREASE >= 15 mmHg	162	0	(0.0)	168	1	(0.6)
ORTHOSTATIC HYPOTENSION		162	0	(0.0)	168	0	(0.0)
WEIGHT (kg)	WEIGHT GAIN >= 7%	144	31	(21.5)	141	12	(8.5)
	WEIGHT LOSS >= 7%	144	4	(2.8)	141	6	(4.3)
TEMPERATURE (°C)	>=37.8°C AND INCREASE >= 1.1°C	162	2	(1.2)	168	0	(0.0)

Note: Orthostatic hypotension defined as ≥20 mmHg decrease in SBP and ≥25 bpm increase in heart rate from supine to sitting/standing. Complete criteria for vital signs of potential clinical relevance are provided in CT-11.2.
Note: Ne is the total number of subjects with at least one postbaseline numeric result for the given vital sign parameter; n is the number of subjects with vital sign of potential clinical relevance. The denominator for percentage calculation is Ne.
Source: CT-14.1.

Of note, the sponsor's definition of orthostatic hypotension is included as a footnote to Table 16. Although this definition might be too narrow, during the Acute Treatment Phase, only 1/167 (0.6%) aripiprazole IM depot subjects vs. 2/172 (1.2%) placebo

subjects had TEAEs related to orthostasis. These events were pre-syncope in 1/167 (0.6%) aripiprazole IM depot subjects, syncope in 1/172 (0.6%) placebo subjects, and orthostatic hypotension in 1/172 (0.6%) placebo subjects.

7.4.4 Electrocardiograms (ECGs)

Twelve lead ECGs were obtained at Screening and Week 12 (or Early Termination). According to the sponsor, no clinically relevant mean changes from baseline in ECG parameters were observed during the Acute Treatment Phase.

Potentially clinically relevant ECG abnormalities reported for ≥1% of aripiprazole IM depot subjects (change relative to baseline of "not present" to "present") were premature ventricular beat (5/142, [3.5%]) and symmetrical T-wave inversion (5/142 [3.5%]); this is compared with 2/172 (1.4%) and 3/172 (2.1%), respectively, for the placebo group. Although these events met the criteria for potential clinical relevance, the investigator did not consider them to be clinically meaningful, and no aripiprazole IM depot subjects had a TEAE related to an abnormal ECG measurement.

QTc Intervals

No TEAEs related to QT intervals were reported in either treatment group during the Acute Treatment Phase. In addition, no subjects in either treatment group had a new onset QTc interval >500 msec or had a change from baseline QTc value that was ≥60 msec, regardless of the correction method used (i.e., QTcB, QTcF, QTcN). The incidence of ECG QTc categorical increases is summarized in Table 17.

Based on the sponsor's appendix table CT-15.2, at Week 12, there was a mean±SD change from the baseline QTcF measurement for the aripiprazole IM depot group of -6.2±15.2 msec (n=99) compared to -1.6±12.4 msec (n=66) for the placebo group. At the last visit, there was a mean±SD change from the baseline QTcF measurement for the aripiprazole IM depot group of -5.0±14 msec (n=142) compared to -2.8±12.5 msec (n=140) for the placebo group.

Table 17 Incidence of Categorical Increase in ECG-QTc (Safety Sample) in Study 31-12-291

		Aripiprazole IM Depot 400/300mg (N=167)			Placebo (N=172)		
CLASSIFICATION	CATEGORY	Ne	n	(%)	Ne	n	(%)
QTcB	NEW ONSET > 500 MSEC	142	0	(0.0)	140	0	(0.0)
	NEW ONSET > 480 MSEC	142	3	(2.1)	140	2	(1.4)
	NEW ONSET > 450 MSEC	142	8	(5.6)	140	11	(7.9)
	CHANGE >= 30, <60 MSEC	142	4	(2.8)	140	5	(3.6)
	CHANGE >= 60 MSEC	142	0	(0.0)	140	0	(0.0)
QTcF	NEW ONSET > 500 MSEC	142	0	(0.0)	140	0	(0.0)
	NEW ONSET > 480 MSEC	142	0	(0.0)	140	0	(0.0)
	NEW ONSET > 450 MSEC	142	3	(2.1)	140	4	(2.9)
	CHANGE >= 30, <60 MSEC	142	2	(1.4)	140	2	(1.4)
	CHANGE >= 60 MSEC	142	0	(0.0)	140	0	(0.0)
QTcN	NEW ONSET > 500 MSEC	142	0	(0.0)	140	0	(0.0)
	NEW ONSET > 480 MSEC	142	0	(0.0)	140	0	(0.0)
	NEW ONSET > 450 MSEC	142	3	(2.1)	140	4	(2.9)
	CHANGE >= 30, <60 MSEC	142	3	(2.1)	140	2	(1.4)
	CHANGE >= 60 MSEC	142	0	(0.0)	140	0	(0.0)

Note: New onset >500 (480/450) msec was defined as the incidence of QTc >500 (480/450) msec during treatment and QTc ≤500 (480/450) msec or not evaluated at baseline.
Note: Ne is the total number of randomized and treated subjects with at least one postbaseline numeric result for the given ECG parameter for "new onset" category or Ne is the total number of subjects with baseline and at least one postbaseline numeric result for "change" category; n is the number of subjects with specified categorical increase.
Source: CT-15.3.

7.4.5 Other Safety Variables (Topics of Special Interest)

Extrapyramidal Symptoms

During the Acute Treatment Phase, 32/167 (19.2%) aripiprazole IM depot subjects and 14/172 (8.1%) placebo subjects had EPS-related TEAEs. Except for akathisia and tremor, the incidence of EPS-related TEAEs was comparable between the treatment groups. Akathisia accounted for approximately half of the EPS-related TEAEs in the aripiprazole IM depot group during this trial. Akathisia was reported in 19/167 (11.4%) aripiprazole IM depot subjects compared to 6/172 (3.5%) placebo subjects. The incidences of EPS-related TEAEs are summarized in Table 18.

Table 18 EPS-related Treatment-emergent Adverse Events (Safety Sample) in Study 31-12-291

		Aripiprazole IM Depot 400/300mg (N=167)	Placebo (N=172)
CATEGORY	MEDDRA PREFERRED TERM	n (%)	n (%)
AKATHISIA EVENT	TOTAL	19 (11.4)	6 (3.5)
	AKATHISIA	19 (11.4)	6 (3.5)
DYSKINETIC EVENT	TOTAL	1 (0.6)	0 (0.0)
	TARDIVE DYSKINESIA	1 (0.6)	0 (0.0)
DYSTONIC EVENT	TOTAL	7 (4.2)	5 (2.9)
	DYSTONIA	3 (1.8)	1 (0.6)
	MUSCLE SPASMS	3 (1.8)	4 (2.3)
	TRISMUS	1 (0.6)	0 (0.0)
PARKINSONISM EVENT	TOTAL	9 (5.4)	4 (2.3)
	BRADYKINESIA	1 (0.6)	0 (0.0)
	COGWHEEL RIGIDITY	1 (0.6)	1 (0.6)
	EXTRAPYRAMIDAL DISORDER	2 (1.2)	2 (1.2)
	TREMOR	5 (3.0)	1 (0.6)
RESIDUAL EVENT	TOTAL	1 (0.6)	0 (0.0)
	MUSCLE TWITCHING	1 (0.6)	0 (0.0)
TOTAL		32 (19.2)	14 (8.1)
TOTAL EXCLUDING AKATHISIA		16 (9.6)	9 (5.2)

Note: A TEAE was defined as an AE that began after start of IMP treatment; or if the event was continuous from baseline and was serious, IMP-related, or resulted in death, discontinuation, interruption or reduction of IMP. Multiple occurrences of TEAE were counted once per specific MedDRA (version 15.0) preferred term. Subjects with multiple TEAE within the same category were counted only once towards the total for the category and overall.
Source: CT-8.2.5.1.

Prolactin

At Week 12, there were mean decreases from baseline in prolactin for the aripiprazole IM depot group (−6.4±13.5 ng/mL) and the placebo group (−1.1±14.5 ng/mL) overall and also for male and female subjects separately. Similar results were obtained when looking at the mean decreases from baseline to the last visit. These decreases are most likely the result of subjects being switched from an antipsychotic more likely to cause prolactin elevation (taken before the trial) to aripiprazole.

Assessment of Suicidality

The C-SSRS was administered at each study visit. The incidence of treatment-emergent suicidal ideation according to C-CASA category analyses was 6/167 (3.6%) for the aripiprazole IM depot subjects and 5/172 (2.9%) for placebo subjects. It appears that no subjects in either treatment group met criteria for any other treatment-emergent symptoms based on C-CASA analyses.

Injection Site Assessments

Nine (5.4%) of 167 aripiprazole IM depot and 2/172 (1.2%) placebo subjects experienced TEAEs related to the injection site. In the aripiprazole IM depot group, each injection site-related TEAE was injection site pain. Injection site related TEAEs reported by placebo subjects were injection site irritation (1/172, 0.6%) and injection site pain (1/172, 0.6%). Each injection site reaction was reported to be mild in severity.

Injection site assessments occurred at Day 0, Week 4, Week 8, and Week 12/ET. When a visit included administration of an injection, these assessments were completed after all other trial assessments (i.e.1 hour±15min post-injection).

- Subjects rated injection site pain using a visual analog scale (VAS). Possible ratings ranged from 0 mm (no pain) to 100 mm (unbearably painful).
- Investigators (or qualified designees) rated localized pain, swelling, redness, and induration at the most recent injection site using a 4-point categorical scale.

The mean pain score reported by aripiprazole IM depot subjects was 7.1 (SD 14.5; Max 99.0) after the first injection, 7.7 (SD 15.5; Max 91) after the third injection, 3.7 (SD 11.8; Max 82) at Week 12/ET, and 4.8 (SD 12.4; Max 82) at the last visit. The mean pain score reported by placebo subjects using the VAS was 5.7 after the first injection, 8.6 after the third injection, 4.2 at Week 12/ET, and 5.5 at the last visit.

Investigators rated pain, swelling, redness, and induration at the injection site as absent for most subjects in both treatment groups. However, one should note that many injection site reactions (especially induration) can take much longer than 1 hour to appear.

7.4.6 Immunogenicity

The incidence of immune- or allergy-related adverse events was not examined for Study 31-12-291.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In Study 31-12-291, the dose of aripiprazole IM depot was 400 mg q4 weeks with allowed decrease to 300 mg for safety and return to 400 mg for efficacy if needed (this is consistent with the current labeling). Due to this flexible dosing and the fact that a vast majority of subjects received only the 400 mg dose, it was not possible to assess dose dependency of any adverse events.

7.5.2 Time Dependency for Adverse Events

No analyses looking at the time dependency of adverse events, in particular tolerance to events and late onset events, is available.

7.5.3 Drug-Demographic Interactions

According to the sponsor, for Study 31-12-291, "the Breslow-Day test of the homogeneity of the AE odds ratios was performed across demographic subgroup categories for TEAEs experienced by ≥5% of aripiprazole IM depot subjects at ≥2 times the placebo rate (i.e., increased weight, akathisia, injection site pain, and sedation). No statistically significant differences in odds ratios (i.e., aripiprazole IM depot 400 mg/300 mg group vs placebo group) were noted between demographic subgroup categories for these TEAEs, supporting the current prescribing information that no dosage adjustment is needed on the basis of the patient's age, gender, and race." However, there were few subjects >65 year of age. Also, our statistical reviewer did not examine this analysis.

7.5.4 Drug-Disease Interactions

No new data are available on drug-disease interactions. The ABILIFY MAINTENA label currently includes class labeling on patients with concomitant illnesses.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were examined as part of the original ABILIFY review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new data on human carcinogenicity are available.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled trials with aripiprazole in pregnant women. Aripiprazole is excreted in human breast milk.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and efficacy of ABILIFY MAINTENA has not been established in individuals below the age of 18.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No new data on overdose, drug abuse potential, and withdrawal/rebound are available.

7.7 Additional Submissions / Safety Issues

The sponsor submitted a 120-day Safety Update on 9 June 2014. One of the reasons for requesting the update was that at the time of this sNDA submission, the cutoff date for Study 31-12-297 was 30 June 2013. However, the sponsor has since submitted the final report for that study (dated 10 May 2014), which was used for this review. The 120-day Safety Update also included, as requested, more recent literature searches (see Section 9).

8 Postmarketing Experience

Aripiprazole IM depot was approved for marketing by the U.S. FDA in Feb. 2013, by the EC in Nov. 2013, and by Health Canada in Feb. 2014. Postmarketing information through Feb 2014 is available. The Periodic Adverse Drug Event Reports (PADERS; most recent 26 March 2014) are being examined by the primary clinical reviewer for NDA 202971. However, in the opinion of the sponsor:

> A review of the safety data included in these PADERs did not reveal any new clinically relevant safety issues. The safety profile of aripiprazole IM depot remains similar to the profile established in the current reference safety documents. The benefit-risk profile of aripiprazole IM depot remains positive, and changes to the current prescribing information are not warranted at this time.

9 Appendices

9.1 Literature Review

At the time of this sNDA submission, the sponsor included a "Warrant Statement for Safety Literature Search" (including the CVs of those who conducted the search):

January 16, 2014

Aripiprazole IM Depot

Subject: Literature Search for Safety Information

This is to certify that the published literature has been searched from July 16, 2011 through July 17, 2013, and the search results have been reviewed in detail for safety information pertaining to Aripiprazole IM Depot. Based on this review, it has been determined that the literature contains no new adverse safety findings associated with Aripiprazole IM Depot.

Sincerely,

Uma Arunagiri, M.D.
Director, Clinical Safety and Pharmacovigilance
Otsuka Pharmaceutical Development & Commercialization, Inc.

The 120-day Safety Update contained two similar warrant statements. The first was dated 29 May 2014 and covered the periods 18 July 2013 to 31 December 2013. The second, also dated 29 May 2014, covered the periods 1 January 2014 to 31 March 2014 (but was signed instead by Matthew Butler, M.D., Associate Director, Clinical Safety and Pharmacovigilance).

9.2 Labeling Recommendations

The sponsor submitted a revised label for ABILIFY MAINTENA with track changes. We then made some significant revisions and added a number of comments, also using track changes. This version of the label will be entered into DARRTS separately and then sent to the sponsor. Some of the more significant proposed revisions from a clinical perspective are below.

Please also see the important recommend labeling changes under "Additional Comments/Concerns" in Section 6.1 as well as under "Hematology" in Section 7.4.2 of this review.

Highlights:

- Under "Indications and Usage", the proposed language was: "ABILIFY MAINTENA is an atypical antipsychotic indicated for the treatment of schizophrenia. (b) (4) This information belongs in Section 14.

- Under "Dosage and Administration," for the bullet "In conjunction with first dose, take 14 consecutive days of concurrent oral aripiprazole (10 mg to 20 mg) or current oral antipsychotic", we deleted "current oral antipsychotic." Only oral aripiprazole was used in Study 31-12-291.

Section 1: Indications and Usage

- We deleted the paragraph (b) (4) Information regarding efficacy should be placed in Section 14.

Section 2: Dosage and Administration

- (b) (4)

Section 6: Adverse Reactions

- We commented that the 2% table (b) (4) (as the sponsor had done)

Section 14: Clinical Studies

We rewrote the first part of this section due to a number of concerns, (b) (4) (b) (4) the short-term and longer-term (i.e. randomized withdrawal) pivotal efficacy studies should be described under Section 14. For an explanation of other changes made to this section of labeling, please see "Comments" under Section 6.1 of this review.

Below is the revised version of the first part of Section 14. Of note, for greater readability, we have accepted most of our and the sponsor's track changes.

2 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

9.3 Advisory Committee Meeting

No advisory committee meeting was held for the original NDA or is planned for this application.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PHILLIP D KRONSTEIN
11/16/2014

JING ZHANG
11/17/2014