Common Drug Review
Clinical Review Report

February 2017

Drug	Aripiprazole prolonged release suspension for injection (ABILIFY MAINTENA) (300 mg and 400 mg vial)
Indication	For the maintenance treatment of schizophrenia in stabilized adult patients.
Listing request	For the treatment of schizophrenia in patients judged to be at risk of non-adherence, or who demonstrate: • inadequate disease control or significant adverse events from one or more oral antipsychotic medications, or • inadequate disease control or significant adverse events from one or more conventional long-acting injectable antipsychotic agents
Manufacturer	Otsuka Canada Pharmaceutical Inc. & Lundbeck Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in psychiatry who provided input on the conduct of the review and the interpretation of findings.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

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ABBREVIATIONS

AAP	atypical antipsychotic
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ANCOVA	analysis of covariance
ARIP	aripiprazole
BARS	Barnes Akathisia Rating Scale
BPRS	Brief Psychiatric Rating Scale
CGI	Clinical Global Impression
CGI–S	CGI — Severity Scale
CGI–SS	CGI — Severity of Suicidality
CGI–I	CGI — Improvement Scale
CI	confidence interval
DAI	Drug Attitude Inventory
DB	double-blind
DIC	deviance information criterion
EPS	extrapyramidal symptoms
ESRS	Extrapyramidal Symptom Rating Scale
IAQ	Investigator's Assessment Questionnaire
IM	intramuscular
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	intention-to-treat
LAI	long-acting injectable
LOCF	last observation carried forward
MAQ	Medication Adherence Questionnaire
MCID	minimal clinically important difference
MTC	mixed treatment comparison
NMA	network meta-analysis
PANSS	Positive and Negative Syndrome Scale
PBO	placebo
PP	per-protocol
PSMQ	Patient Satisfaction with Medication Questionnaire
PSP	Personal and Social Performance
RCT	randomized controlled trial
SAE	serious adverse event
SAS	Simpson–Angus Scale
SE	standard error
SSC	Schizophrenia Society of Canada
SSO	Schizophrenia Society of Ontario

TAP	typical antipsychotics
TEAE	treatment-emergent adverse event
TOL	Tower of London
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Schizophrenia is a chronic mental illness that requires lifelong treatment.[1,2] Patients with schizophrenia are at an increased risk for numerous other medical illnesses, including suicide.[1] In Canada, the disease affects about 1% of the population,[2] or about 234,000 people (2004 data).[3] Antipsychotic medications form the cornerstone of treatment for schizophrenia.[2,4] Existing antipsychotic therapies fall into one of two classes: typical antipsychotics (TAP) and atypical antipsychotics (AAP). Both classes are considered equally effective in the treatment of positive symptoms. AAPs appear to be more effective in the treatment of negative symptoms.[1] TAPs are associated with an increased incidence of adverse events (AEs) known as extrapyramidal symptoms (EPS);[1] however, AAPs are associated with an increased risk of weight gain and metabolic AEs.[1]

Treatment of schizophrenia is typically divided into three phases: acute, stabilization, and maintenance. In the acute phase, the patient routinely experiences psychotic symptoms, with pharmacotherapy being initiated or adjusted as soon as possible.[5,6] The role of antipsychotic maintenance medication in symptom control and the prevention of relapse of schizophrenia is well established. The underlying principles, when considering pharmacotherapy, include the individualization of medication (including patient preferences), uncomplicated medication regimens, appropriate dosing, regular evaluation of responses in general (including AEs), and short- and long-term clinical efficacy and safety.

Aripiprazole prolonged release suspension for injection (Abilify Maintena, 300 mg or 400 mg intramuscularly [IM] monthly), an AAP, is approved by Health Canada for the maintenance treatment of schizophrenia in stabilized adult patients. The objective of this report is to evaluate the beneficial and harmful effects of aripiprazole IM for the maintenance treatment of schizophrenia in stabilized adult patients.

Results and Interpretation

Included studies

Two double-blind, randomized controlled trials (RCTs) (Study 246[7] and Study 247[8]) were identified that met the inclusion criteria for the review. Study 246 was a 52-week, placebo-controlled RCT consisting of a screening phase and four treatment phases: conversion, oral stabilization, IM stabilization, and double-blind, placebo-controlled RCT phases. The objective of the screening phase was to select patients with schizophrenia; the objective of the conversion phase was to convert any non-aripiprazole oral antipsychotic(s) to oral aripiprazole monotherapy. The objective of the oral or IM aripiprazole stabilization phases was to ensure patients responded well and were stabilized with oral or IM treatment. The objective of the RCT phase of Study 246 (N = 403) was to evaluate the efficacy of aripiprazole IM compared with placebo, as measured by time to relapse, in patients with schizophrenia who were stabilized on aripiprazole IM. Study 246 was designed as a withdrawal RCT — that is, patients stabilized with aripiprazole IM prior to randomization and were subsequently randomized to continue treatment with aripiprazole IM or placebo (i.e., withdrawal from aripiprazole IM). Study 247 was a 38-week, active-controlled, randomized noninferiority study. The study consisted of a screening phase and three treatment phases: conversion, oral stabilization, double-blind, and oral aripiprazole controlled RCT phases. The objective of the RCT phase of Study 247 (N = 662) was to evaluate the comparative efficacy, safety, and tolerability of aripiprazole IM compared with oral aripiprazole maintenance treatment in stabilized patients with schizophrenia. The primary outcomes were the time to relapse in Study 246 and the relapse rate in Study 247. The secondary outcomes assessed in both studies were remission,

response, scores on psychotic symptom scales (such as Positive and Negative Syndrome Scale [PANSS]), and Personal and Social Performance (PSP). Safety outcomes included mortality, hospitalization, serious treatment-emergent adverse events (TEAEs), overall treatment adverse events, and withdrawal due to adverse events (WDAE).

The main limitations of the body of evidence for aripiprazole IM used in the maintenance treatment of schizophrenia are the highly restricted population (i.e., stable patients); the withdrawal design used in Study 246 (i.e., patients assigned to placebo had treatment withdrawn); the absence of comparison between noninferiority analysis for the intention-to-treat (ITT) and per-protocol populations in Study 247; and the lack of head-to-head IM comparisons.

Efficacy
Very rare events of mortality, hospitalization, or suicidality were reported in both studies; therefore, the comparative effectiveness between treatment groups on these outcomes is inconclusive.

Quality of life was not assessed.

Regarding function capacity measured with PSP, the decline in social functioning from baseline was greater with placebo than with aripiprazole IM (–6.2 versus –1.7; $P = 0.0002$) in Study 246. However, the difference is not considered clinically meaningful because it only accounts for half of the minimal clinically important difference (MCID) of 10 points for PSP. In Study 247, no statistically significant difference was observed between aripiprazole IM and oral aripiprazole in terms of changes from baseline in PSP.

In Study 246, the remission rate was [redacted]% in the aripiprazole IM group versus [redacted]% for the placebo group (P = [redacted]). In Study 247, the remission rates were 48.8% and 53.2%, respectively ($P = 0.37$). In Study 246, the response rate was [redacted]% in the aripiprazole IM versus [redacted]% in the placebo group (P [redacted]). In Study 247, the rates were 89.8% and 89.4%, respectively ($P = 0.88$).

Relapse rate was the key secondary outcome in Study 246, but was the primary outcome in Study 247. Time to relapse was the primary outcome in Study 246, but was the secondary outcome in Study 247. In Study 246, both the interim and final analyses showed a significantly lower relapse rate compared with placebo (interim analysis, aripiprazole IM versus placebo: 10% versus 37%; $P < 0.0001$; final analysis: 10% versus 40%; $P < 0.0001$). The relapse rate dropped by 30% in the aripiprazole IM group compared with placebo (absolute risk difference: –0.30; 95% confidence interval [CI], –0.39 to –0.20; $P < 0.001$). For both treatment groups, the most common criterion for relapse was the Clinical Global Impression — Improvement Scale (CGI–I) + PANSS scores criterion. In Study 247, the between-group difference in relapse rates was −0.64% (95% CI, −5.26 to 3.99) by the end of week 26, which was lower than the predefined noninferiority margin, 11.5%. Therefore aripiprazole IM was found to be noninferior to oral aripiprazole. In terms of time to relapse, in Study 246, results from both the interim and final analyses showed that time to relapse was significantly shorter for patients in placebo compared with patients in aripiprazole IM ($P < 0.0001$). The median time to relapse in the placebo group was 209 days; however, the median time to relapse was not estimable for the aripiprazole group because the relapse rate was too low. The risk of relapse was approximately five times greater (hazard ratio [placebo versus aripiprazole IM]: 4.72; 95% CI, 2.81 to 7.94; $P < 0.0001$) with placebo than with aripiprazole IM.

In Study 246, symptoms, as measured using the PANSS total score, were worse with placebo versus aripiprazole IM. The adjusted mean change from baseline at week 52 for the PANSS total score, where a

higher score indicates symptom worsening, was statistically significantly lower in the aripiprazole IM group than in the placebo group (aripiprazole IM versus placebo: 1.43 versus 11.55; $P < 0.0001$). Since the MCID for PANSS was unspecified, the clinical significance of the difference between treatment groups observed above remains uncertain. In Study 247, the mean PANSS total score remained relatively stable across the RCT phase in both groups.

There were no statistically or clinically relevant between-group differences in changes from baseline in terms of cognition measured by Trail A score, Tower of London Item Scores, and University of Maryland: Letter–Number Span Total Score in either of the studies. However, based on discussion with the clinical expert involved in this review, these measures of cognition are limited in that they only measure part of cognition, and cognition could have been assessed in a more comprehensive way (such as by MATRICS Consensus Cognitive Battery [MCCB]).

Findings for patient satisfaction were similar between the two treatment groups in both Study 246 and Study 247. There were no statistically significant differences observed in the Medication Adherence Questionnaire (MAQ) Total Score, Drug Attitude Inventory Score, and Investigator's Assessment Questionnaire (IAQ) Total Score.

Based on a 52-week, single-arm extension study,[9] the effect of monthly administration of aripiprazole IM achieved in the RCT phase appeared to be maintained at 52 weeks.

In the absence of a head-to-head comparison between aripiprazole IM and other IM antipsychotics, the manufacturer submitted an indirect comparison of IM antipsychotic s. In terms of relapse and discontinuation from treatment, the mixed treatment comparison (MTC) submitted by the manufacturer reported that aripiprazole IM showed similar efficacy compared with other IM antipsychotics, including AAP or TAP IMs. However, the findings should be interpreted with caution, because the key limitations of the MTC were that the efficacy of different doses of different drugs (e.g., olanzapine IM and haloperidol IM) was assumed to be equal and therefore they were considered as a single treatment category. The efficacy of sub-therapeutic dosing in some included RCTs was considered equal to that of placebo.

Harms

Overall, serious adverse events (SAEs) were infrequent and comparable between treatment groups in both studies. In Study 246, the only SAE reported for ≥ 1% was psychotic disorder (1.5% in aripiprazole IM versus 3.0% in placebo). In Study 247, the SAEs reported for ≥ 1% of patients were schizophrenia (1.9% in aripiprazole IM versus 0.8% in oral aripiprazole) and psychotic disorder (1.5% versus 0.8%). The overall frequency of TEAEs was similar between treatment groups in both studies (aripiprazole IM versus placebo: 63.2% versus 61.9% in Study 246; aripiprazole IM versus aripiprazole oral: 83% versus 80% in Study 247). However, in Study 246, arthralgia, fatigue, sedation, and tremor occurred more frequently (with at least twice the frequency) in the aripiprazole IM group compared with placebo. The only TEAE reported by ≥ 5% of aripiprazole patients and with at least twice the frequency of the placebo group was tremor (aripiprazole IM versus placebo: 5.9% versus 1.5%). In Study 247, TEAEs reported for ≥ 5% of aripiprazole IM patients were also comparable to those in the oral aripiprazole group, with the exception of akathisia (aripiprazole IM versus aripiprazole oral: 10.6% versus 6.8%). In Study 246, numerically more patients on aripiprazole IM (6.4%) experienced potentially clinically important weight gain (≥ 7% gain) than those who received placebo (5.2%), while in Study 247, numerically more patients treated with oral aripiprazole (11.7%) experienced potentially clinically important weight gain than those who received aripiprazole IM (9.5%). Neither sexual dysfunction nor metabolic syndrome was

reported in either of the studies. In both studies, the most frequently reported AE that led to discontinuation was psychotic disorder. In Study 246, more patients discontinued due to an AE (13%) in the placebo group than did patients on aripiprazole IM (7%). In Study 247, discontinuation due to AE was similar in both treatment groups (aripiprazole IM versus aripiprazole oral: 8% versus 7%).

Pharmacoeconomic Summary

The manufacturer submitted a cost-minimization analysis comparing aripiprazole long-acting injectable (LAI) (300 mg or 400 mg every four weeks) with paliperidone LAI (50 mg, 75 mg, 100 mg, or 150 mg every four weeks) and risperidone LAI (12.5 mg, 25 mg, 37.5 mg, or 50 mg every two weeks) in adult patients with schizophrenia over a two-year time horizon from the perspective of a Canadian health ministry, with the second-year costs discounted at 5%.[10] The assumption of similar clinical efficacy, safety, and tolerability was based on a manufacturer-funded, unpublished network meta-analysis (NMA) that compared aripiprazole LAI with risperidone LAI, paliperidone LAI, olanzapine LAI, haloperidol LAI, oral risperidone, and oral aripiprazole.

Costs included in the analysis were drug costs, loading regimen costs (additional oral AAPs or higher LAI doses administered at initiation of LAI therapy to achieve therapeutic levels), and administration costs (physician service and pharmacy dispensing fees).

The CADTH Common Drug Review (CDR) identified a number of key limitations in the manufacturer's analysis, which included:

- Uncertainty in the clinical similarity and dose equivalency of aripiprazole LAI to paliperidone LAI or risperidone LAI
- Absence of oral AAPs as comparators, given the indicated population of stable patients
- Uncertainty in the assumptions and data sources used in the "real-world" multivariate sensitivity analysis.

At the submitted price of $456.18 per 300 mg or 400 mg single-use vial (daily cost $16.29 per day, if administered every four weeks), aripiprazole LAI costs substantially more than both oral antipsychotics, including oral aripiprazole (daily cost: $4.13 to $4.88) and long-acting TAPs. When compared with other available LAI AAPs, and when loading regimens and administration costs are considered, based on utilization data, aripiprazole LAI could generate savings ranging from $166 to $6,024 when compared with paliperidone LAI, and savings ranging from $820 to $4,071 when compared with risperidone LAI over two years. The clinical similarity of aripiprazole LAI to paliperidone LAI and risperidone LAI is uncertain due to limitations in the manufacturer's NMA, and the fact that doses used in clinical practice appeared somewhat higher than those used in clinical trials included in the NMA.

Conclusions

Findings in this review suggest that switching from oral aripiprazole (10 mg to 30 mg) to aripiprazole IM (400 mg or 300 mg) in the maintenance treatment of adult patients with schizophrenia stabilized on oral aripiprazole was noninferior to continuing oral aripiprazole in terms of relapse rate at week 26. In addition, for patients stabilized on aripiprazole IM, aripiprazole IM maintenance treatment significantly delayed the time to relapse compared with those who discontinued the treatment. The general safety profile of aripiprazole IM is similar to that of oral aripiprazole. A manufacturer-submitted MTC suggested no significant differences with respect to efficacy and safety between aripiprazole IM and other IM antipsychotics. However, the body of evidence for aripiprazole IM used in maintenance treatment of schizophrenia is limited by a highly restricted population; no evidence for patients

stabilized with other non-aripiprazole AAPs or inadequately controlled with oral or existing IM antipsychotics; the withdrawal design and early termination of the placebo-controlled study (Study 246); the absence of a per-protocol analysis in the noninferiority study; and the lack of head-to-head IM comparisons. As well, the included studies were not designed to adequately assess the key outcomes, including mortality, hospitalization, suicidality, quality of life, functional capacity, and cognition.

TABLE 1: SUMMARY OF RESULTS

Outcome	Study 246		Study 247	
	ARIP IM (N = 269)	**PBO (N = 134)**	**ARIP IM (N = 265)**	**Oral ARIP (N = 266)**
Remission Rate[a]				
n, N (%)	[redacted]	[redacted]	105/215 (48.8) *P* = 0.37	107/201 (53.2)
RR (CI)	[redacted]		0.92 (0.76 to 1.11)	
NNT	[redacted]		NE	
Response Rate				
n, N (%)	[redacted]	75/134 (55.97)	237/264 (89.8) *P* = 0.88	235/263 (89.4)
RR (CI)	[redacted]		1.00 (0.95 to 1.06)	
NNT	[redacted]		NE	
Relapse Rate				
n, N (%)	27/269 (10.0) *P* < 0.0001	53/134 (39.6)	22/265 (8.30) *P* = 0.86	21/266 (7.89)
RR (CI)	0.25 (0.17 to 0.38)		1.05 (0.59 to 1.87)	
ARD (CI)	–0.30 (–0.39 to –0.20);[b] *P* < 0.0001		−0.64 (−5.26 to 3.99);[c] *P* = 0.79	
NNT	4 (3, 5)		NE	
PANSS Total				
Baseline	54.41 (0.73)	54.35 (1.02)	57.94 (0.786)	56.57 (0.782)
Change From Baseline	1.43 (0.76)	11.55 (1.07)	−1.66 (0.718)	0.58 (0.714)
Between-Group Difference of Changes from Baseline	**−10.11 (−12.68, −7.54) *P* < 0.0001**	-	**−2.24 (−4.23, −0.25) *P* = 0.0272**	
Withdrawals				
n, N (%)	246/269 (91.4)	131/134 (97.8)	69/265 (26.0)	88/266 (33.1)
Serious TEAEs				
n, N (%)	11/269 (4.1)	9 /134 (6.7)	15/264 (5.7)	15/266 (5.6)
RR (CI)	0.61 (0.26 to 1.43)		1.19 (0.65 to 2.20)	
NNH	NE		NE	
WDAEs				
n, N (%)	11/269 (4.1)	13/134 (9.7)	13 /265 (4.9)	12/266 (4.5)
RR (CI)	0.42 (0.19 to 0.92)		0.69 (0.35 to 1.36)	
NNH	NE		NE	
Notable Harms(s)				

Outcome	Study 246		Study 247	
	ARIP IM (N = 269)	PBO (N = 134)	ARIP IM (N = 265)	Oral ARIP (N = 266)
EPS or EPS-Related Events				
n, N (%)	40/269 (14.9)	13/134 (9.7)	58/265 (21.9)	31/266 (11.7)
RR (CI)	1.53 (0.85 to 2.77)		1.88 (1.26 to 2.81)	
NNH	NE		NE	
Weight Gain				
n, N (%)	17/267 (6.4)	7/134 (5.2)	25/264 (9.5)	31/266 (11.7)
RR (CI)	1.22 (0.52 to 2.87)		0.81 (0.49 to 1.34)	
NNH	NE		NE	

AE = adverse event; ARD = absolute risk difference; ARIP = aripiprazole; CI = confidence interval; EPS = extrapyramidal symptoms; IM = intramuscular; n = number of patients with the events; N = total number of patients evaluated; NE = not estimable; NNH = number needed to harm; NNT = number need to treat; PANSS = Positive and Negative Syndrome Scale; PBO = placebo; RR = relative risk; SAE = serious adverse event; SE = standard error; MD = mean difference; WDAE = withdrawal due to adverse event.

[a] Remission included only those patients who stayed in the study for 6 months.

[b] The ARD for relapse rates in Study 246 was calculated by CADTH.

[c] The ARD for relapse rates in Study 247 was reported by the manufacturer and estimated using the Kaplan–Meier curve for time to impending relapse at day 182 (week 26) (see Table 20).

Note: RR, NNT, and NNH were calculated by CADTH.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Schizophrenia is a mental illness that requires lifelong treatment[1] and is associated with symptoms that include hallucinations, delusions, cognitive impairment, disorganized thoughts, social withdrawal, and amotivation.[2] The worldwide prevalence is 0.5% to 1.5%.[4] In Canada, it affects about 1% of the population[2] or about 234,000 people (2004 data).[3] Schizophrenia is a chronic or recurrent illness; patients are at an increased risk for numerous other medical illnesses, as well as suicide, substance abuse, homelessness, and unemployment.[1]

1.2 Standards of Therapy

Antipsychotic medications form the cornerstone of treatment for schizophrenia, as they target the characteristic symptoms of the disease.[2,4] These symptoms can be positive or negative in nature.[4] The positive symptoms reflect a distortion or abundance of normal functions and negative symptoms reflect a loss or restriction of normal functions.[11]

Existing antipsychotic therapies fall into one of two classes. The typical antipsychotics (TAP) (also known as conventional antipsychotics or neuroleptics) are of the first generation antipsychotic class. These drugs have antagonistic activity at dopamine D_2 receptors[12] and are associated with an increased incidence of extrapyramidal (EPS) side effects.[1] The atypical or second-generation antipsychotics (AAP) have antagonistic activity at both D_2 receptors and serotonin ($5\text{-}HT_{2a}$) receptors. The risk of EPS incidence appears to be reduced with AAPs; however, differences between TAP and AAP drugs can be variable in this respect.[13,14] Both classes are considered equally effective in the treatment of positive symptoms. AAPs appear to be more effective in the treatment of negative symptoms;[1] however, their use is also associated with an increased risk of weight gain and metabolic adverse effects.[1]

Treatment of schizophrenia is typically divided into three phases: acute, stabilization, and maintenance. In the acute phase, the patient is routinely experiencing psychotic or positive symptoms, with pharmacotherapy being initiated or adjusted as soon as possible.[5,6] Oral medications represent first-line treatment, although the formulations administered may differ under certain circumstances (e.g., nonadherence, need for rapid control of symptoms). Examples of alternative formulations that may be used in these situations include rapidly dissolving tablets of olanzapine or risperidone, sublingual asenapine, liquid haloperidol, intravenous or intramuscular (IM) haloperidol, paliperidone palmitate IM, and risperidone IM.

The role of antipsychotic maintenance medication in symptom control and prevention of relapse of schizophrenia is well established. The underlying principles for the administration of pharmacotherapy include the individualization of medication (including patient preferences), simple medication regimens, appropriate dosing, attention to side-effect profiles, regular evaluation of responses (including adverse events), and short- and long-term clinical efficacy, safety, and tolerability.[1]

1.3 Drug

Aripiprazole for prolonged release injectable suspension (Abilify Maintena), 300 mg or 400 mg, IM injection in the treatment of schizophrenia.

Indication under review
For the maintenance treatment of schizophrenia in stabilized adult patients.
Listing criteria requested by sponsor
For the treatment of schizophrenia in patients judged to be at risk of non-adherence, or who demonstrate: • Inadequate disease control or significant adverse events from one or more oral antipsychotic medications, or • Inadequate disease control or significant adverse events from one or more conventional long-acting injectable antipsychotic agents.

TABLE 2: KEY CHARACTERISTICS OF ARIPIPRAZOLE IM, PALIPERIDONE PALMITATE, RISPERIDONE IM, AND ORAL ARIPIPRAZOLE

	Aripiprazole IM	Paliperidone Palmitate IM	Risperidone IM	Oral Aripiprazole
Mechanism of Action	Effects may be mediated through a dose-dependent combination of partial agonist activity at D2 and 5-HT1A receptors and antagonist activity at 5-HT2A receptors.	Effects may be mediated through a combination of D2 and 5-HT2A receptor antagonism. Antagonism at receptors other than D2 and 5HT2A may explain some of the other effects.	Binds with high affinity to 5-HT2, D2, and alpha-1 adrenergic receptors. Binds with lower affinity to the alpha-2 adrenergic and histamine H1 receptors. Risperidone does not bind to dopamine D1 and has no affinity (when tested at concentrations > 10^{-5} M) for muscarinic cholinergic receptors.	Effects may be mediated through a dose-dependent combination of partial agonist activity at D2 and 5-HT1A receptors and antagonist activity at 5-HT2A receptors.
Indication[a]	For the maintenance treatment of schizophrenia in stabilized adult patients	For the treatment of schizophrenia	For the management of schizophrenia	For the treatment of schizophrenia and related psychotic disorders in adults
Route of Administration	IM injection	IM injection	IM injection	Oral

	Aripiprazole IM	Paliperidone Palmitate IM	Risperidone IM	Oral Aripiprazole
Recommended Dose	400 mg, once monthly	Initial dose: 150 mg on day 1 and 100 mg on day 8 (one week later) Monthly maintenance dose: 75 mg (can be adjusted from 50 mg to 150 mg)	25 mg every 2 weeks	Starting and target dose: 10 mg or 15 mg/day, once daily; maximum daily dose should not exceed 30 mg/day
Serious Side Effects or Safety Issues	Increased mortality in elderly patients with dementia			

D2 = dopamine type 2; IM = intramuscular; LAI = long-acting injection; 5HT1 = serotonin type 1; 5HT2 = serotonin type 2.
[a] Health Canada indication under this review.
Source: Product monographs,[15-18] Kane et al.[19]

2. OBJECTIVES AND METHODS

2.1 Objectives

To evaluate the beneficial and harmful effects of aripiprazole prolonged release injectable suspension (Abilify Maintena, 300 mg or 400 mg vials) for the maintenance treatment of schizophrenia in stabilized adult patients.

2.2 Methods

Studies selected for inclusion in the systematic review included the pivotal studies provided in the manufacturer's submission to the CADTH Common Drug Review (CDR) as well as those meeting the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Stabilized adult patients with schizophrenia
Intervention	Aripiprazole prolonged release injectable suspension 300 mg or 400 mg IM injection monthly
Comparators	Paliperidone palmitate, IM injection, monthly Risperidone, IM injection, biweekly Oral aripiprazole Other IM antipsychotics Other oral AAPs
Outcomes	**Efficacy outcomes** • Mortality • Hospitalization • Suicidality • Quality of life and health-related quality of life • Functional capacity (e.g., PSP, employment) • Remission • Response

	• Relapse • Symptoms (e.g., positive, negative, global, cognition) • Other outcomes, such as adherence to or persistence with therapy, patient satisfaction with medication **Harms outcomes:** • SAEs • AEs • WDAEs • Notable AEs: Movement disorders (EPS, tardive dyskinesia, etc.), weight gain, sexual dysfunction, metabolic syndrome.
Study Design	Published and unpublished RCTs

AAP = atypical antipsychotics; AEs = adverse events; AP = antipsychotics; EPS = extrapyramidal symptoms; IM = intramuscular; PSP = Personal and Social Performance; RCTs = randomized controlled trials; SAEs = serious adverse events; WDAEs = withdrawals due to adverse events.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records & daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's Medical Patient Headings (MeSH), and keywords. The main search approach combined terms for aripiprazole and once-monthly injections.

No filters were applied to limit retrieval by study type. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on July 29, 2014. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on November 19, 2014. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): health technology assessments, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, and databases. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

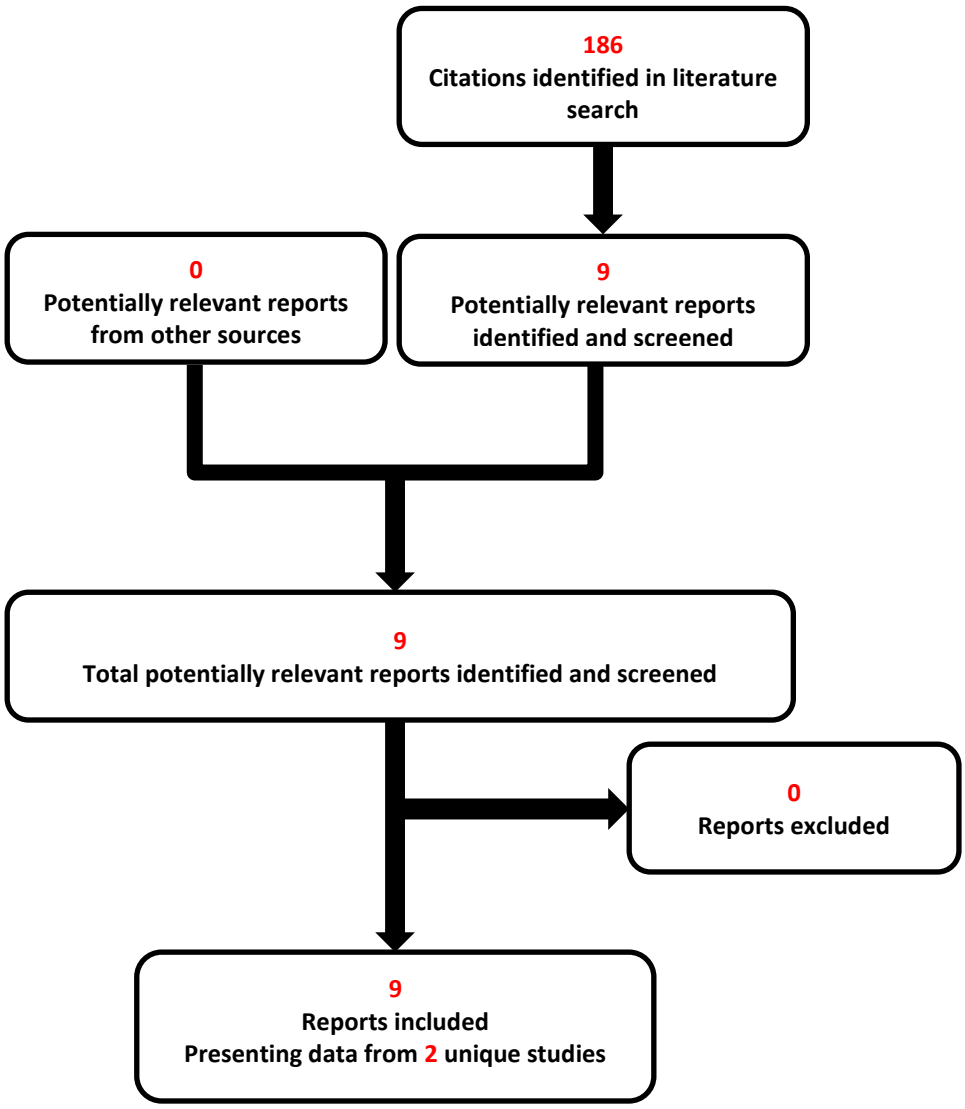


TABLE 4: DETAILS OF INCLUDED STUDIES

		Study 31-07-246[a]	Study 31-07-247
DESIGNS & POPULATIONS	**Study Design**	DB withdrawal RCT, placebo-controlled	DB RCT, active-controlled, NI trial
	Locations	108 sites in the US, Mexico, Argentina, Bulgaria, Romania, Serbia, Slovakia, Russia, India, Taiwan, Malaysia, and the Philippines	98 enrolling sites of 105 initiated sites in Austria, Belgium, Bulgaria, Chile, Croatia, Estonia, France, Hungary, Italy, South Korea, Poland, South Africa, Thailand, and the US
	Randomized (N)	403	662

	Inclusion Criteria	• Age 18 to 60 years, inclusive
		• Diagnosis of SCZ by DSM-IV-TR criteria for at least 3 years prior to screening
		• Conversion to oral ARIP 4 to 6 weeks
		• Meet stability criteria[b] for at least 4 consecutive weeks on oral aripiprazole
		• To be randomized into the double-blind comparison phase, patients must:
		  ○ Meet stability criteria for at least 12 consecutive weeks on IM depot prior to being randomized in the DB RCT trial
			• Age 18 to 60 years, inclusive
			• Diagnosis of SCZ by DSM-IV-TR criteria for at least 3 years prior to screening
			• Conversion to oral ARIP 4 to 6 weeks
			• To be randomized into the double-blind comparison phase, patients must:
			  ○ Meet stability criteria[b] for at least 8 consecutive weeks on oral aripiprazole prior to being randomized in the DB RCT trial

	Exclusion Criteria	• Patients with a current DSM-IV-TR diagnosis other than schizophrenia • Patients with a history of failure with clozapine treatment or response to clozapine treatment only • Patients with other medical conditions, such as known hypothyroidism • Patients who had more than one excursion from stability criteria after achieving a response to single-blind aripiprazole IM treatment • Patients who had not achieved stability criteria on aripiprazole IM depot for 12 consecutive weeks (6 consecutive biweekly visits) by week 36 of the IM Stabilization Phase or who had consecutive excursions at weeks 26 and 28	• Patients with a current DSM-IV-TR diagnosis other than schizophrenia • Patients with a history of failure with clozapine treatment or response to clozapine treatment only • Patients with other medical conditions, such as known hypothyroidism • Patients who had more than one excursion from stability criteria after achieving a response to oral aripiprazole • Patients who had not achieved stability criteria on oral aripiprazole for 8 consecutive weeks
DRUGS	**Intervention**	Aripiprazole, IM 400 mg, monthly	Aripiprazole, IM 400 mg,[c] monthly
	Comparator(s)	Placebo (withdrawal from ARIP IM)	Oral aripiprazole, 10 mg to 30 mg daily
	Phase		
	Screen	–42 days to –2 days	–42 days to –2 days
	Conversion Phase	4 to 6 weeks	4 to 6 weeks

		Study 31-07-246[a]	Study 31-07-247
	Oral Aripiprazole Stabilization	4 to 12 weeks	8 to 28 weeks
	Aripiprazole IM Stabilization	12 to 36 weeks	NA
	Double-Blind	52 weeks	38 weeks
	Follow-up	26 weeks	Up to 26 weeks (for oral group: 4 weeks)
OUTCOMES	**Primary End Point**	Time to relapse	Relapse rate
OUTCOMES	**Other End Points**	Relapse rate Symptom score Psychosocial functioning AEs	Time to relapse Symptom score Psychosocial functioning AEs
NOTES	**Publications**	Kane et al., 2012[19] Fleishhacker et al., 2013[20]	Fleishhacker et al., 2014[21]

AE = adverse event; ARIP = aripiprazole; DB = double-blind; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; IM = intramuscular; NI = noninferiority; RCT = randomized controlled trial; SCZ = schizophrenia.
[a] Early-terminated trial.
[b] Stabilization was defined as meeting ALL of the following criteria for 8 to 28 consecutive weeks in Study 247 and 12 to 36 weeks in Study 246, including at the last visit prior to entering the DB RCT phase: 1) outpatient status; 2) Positive and Negative Syndrome Scale (PANSS) total score ≤ 80; 3) lack of specific psychotic symptoms as measured by a score of ≤ 4 on the following PANSS items: conceptual disorganization, suspiciousness, hallucinatory behaviour, unusual thought content; 4) Clinical Global Impression (CGI) Severity ≤ 4 (moderately ill); 5) CGI — Severity of Suicidality ≤ 2 (mildly suicidal) on Part 1 and ≤ 5 (minimally worsened) on Part 2.
[c] The randomized phases included three treatment groups: aripiprazole IM 400 mg monthly; aripiprazole IM 50 mg monthly; and oral aripiprazole 10 mg to 30 mg daily. However, the results of aripiprazole IM 50 mg monthly will not be reported in this review because it is not a Health Canada–approved dose.
Note: Six additional reports were included: CADTH Common Drug Review submission,[22] Clinical Study Reports,[7,8] FDA reports,[23,24] Health Canada report.[25]
Source: Clinical Study Reports.[7,8]

3.2 Included Studies

3.2.1 Description of studies

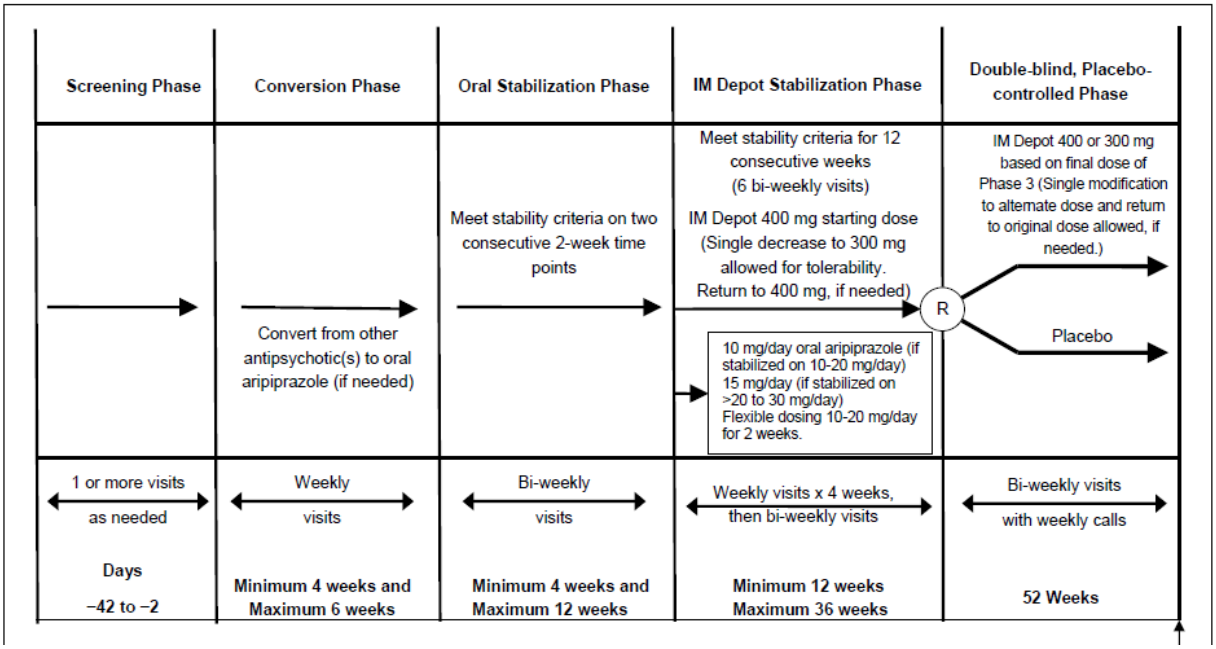
Two double-blind, randomized controlled studies (Study 246[7] and Study 247[8]) were identified that met the inclusion criteria for the review.

Study 246 was a randomized, double-blind, placebo-controlled trial consisting of a screening phase and four treatment phases: conversion, oral stabilization, IM injection stabilization, and double-blind, placebo-controlled, randomized controlled trial (RCT) phases. A schematic of the trial design is provided in Figure 2 and Figure 3. A brief summary of the trial design by phase follows. Screening phase: eligibility was determined during a screening phase of two to 42 days. Eligible candidates for this phase were adult patients with schizophrenia. Conversion phase: the objective was to convert any non-aripiprazole oral antipsychotic(s) to oral aripiprazole monotherapy by cross-titrating and to achieve a monotherapy target dose of 10 mg or 15 mg per day oral of aripiprazole at week 4 and no later than week 6. During the oral stabilization phase (four to 12 weeks), patients were assessed biweekly and stabilized on an oral dose of aripiprazole ranging from 10 mg to 30 mg daily. Stability was defined as the fulfillment of all criteria specified in Table 4 for four consecutive weeks. IM stabilization phase: patients switched to

aripiprazole IM monthly for 12 to 36 weeks in a single-blind fashion. All patients received aripiprazole IM 400 mg (or 300 mg if necessary) as the initial dose in the IM stabilization phase, irrespective of the final oral dose in the oral stabilization phase. During the IM stabilization phase, oral dosing with aripiprazole (10 mg to 20 mg per day) continued for the first two weeks, concomitant to the first IM injection in the IM phase. Patients who were stabilized with aripiprazole IM were randomly assigned in a 2:1 ratio to treatment with aripiprazole IM or placebo (i.e., withdrawal from aripiprazole IM), respectively. It was projected that the target number of relapse events (125) could be observed with 225 patients randomized into this phase. Any signs of relapse (see Section 3.2.4, Outcomes, for relapse criteria) resulted in withdrawal from the trial. The primary outcome was time to relapse. The trial design included two pre-specified interim analyses for efficacy in order to minimize continued exposure to placebo and the risk of relapse; one was to occur after accrual of 50% of the 125 targeted events (63 events) and the second was to occur after accrual of 75% of the events (94 events).

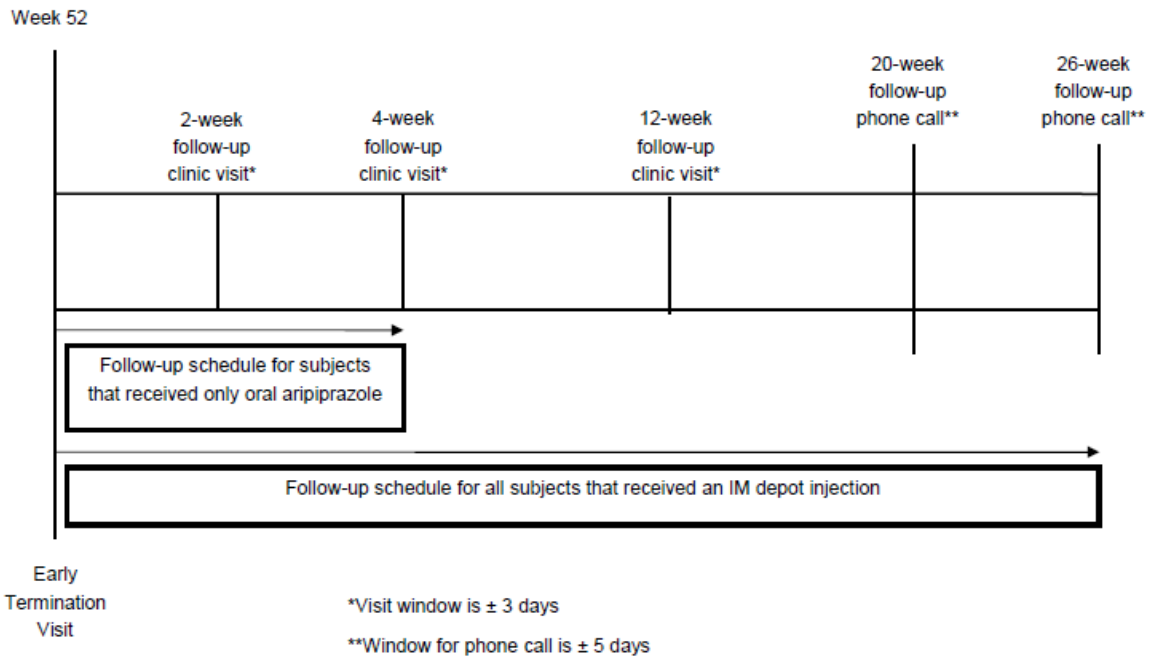
Study 247 was a 38-week, randomized, double-blind, active-controlled, noninferiority study to evaluate the efficacy, safety, and tolerability of aripiprazole IM as maintenance treatment in patients with schizophrenia. The study consisted of a screening phase and three treatment phases: conversion, oral stabilization, and double-blind, active-controlled RCT phases. A schematic of the trial design is provided in Figure 4 and Figure 5. The screen phase, conversion phase, and oral aripiprazole stabilization phase processes are similar to those in Study 246, except that the oral stabilization phase lasted at least eight weeks. After stabilization with oral aripiprazole, eligible patients who were stabilized with aripiprazole IM were randomized (2:2:1) to aripiprazole IM 400 mg monthly (i.e., switched from aripiprazole oral to IM); oral aripiprazole (i.e., stayed in oral aripiprazole, 10 mg to 30 mg per day); or aripiprazole IM 50 mg once monthly. In this review, aripiprazole 50 mg once monthly was not reported because it is not the Health Canada–recommended dose (i.e., a sub-therapeutic dose). Patients treated with aripiprazole 400 mg once monthly received concomitant oral aripiprazole (10 mg to 20 mg) for the first two weeks. The primary outcome was the relapse rate at week 26. It should be emphasized that the primary outcome was changed from time to relapse at week 38 to Kaplan–Meier estimated relapse rates at week 26 after the trial started, due to an observed very low relapse rate. The objective of the primary efficacy analysis was to demonstrate noninferiority of aripiprazole IM depot (400 mg or 300 mg) to oral aripiprazole tablets (10 mg to 30 mg) with regard to relapse.

FIGURE 2: STUDY 246 TRIAL DESIGN SCHEMATIC — SCREEN AND TREATMENT



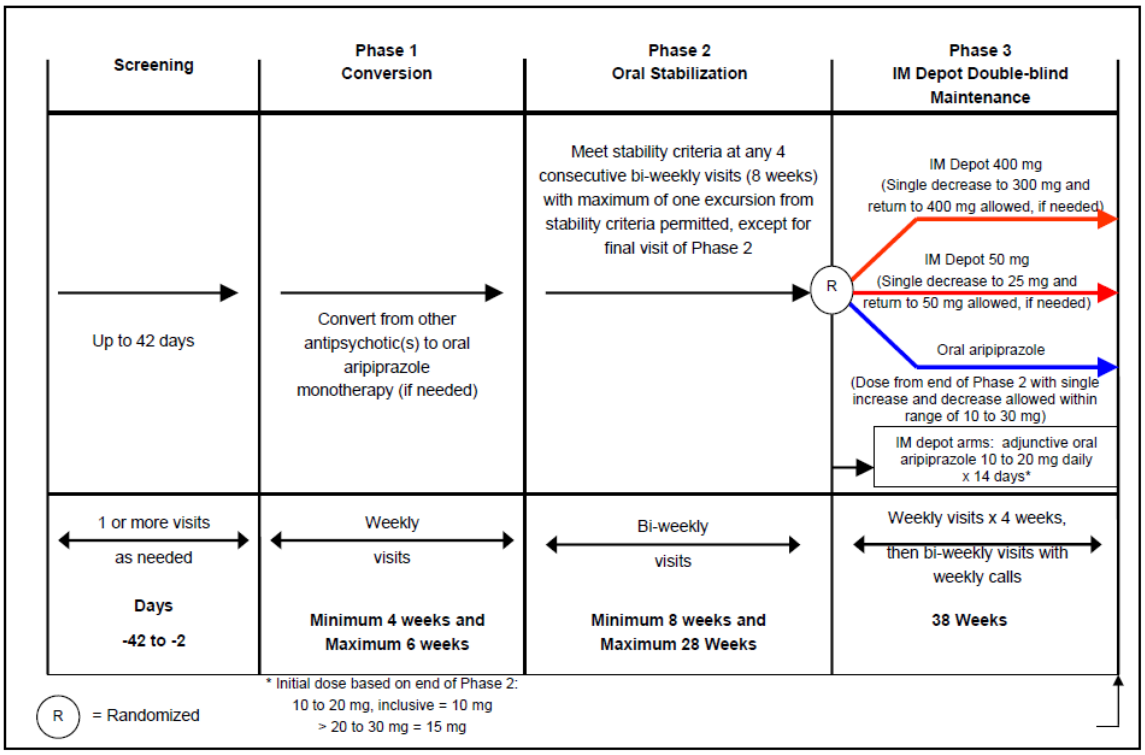
IM = intramuscular; R = randomized.
Source: Clinical Study Reports.[7]

FIGURE 3: STUDY 246 TRIAL DESIGN SCHEMATIC — FOLLOW-UP



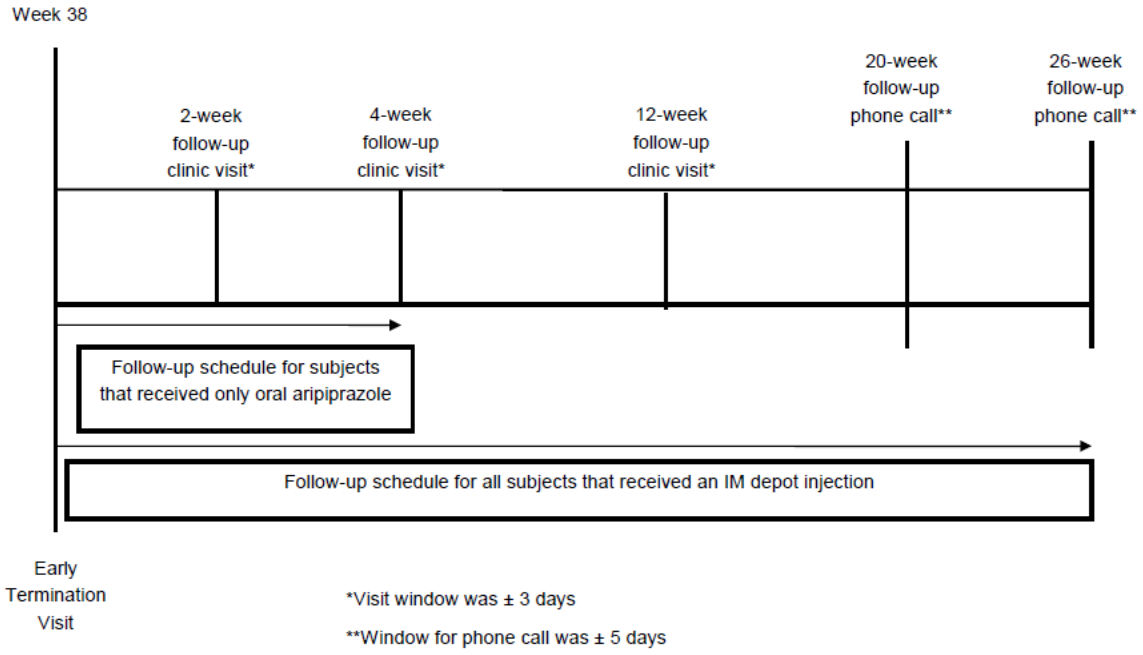
IM = intramuscular.
Source: Clinical Study Reports.[7]

FIGURE 4: STUDY 247 TRIAL DESIGN SCHEMATIC — SCREEN AND TREATMENT



IM = intramuscular.
Source: Clinical Study Reports.[8]

FIGURE 5: STUDY 247 TRIAL DESIGN SCHEMATIC — FOLLOW-UP



IM = intramuscular.
Source: Clinical Study Reports.[8]

3.2.2 Populations

a) Inclusion and exclusion criteria

The inclusion criteria for the screening, oral conversion, and oral stabilization phases were similar in Study 246 and Study 247, which included age of 18 to 60 years; diagnosis of schizophrenia for three or more years; responded to antipsychotic treatment (other than clozapine) in the past year. Stabilization was defined as meeting the following criteria: outpatient status; Positive and Negative Syndrome Scale (PANSS) total score ≤ 80 with a score of ≤ 4 (moderate) on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behaviour, and unusual thought content; Clinical Global Impression — Severity (CGI–S) score ≤ 4 (i.e., at most, moderately ill); and Clinical Global Impression—Severity of Suicidality (CGI–SS) score ≤ 2 (i.e., at most mildly suicidal) on Part 1, and ≤ 5 (i.e., at most, minimally worsened) on Part 2. The inclusion criteria for the RCT phase were stabilized with aripiprazole IM for 12 to 36 weeks for Study 246; and with oral aripiprazole for 8 to 28 weeks for Study 247. The key exclusion criteria included uncontrolled thyroid function abnormalities, a history of seizures, or neuroleptic malignant syndrome. Individuals were also excluded if they were diagnosed with substance dependence, including dependency on alcohol and benzodiazepines, but excluding nicotine and caffeine.

b) Baseline characteristics

The term "baseline" in this review refers to the last available measurement prior to or on the start day of RCT phase dosing. The demographic and baseline (i.e., at the end of the aripiprazole IM stabilized phase in Study 246 or the oral stabilized phase in Study 247) characteristics of the RCTs are shown in Table 5 and Table 6. Overall, in both studies, the demographic characteristics were similar for patients in both treatment groups, except more Caucasian patients were included in the placebo arm compared with the aripiprazole arm in Study 246. The mean age of the randomized patients was 40 to 42 years

(range: 18 to 61 years). The majority of patients were male (59 % to 63%) and Caucasian (57% to 68%). The baseline psychiatric characteristics were similar between treatment groups in the randomized population.

TABLE 5: SUMMARY OF DEMOGRAPHIC CHARACTERISTICS

Characteristics	Study 246		Study 247	
	ARIP IM (N = 269)	PBO (N = 134)	ARIP IM (N = 265)	Oral ARIP (N = 266)
Sex, n (%)				
Male	162 (60.2)	79 (59.0)	160 (60.4)	168 (63.2)
Female	107 (39.8)	55 (41.0)	105 (39.6)	98 (36.8)
Age (years)				
Mean (SD)	40.1 (11.0)	41.7 (10.5)	41.7 (10.4)	41.2 (10.8)
Range	18 to 60	20 to 61	18 to 60	18 to 60
Weight (kg)				
Mean (SD)	80.6 (20.4)	84.8 (23.3)	83.40 (20.90)	83.70 (19.20)
Range	43.2 to 178.2	43.3 to 178.4	47.70 to 164.20	48.00 to 150.00
BMI (kg/m^2)				
Mean (SD)	28.1 (6.9)	29.5 (7.5)	28.9 (6.7)	28.7 (5.9)
Range	15.7 to 58.2	16.9 to 53.3	17.8 to 53.9	18.4 to 53.9
Race n (%)				
Caucasian	152 (56.5)	92 (68.7)	160 (60.4)	153 (57.5)
Black or African American	59 (21.9)	22 (16.4)	56 (21.1)	64 (24.1)
Asian	45 (16.7)	13 (9.7)	29 (10.9)	26 (9.8)
Other	13 (4.8)	7 (5.2)	20 (7.5)	23 (8.7)
Region n (%)				
US	122 (45.4)	61 (45.5)	97 (36.6)	98 (36.8)
Non-US	147 (54.6)	73 (54.5)	168 (63.4)	168 (63.2)
Last Dose in IM Stabilization Phase[a] n (%)				
400 mg	246 (91.4)	123 (91.8)	NR	NR
300 mg	23 (8.6)	11 (8.2)	NR	NR

ARIP = aripiprazole; IM = intramuscular; PBO = placebo; SD = standard deviation.
[a] Last ARIP IM dose level in the IM stabilization phase.
Source: Study 246 Clinical Study Report, T8.2.4-1, p. 202; Study 247 Clinical Study Report, T8.2.3-1, p.186.

TABLE 6: SUMMARY OF BASELINE DISEASE SEVERITY

Characteristics	Study 246		Study 247	
	ARIP IM (N = 269)	PBO (N = 134)	ARIP IM (N = 265)	Oral ARIP N = 266)
Age at First Diagnosis of Schizophrenia				
Mean (SD)	25.8 (8.3)	26.5 (8.8)	28.2 (9.3)	26.9 (9.1)
Range	9 to 50	12 to 55	13 to 55	8 to 50
PANSS Total Score				
Mean (SD)	[redacted]	[redacted]	58.0 (12.9)	56.6 (12.7)
Median	[redacted]	[redacted]	58	58
Range	[redacted]	[redacted]	30 to 80	30 to 79
Conceptual Disorganization (P2)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Suspiciousness (P6)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Hallucinatory (P3)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Unusual Thought Content (G9)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
CGI–S				
Mean (SD)	[redacted]	[redacted]	3.1 (0.7)	3.1 (0.8)
Median	[redacted]	[redacted]	3	3
Range	[redacted]	[redacted]	1 to 4	1 to 4
CGI–I				
Mean (SD)	[redacted]	[redacted]	3.2 (0.9)	3.3 (0.9)
Median	[redacted]	[redacted]	3	3
Range	[redacted]	[redacted]	1 to 5	1 to 6
CGI–SS Severity Score				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
CGI–SS Change Score				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	Study 246		Study 247	
	ARIP IM (N = 269)	PBO (N = 134)	ARIP IM (N = 265)	Oral ARIP N = 266)
Outpatient status				
Yes	[redacted]	[redacted]	[redacted]	[redacted]

ARIP = aripiprazole; CGI–I = Clinical Global Impression Improvement Score; CGI–S = Clinical Global Impression — Severity Score; CGI–SS = Clinical Global Impression — Severity of Suicidality; IM = intramuscular; PANSS = Positive and Negative Syndrome Scale; PBO = placebo; SD = standard deviation.
Source: Study 246 Clinical Study Report, Table 8.2.4-2, p. 204 and Study 247 Clinical Study Report, Table 8.2.3-2, p. 187.

3.2.3 Interventions

In the RCT phase, patients were randomized to aripiprazole IM (400 mg) or placebo in Study 246; or to aripiprazole IM (400 mg) or oral aripiprazole (10 mg to 20 mg) in Study 247. Patients randomized to the aripiprazole IM group also received concomitant oral aripiprazole (10 mg to 20 mg) for the first two weeks.

3.2.4 Outcomes

The efficacy and safety outcomes were assessed biweekly during the RCT phase in both studies. In Study 246, the primary outcome was the time to relapse; the key secondary outcome was the relapse rate at interim analysis and at the end of week 52. In Study 247, the primary outcome was the relapse rate at the end of week 26; the key secondary outcome was the time to relapse. In both studies, relapse was defined as meeting any or all of the following four criteria:
1) CGI–I of ≥ 5 (minimally worse) and an increase in symptom severity on any of the individual PANSS items (conceptual disorganization, hallucinatory behaviour, suspiciousness, unusual thought content) to a score > 4 with an absolute increase of ≥ 2 on that specific item since randomization or an increase on any of the individual PANSS items (conceptual disorganization, hallucinatory behaviour, suspiciousness, unusual thought content) to a score > 4 and an absolute increase of ≥ 4 on the combined PANSS items.
2) Hospitalization due to worsening of psychotic symptoms, including partial hospitalization programs but excluding hospitalization for psychosocial reasons.
3) CGI–SS of 4 (severely suicidal) or 5 (attempted suicide) on Part 1, and/or 6 (much worse) or 7 (very much worse) on Part 2.
4) Violent behaviour resulting in clinically relevant self-injury, injury to another person, or property damage.

Suicidality was defined as reporting any suicidal ideation or behaviour. It was assessed using the CGI–SS, Columbia Classification Algorithm of Suicide Assessment (C–CASA), and the Columbia–Suicide Severity Rating Scale (C–SSRS). The CGI–SS scale is a derivative of CGI that has been adapted to assess global severity of suicidality.[26] It is rated on a 5-point scale where 1 = not at all suicidal; 2 = mildly suicidal; 3 = moderately suicidal; 4 = severely suicidal; and 5 = attempted suicide.[26] (See APPENDIX 5). The C–CASA is a standardized suicidal rating system that provides data for the analysis of suicidality risk of antidepressants. The C–SSRS scale consists of a baseline evaluation that assesses the lifetime experience of the patient with suicide events and suicidal ideation and a post-baseline or "Since Last Visit" evaluation that focuses on suicidality since the last trial visit. The "Since Last Visit" C–SSRS form was completed at all subsequent visits. No minimal clinically important differences (MCIDs) for CGI–SS, C–CASA or C–SSRS were specified.

The Personal and Social Performance (PSP) is a validated, clinician-rated scale that measures personal and social functioning in four domains: socially useful activities (e.g., work and study), personal and

social relationships, self-care, and disturbing and aggressive behaviours. A single score from 0 to 100 is assigned by the clinician, with a higher score indicating higher functioning. The MCID of 10 points was specified. (See APPENDIX 5.)

Remission and response: Remission was defined as patients who achieved a score of ≤ 3 on each of the following specific PANSS items: delusions (P1), unusual thought content (G9), hallucinatory behaviour (P3), conceptual disorganization (P2), mannerisms/posturing (G5), blunted affect (N1), social withdrawal (N4), and lack of spontaneity (N6); and if they maintained this score for a period of six months. Response was defined as patients who met all of the stability criteria as defined in Section 3.2.2.1: Inclusion and exclusion criteria.

PANSS is a 30-item rating scale, with 7 rating points for each item (1 = absent; 2 = minimal; 3 = mild; 4 = moderate; 5 = moderate–severe; 6 = severe; 7 = extreme). Therefore, the total possible score ranges from 30 to 210. Seven items are related to positive symptoms (score ranges 7 to 49), seven items to negative symptoms (score ranges 7 to 49), and 16 items to general psychopathology (score ranges 16 to 112). (See APPENDIX 5.) No MCID for PANSS was specified.

The CGI is a three-item scale (CGI–S, CGI–I, and CGI Efficacy Index [CGI–E]) used to assess the overall severity and response to treatment of mental disorders.[27] It is not specific to schizophrenia, although efforts to adapt the scale specifically to this disorder have been undertaken.[28] The more usual CGI scale items include severity of illness (CGI–S) at the time of the assessment on a 7-point scale (1 = normal; 7 = extremely ill); and global improvement (CGI–I) relative to baseline on a 7-point scale (1 = very much improved; 7 = very much worse).[27] However, there is no total score for the CGI. Rather, scores on the individual items are considered separately. The MCID for CGI–S or CGI–I is one point (see APPENDIX 5).

Other outcome measurements included cognition (measured with the Trail A, Tower of London [TOL] Test, University of Maryland: Letter–Number Span Test); adherence (measured with the Medication Adherence Questionnaire [MAQ] or Medication Adherence Rating Scale [MARS]); patient satisfaction (assessed with the Drug Attitude Inventory Score [DAI–10 and DAI–30]) and the Investigator's Assessment Questionnaire (IAQ). No MCIDs for any of these scales were specified.

Reported safety outcomes included mortality, hospitalization, serious adverse events (SAEs), and adverse events (AEs), including EPS-related AEs and body weight gain.

3.2.5 Statistical analysis

Study 246 was designed to show the superiority of aripiprazole IM (400 mg or 300 mg) over placebo in terms of time to relapse (the primary outcome). For the purposes of the sample size calculation, data from a previous trial,[29] which compared oral aripiprazole to placebo with regard to time to impending relapse (37% for oral aripiprazole and 61% for placebo), were taken into consideration for projecting relapse rates. The six-month rates for relapse were assumed to be 55% for placebo and 35% for aripiprazole IM. Sample sizes were estimated using a 2:1 randomization ratio (aripiprazole IM: placebo) to achieve 90% power and to preserve an overall nominal alpha level of 0.05 (two-sided), allowing for two interim looks at 50% and 75% of events accrual time points. The Haybittle–Peto group sequential boundaries were applied, corresponding to an alpha level of 0.001 at each of the two interim looks. The alpha level for the final analysis was 0.0498. Due to the lower-than-expected relapse rate, enrolment and randomization continued beyond the planned estimates (225 planned; 403 actual) to achieve the target number of impending relapse events.

The risk of relapse was presented using Kaplan–Meier plots. The hazard ratio was calculated from the Cox proportional hazard model with treatment as term. The log-rank test was used to test for statistical significance of differences between the two survival curves. Multiple imputation was used for the discontinued patients (other than patients discontinued when the sponsor terminated the trial) who did not meet the relapse criteria.

In Study 246, the treatment comparison of the key secondary end point (i.e., relapse rate) was tested only if the primary hypothesis was rejected at an overall nominal alpha level of 0.05. In this hierarchical testing procedure, the hypotheses for the secondary end points were tested at the same significance level as that of the primary end point in both the interim and final analyses. The key secondary efficacy end point was analyzed using the chi-square test. For continuous efficacy outcomes, the between-group difference in changes from baseline was tested using analysis of covariance (ANCOVA) models that were adjusted for the study centre and baseline assessments (such as PANSS). In order to assess the sensitivity of results due to missing data, two types of analyses were performed for analyses by visit in the RCT phase; i.e., last observation carried forward (LOCF) and observed case (OC). The primary datasets for efficacy analyses by visit were the LOCF datasets derived from the RCT efficacy sample. They included data recorded at a scheduled RCT visit. If no observation was recorded at that visit, data were carried forward from previous visits. Baseline data in each phase were not carried forward to impute missing values. The OC datasets consisted of the actual observations recorded at each visit. LOCF and OC datasets were performed for PANSS total score, PANSS positive and negative subscale scores, CGI–S score, CGI–I score, EPS rating scales (Simpson–Angus Scale [SAS] total score, Abnormal Involuntary Movement Scale [AIMS] score, and Barnes Akathisia Rating Scale [BARS] global score), and suicidality (CGI–SS score, change in suicidality score, and C–SSRS total score).

In Study 247, the objective of the primary efficacy analysis was to demonstrate noninferiority of aripiprazole IM to oral aripiprazole with regard to relapse rate by the end of 26 weeks. The sample sizes were estimated to achieve about 93% power for the primary noninferiority comparison at the 0.05 significance level (two-sided) using large sample normal approximations for the distribution of the difference in binomial proportions. The assumed population proportion of relapse at or before week 26 (day 182) for oral aripiprazole was 18%, and the predefined noninferiority margin was 11.5%. The resulting sample size was projected to be 260 patients for both IM and oral aripiprazole. A previous study[29] was taken into consideration in setting the noninferiority margin. From that study, the estimated relapse rates by the end of week 26 (from Kaplan–Meier estimates) were 37.4% for oral aripiprazole and 60.6% for placebo. The assumption that the difference between estimated relapse rates was approximately normally distributed led to a one-sided 97.5% lower confidence limit of 15% for the difference in relapse rate at day 182. Given the compliance advantage of a depot formulation, 11.5% was selected as the margin in this trial, which was also less than half the treatment difference between oral aripiprazole and placebo that trial.[29] In total, it was estimated that 650 patients would be randomized. The LOCF method was used to impute the missing data at post-baseline visits in RCT phases for the efficacy and safety analyses.

The dichotomous outcomes were analyzed using the chi-square test. For continuous efficacy outcomes, the between-group differences in changes from baseline were tested using ANCOVA models that were adjusted for the study centre and baseline assessments (such as PANSS). No statistical methods were employed to control for multiple testing (or multiplicity) with the secondary outcomes in Study 247.

a) Analysis populations

Efficacy and safety analyses were conducted. In both studies, the efficacy sample included all patients who entered the RCT phase. Safety sample analysis included all patients who were randomly assigned to RCT and received at least one dose of trial medication. The intention-to-treat (ITT) analysis was based on all patients randomized in both studies.

3.3 Patient Disposition

Detailed information on patient dispositions in the RCT phase is presented in Table 7. Interim phase patient disposition for Study 246 is presented in Appendix 4, Table 10.

In Study 246, 403 patients were randomized to RCT (aripiprazole IM, 269; placebo, 134). Based on the preplanned interim analysis conducted after 64 relapse events, the study was terminated early to avoid unnecessary exposure to placebo. About 50% of patients in the aripiprazole IM group and 30% in the placebo injection group received only fifth injections (i.e., they terminated at five months or 20 weeks); 9% in aripiprazole IM and 28% in placebo received 13 injections (i.e., they finished the trial at week 52).

All patients were brought in for a final visit. Therefore, the main reason for discontinuation was early study termination (67% in the aripiprazole IM group and 43% in in the placebo group). In Study 247, 662 patients were randomized. Patients who completed the study at week 38 were 74% and 68% in aripiprazole IM and aripiprazole oral, respectively. The main reason for discontinuation was patient withdrawal of consent. The number of individuals who withdrew due to adverse events (WDAE) was low in both the aripiprazole IM and oral aripiprazole groups.

TABLE 7: PATIENT DISPOSITION (RANDOMIZED CONTROLLED TRIAL PHASE)

	Study 246		Study 247	
	ARIP IM	PBO	ARIP IM	ARIP Oral
	n (%)	n (%)	n (%)	n (%)
Screen	1,025		1,118	
Conversion phase (F)	633 (100)		709 (100)	
Oral stabilization phase (F)[a]	710 (100)		842 (100)	
ARIP IM stabilization phase (F)	576 (100)		NA	
Randomized interim phase	230 (100)	114 (100)	NA	NA
Randomized Final phase	269 (100)	134 (100)	265 (100)	266 (100)
Discontinued	**246 (91.4)**	**131 (97.8)**	**69 (26.0)**	**88 (33.1)**
Sponsor discontinued study[b]	179 (66.5)	58 (43.3)	NA	NA
Other reasons	67 (24.9)	73 (54.5)		
Lost to follow-up	5 (1.9)	3 (2.2)	4 (1.5)	10 (3.8)
Met withdrawal criteria	2 (0.7)	2 (1.5)	4 (1.5)	6 (2.3)
Withdrawn by investigator	8 (3.0)	6 (4.5)	8 (3.0)	12 (4.5)
Withdrew consent	14 (5.2)	4 (3.0)	21 (7.9)	29 (10.9)
Protocol deviation	2 (0.7)	0 (0.0)	2 (0.8)	3 (1.1)
AE without impending relapse	9 (3.3)	5 (3.7)	8 (3.0)	7 (2.6)
Impending relapse with AE	11 (4.1)	13 (9.7)	13 (4.9)	12 (4.5)
Impending relapse without AE	16 (5.9)	40 (29.9)	9 (3.4)	9 (3.4)
Death	1	0		1
Completed[c]	23 (8.6)	3 (2.2)	196 (74.0)	178 (66.9)

	Study 246		Study 247	
	ARIP IM	PBO	ARIP IM	ARIP Oral
	n (%)	n (%)	n (%)	n (%)
Analyzed for safety[d]	269 (100)	134 (100)	265 (100.0)	266 (100.0)
Analyzed for efficacy[e]	269 (100)	134 (100)	265 (100.0)	266 (100.0)
ITT, N	269 (100)	134 (100)	265 (100)	266 (100)
PP, N	NR	NR	NR	NR
Safety, N	269 (100)	134 (100)	264 (99.6)	266 (100.0)

AE = adverse event; ARIP = aripiprazole; F = final phase (80 events); I = interim phase (64 events); IM = intramuscular; ITT = intention-to-treat; PBO = placebo; PP = per-protocol.
[a] Some patients who were on oral aripiprazole did not need to enter the conversion phase and directly entered the oral stabilization phase.
[b] The study was terminated early because of positive results from the interim analysis.
[c] Patients completed the RCT, week 52 visit.
[d] Patients receiving at least one dose of trial medication in the RCT were included in the safety analysis.
[e] Patients evaluated for at least one efficacy end point in the RCT were included in the efficacy analysis.
Source: Clinical Study Report Study 246 T8.1–1, T 8.1–4 and T 8.1–4 p.90-94; Clinical Study Report Study 247: T 8.1–1 and T8.1.2, p. 176–178.
Note: For Study 247, data on the group of ARIP IM 50 mg or 25 mg were not reported in this review.

3.4 Exposure to Study Treatments

Detailed information on medication exposure is presented in Appendix 4 (Table 11, Table 12, Table 13, and Table 14).

3.4.1 Study medication use

In Study 246, 403 patients were treated with a median average injection dose of 400 mg once every four weeks for each injection. Ninety-one per cent of patients received an initial dose of 400 mg and 9% received an initial dose of 300 mg; 52% patients received five injections and fewer than 10% patients stayed in the trial until week 52, receiving 13 injections. In Study 247, 85% of patients received five injections and 73% stayed in the trial to the end (week 38), receiving 10 injections. Patients took a mean average daily dose of 15.2 mg ± 6.28 mg oral aripiprazole in Study 247 (Appendix 4, Table 11 and Table 12).

3.4.2 Concomitant drug use

Overall, 67.7% patients on aripiprazole IM and 61.9% in placebo in Study 246, and 78.9% in both groups in Study 247, used concomitant medications. Concomitant medications used by ≥ 3% of patients in either treatment group are summarized in Appendix 4, Table 13. More patients used benzodiazepines and anticholinergics compared with those in the placebo (20% versus 17% for anticholinergics and 39% versus 33% for anticholinergics) or oral aripiprazole groups (1.2% versus 1.0% for anticholinergics and 2.5% versus 2.3% for anticholinergics) in Study 246 or Study 247, respectively (Appendix 4, Table 14).

3.5 Critical Appraisal

3.5.1 Internal validity

The two included studies were double-blind, multi-centre RCTs. The research objectives were clearly defined. The randomizing process, including allocation concealment and blinding method, was well described and performed. Overall, the important baseline characteristics were comparable in the two treatment arms in both studies, except more Caucasian patients were included in the placebo arm compared with the aripiprazole arm in Study 246.

In Study 246, to preserve the overall type I error rate at alpha 0.05, the treatment comparison of the key secondary end point was tested only if the primary hypothesis of comparing time to exacerbation of psychotic symptoms between aripiprazole IM and placebo was rejected at an overall nominal alpha level of 0.05. In this hierarchical testing procedure, the hypotheses for the secondary end points were tested at the same significance level as that of the primary end point in both the interim and final analyses. For Study 247, the validity of the noninferiority margin was based on a previous study and approved by the European Medicines Agency.

However, several limitations that may have an effect on the internal validity of the study are discussed below. First, the key limitation for Study 246 is the "withdrawal" design and early termination. A drawback of this design is that patients may have symptoms precipitated by withdrawal. Early trial termination may overestimate the treatment effect (especially the secondary outcomes, such as symptom scores). This notion has been supported based on findings from a systematic review that reported early-terminated RCTs were associated with greater effect size than RCTs not terminated early.[30] The comparison between aripiprazole IM and placebo may represent maintenance versus provoked relapse, but not the actual effect for treatment of schizophrenia. Second, numerically more patients treated with aripiprazole IM used benzodiazepines and anticholinergics in Study 247 compared with the oral aripiprazole group. As well, numerically more aripiprazole IM patients used benzodiazepines versus those receiving placebo, but the reverse occurred with respect to concomitant anticholinergics in Study 246. However, the median doses of benzodiazepines and anticholinergics were reportedly higher in patients on aripiprazole IM than for those on placebo. It is not clear whether this numerical differential in concomitant drug use had an impact on the efficacy observed or the frequency of certain adverse events (e.g., movement disorders) in the studies. Third, the hierarchical structure for multiplicity testing should be specified a priori. However, given the generally very small *P* values and the number of tests performed, the results observed in the trial would remain statistically significant if a simple Bonferroni correction were applied. Fourth, in Study 247, due to the very low initial relapse rates, the primary outcome was changed from time to relapse at week 38 to Kaplan–Meier estimated relapse rates at week 26, because time as a variable can have a disproportional impact on time to events when event rates are low. Revising the primary outcome after the trial started may have introduced bias. However, because the relapse events remained low for the duration of the study, the conclusion of noninferiority of aripiprazole IM versus oral aripiprazole was unlikely to have been compromised. Fifth, in Study 247, the PP analysis was not reported. PP analysis is considered to be more conservative than ITT analysis in the noninferiority trial. Declaration of noninferiority should be based on the criteria being met in both the ITT and PP populations. However, it appears that very few randomized patients (0.8% to 1.1%) in either treatment group violated protocol. Therefore, it is unlikely there is a meaningful difference between ITT and PP analysis with respect to noninferiority. Sixth, relapse was not clearly defined in terms of whether it was based on just one visit or on several. The term "impending relapse" was used in the trials, but whether there is a difference between "relapse" and "impending relapse" was not clearly defined. The clinical expert involved in this review pointed out that relapses should be monitored over multiple visits because schizophrenic patients' symptoms often fluctuate clinically. As well, cognition was not measured using more comprehensive tools such as MATRICS Consensus Cognitive Battery [MCCB], so it is unclear what is the true effect of treatment on cognition. In addition, in terms of remission rate measurement, only those patients who remained in the trial for at least six months were included in the calculation of remission rates. In this case, the randomization would not be maintained and the remission rate potentially overestimated. Adherence outcomes scales were patient self-reported and clinician-rated, which may not be reliable. Finally, the duration of Study 247 (38 weeks) may be insufficient to detect potential differences in longer-term efficacy and safety outcomes (such as metabolic syndrome) between aripiprazole IM and oral aripiprazole.

3.5.2 External validity

The generalizability of the findings from both RCTs could be limited because they were conducted in highly selected stabilized patients (e.g., in patients who were treatment resistant and excluding those treated with clozapine). Patients were stabilized with oral or IM aripiprazole, but not with other antipsychotics. It is unclear if the results of the studies can be generalized to elderly patients and the more general population of patients with schizophrenia, such as those stabilized with other non-aripiprazole AAPs, or patients inadequately controlled with oral or existing IM antipsychotics; i.e., those described by the manufacturer's listing request. Furthermore, according to the clinical expert involved in this review, while the importance of a broad selection of effective, safe, and tolerable interventions (including IM antipsychotics) for schizophrenia treatment is recognized, the need to switch a stabilized patient on oral antipsychotics (such as oral aripiprazole) to IM drugs (such as Abilify Maintena) is clinically questionable, unless improved adherence is anticipated with the IM drugs. In clinical practice, there is a need for the new IM antipsychotics in the treatment of patients with schizophrenia — including those who respond inadequately to the available antipsychotic treatments — but those patients were excluded from studies 246 and 247.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data. The summary of main efficacy findings is presented in Table 8.

3.6.1 Mortality

In Study 246, one death was reported during the RCT phase. In Study 247, one patient in the oral aripiprazole group died during the RCT phase. No patient in the aripiprazole IM (400 mg or 300 mg) group died. Neither death was considered by the investigator to be related to trial treatment.

3.6.2 Hospitalization

In Study 246, the hospitalization rate was 5.2% in the aripiprazole IM group and 9% in the placebo group. CDR calculated the relative risk of hospitalization in Study 246 (aripiprazole versus placebo: 0.58; 95% CI, 0.28 to 1.22). In Study 247, the hospitalization rate was 8.7% in the aripiprazole IM group and 7.1% in the oral aripiprazole group (relative risk, 1.22; 95% CI, 0.68 to 2.18). The reasons for hospitalization were mainly psychiatric (other than schizophrenia) or non-psychiatric conditions (see Appendix 4, Table 15).

3.6.3 Suicidality

Suicidality was assessed using the CGI–SS and/or C–CASA/C–SSRS. In Study 246, when assessed with C–CASA/C–SSRS, 2.6% of patients on aripiprazole IM had an event that was considered related to suicidal ideation or suicide. No patients in the placebo group reported suicidality (Appendix 4, Table 16). In Study 247, when assessed with C–SSRS, 3.5% of patients in the aripiprazole IM group and 3.2% in the oral aripiprazole group had an event that was considered related to suicidal ideation or suicide (Appendix 4, Table 17). The mean CGI–SS score was 1.0 for both treatment groups at the baseline, and was stable throughout the RCT phase in both studies.

3.6.4 Quality of life

Quality of life was not assessed.

3.6.5 Functional capacity

Results for the mean change from baseline to the last visit in terms of PSP score are presented in Appendix 4. In Study 246, the PSP total scores decreased from baseline to last visit during the RCT phase by −1.74 points in aripiprazole IM and −6.20 points in placebo. This indicates that the function was statistically significantly worse in the placebo group than in the aripiprazole IM group (*P* = 0.0002). In Study 247, there is no statistically significant difference between aripiprazole IM and oral aripiprazole in terms of changes from baseline of PSP (Appendix 4, Table 24).

3.6.6 Remission

Only those patients who remained in the trial for at least six months were included in the calculation of remission rates. In Study 246, the proportion of patients who achieved remission was [redacted] in the aripiprazole IM group compared with [redacted] in the placebo group, a numerically greater but not statistically different result [redacted] In Study 247, the proportions of patients achieving remission were 48.8% in the aripiprazole IM group compared with 53.2% in the oral aripiprazole group. The differences between the aripiprazole IM and oral aripiprazole groups were not statistically significant (*P* = 0.37). Detailed information on remission rates is presented in Appendix 4, Table 18.

3.6.7 Response

In Study 246, the response rate at the last visit was [redacted] in the aripiprazole IM group compared with [redacted] in the placebo group; a statistically significantly higher response was observed in aripiprazole IM compared with placebo [redacted]. In Study 247, the response rate at end point (up to week 38) in the RCT phase was 89.8% in the aripiprazole IM group compared with 89.4% in the oral aripiprazole group. No statistically significant difference (*P* = 0.88) was observed between aripiprazole IM and oral aripiprazole (Appendix 4, Table 18).

3.6.8 Relapse

The detailed results of relapse are presented in Appendix 4, Table 19 and Table 20. In Study 246, the percentage of patients meeting the relapse criteria was reported as a key secondary outcome. The relapse rate (interim and final analyses) is presented in Table 19. The relapse rate was significantly lower (*P* < 0.0001) in the aripiprazole IM group (interim analysis, 9.6%; final analysis, 10.0%) than in the placebo group (interim analysis: 36.8%; final analysis: 39.6%). For both treatment groups, the most common criteria for relapse were the CGI–I + PANSS scores criterion (see Table 19). In Study 247, the relapse rate was the primary outcome. The estimated relapse rate by end of week 26 was 7.12% in the aripiprazole IM group and 7.76% in the oral aripiprazole group. The between-group difference was −0.64% (95% CI, −5.26 to 3.99) by end of week 26, excluding the predefined noninferiority margin of 11.5% (Table 20). Therefore, aripiprazole IM is considered noninferior to oral aripiprazole.

3.6.9 Time to relapse

Detailed information on time to relapse is presented in Appendix 4 (Table 21, Figure 6, Figure 7, and Figure 8). In Study 246, the primary outcome was time to relapse in the RCT phase, which is presented in Table 21. The interim analysis of efficacy data included 344 patients and 64 events of impending relapse (50% of the projected total of 125 events). The interim analysis showed that time to relapse was significantly shorter for patients on placebo compared with patients on aripiprazole IM (*P* < 0.0001; log-rank test). The median time to relapse in the placebo group was 209 days. However, the median time to relapse was not estimable for the aripiprazole group because the relapse rate was too low. The risk of relapse was five times greater (hazard ratio, [placebo versus aripiprazole IM]: 4.72; 95% CI, 2.81 to 7.94; *P* < 0.0001) with placebo than with aripiprazole IM. The hazard ratio from the Cox proportional hazard model for the placebo to aripiprazole IM comparison was 4.72 (95% CI, 2.81 to 7.94), which indicates

that patients in the placebo group had a 4.72-fold greater risk of relapse than patients in the aripiprazole IM group. The final efficacy analysis included 403 patients and 80 relapse events. Twenty-seven of 269 (10.0%) aripiprazole IM patients and 53 out of 134 (39.6%) placebo patients relapsed. The results from the final analysis were consistent with the interim analysis results in showing that the time to relapse was significantly shorter for patients in the placebo group compared with patients on aripiprazole IM (hazard ratio = 5.03; 95% CI, 3.15 to 8.02; $P < 0.0001$; log-rank test; see Table 21). The final analysis indicated that the patients in the placebo group had a five-fold greater risk of relapse than patients on aripiprazole IM. The median time to relapse was not estimable for the aripiprazole group, as the relapse rate in aripiprazole IM treated patients was too low. The median time to relapse was 209 days for patients in the placebo group (see Table 21, Figure 6, and Figure 7). In Study 247, reported as a secondary outcome, the time to relapse during the 38-week RCT was similar in the aripiprazole IM and oral aripiprazole groups ($P = 0.99$). The risk of relapse was also similar in the aripiprazole IM group and the oral aripiprazole group (hazard ratio = 0.99; 95% CI, 0.55 to 1.80). Median time to relapse (days) was not reported (Table 21, Figure 8).

3.6.10 Symptoms

Details of PANSS (total, positive, and negative scores), CGI–S, CGI–I, and cognition results are presented in Table 22, Table 23, Table 24, Figure 9, and Figure 10.

a) PANSS

In Study 246, for the aripiprazole IM group, the adjusted mean change from baseline at week 52 for the PANSS total score was 1.43, whereas it was 11.55 for the placebo group. Patients in the placebo group showed a statistically significantly higher PANSS total score than those in the aripiprazole IM group ($P < 0.0001$; see Table 22). The treatment effect favoured the aripiprazole IM group numerically at all post-baseline visits (Figure 9). In Study 247, the PANSS total score over time is presented graphically in Figure 10Figure 10. The mean PANSS total score remained relatively stable across the RCT phase. There was a statistically significant difference in favour of aripiprazole IM ($P = 0.027$) (Table 23).

b) CGI–S

A modest but statistically significant difference in favour of aripiprazole was also reported in CGI–S ($P = 0.012$). (See Table 23.)

c) Cognition

There was no statistically significant between-group difference in changes from baseline in terms of cognition measured with the Trail A score, TOL Item Scores, and University of Maryland Letter–Number Span Total Score in either of the studies. The exception is that in Study 246, there was a statistically significant between-group difference in changes from baseline in the University of Maryland: Letter–Number Span Total Score (aripiprazole IM versus placebo: −0.10 versus –1.31; $P < 0.001$; see Table 24).

3.6.11 Other outcomes

a) Patient Satisfaction with Medication Questionnaire — Modified

The investigator used the Modified Patient Satisfaction with Medication Questionnaire (PSMQ–Modified) to assess patient satisfaction with treatment, perception of the frequency of side effects, and preference for current versus previous treatment. In Study 246, by the last visit, 77% of patients on aripiprazole IM and 66% in placebo reported they were extremely or very satisfied with their treatment (Table 25). In addition, the percentage of patients with each category of treatment side effects was similar in both groups (Table 26). Most patients (94.8% and 97.7% in the aripiprazole IM and placebo groups, respectively) preferred their current treatment to previous treatment at the baseline of the RCT.

This preference decreased by the last visit for both treatment groups (86.2% and 85.7% in the aripiprazole IM and placebo groups, respectively; see Table 27). In Study 247, the proportion of patients reporting treatment dissatisfaction (somewhat, very, and extremely unsatisfied) increased from baseline to last visit in both groups (aripiprazole IM from 3.8% to 5.9%; aripiprazole oral from 2.8% to 4.8%). The percentage of patients in each category of treatment adverse effects, and the percentage of patients reporting satisfaction with the current treatment, was similar in the aripiprazole IM and oral aripiprazole groups and remained stable during the RCT phase.

b) Medication Adherence Questionnaire Total Score, Drug Attitude Inventory Score, and Investigator's Assessment Questionnaire Total Score

No statistically significant between-group difference was observed in changes from baseline in the MAQ Total Score, DAI Score, or IAQ Total Score in either study, except that in Study 246, in the aripiprazole IM group, an increase of 3.78 ($P < 0.001$) from baseline was observed in the IAQ Total Score (Table 24).

TABLE 8: KEY EFFICACY OUTCOMES

Outcome	Study 246		Study 247	
	ARIP IM (N = 269)	PBO (N = 134)	ARIP IM (N = 265)	Oral ARIP (N = 266)
Mortality	1	0	0	1
Hospitalization				
n, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
RR (CI)	[redacted]		[redacted]	
NNT	[redacted]		[redacted]	
Completed Suicide	0	0	0	0
Remission Rate[a]				
n, N (%)	[redacted]	[redacted]	105/215 (48.8) *P* = 0.37	107/201 (53.2)
RR (CI)	[redacted]		0.92 (0.76 to 1.11)	
NNT	[redacted]		NE	
Response Rate				
n, N (%)	[redacted]	[redacted]	237/264 (89.8) *P* = 0.88	235/263 (89.4)
ARD (CI)	[redacted]		0.00 (–0.05 to 0.06)	
RR (CI)	[redacted]		1.00 (0.95 to 1.06)	
NNT	[redacted]		NE	
Relapse Rate				
n, N (%)	27/269 (10.0) *P* < 0.0001	53/134 (39.6)	22/265 (8.30) *P* = 0.86	21/266 (7.89)
ARD (CI)	**–0.30 (–0.39 to –0.20); *P* < 0.0001**		–0.64 (–5.26 to 3.99); *P* = 0.79	
RR (CI)	**0.25 (0.17 to 0.38)**		1.05 (0.59 to 1.87)	
NNT	4 (3, 5)		NE	
Time to Relapse				
Median Time to event (days)	NE	209	[redacted]	[redacted]

Outcome	Study 246		Study 247	
	ARIP IM (N = 269)	**PBO (N = 134)**	**ARIP IM (N = 265)**	**Oral ARIP (N = 266)**
HR (95% CI)	0.199 (0.13 to 0.32) *P* < 0.0001		[redacted]	
PANSS Total				
Baseline	54.41 (0.73)	54.35 (1.02)	57.94 (0.786)	56.57 (0.782)
Change from baseline	1.43 (0.76)	11.55 (1.07)	−1.66 (0.718)	0.58 (0.714)
Between-group difference in changes from baseline	**−10.11 (−12.68 to −7.54) *P* < 0.0001**		**−2.24 (−4.23 to −0.25) *P* = 0.0272**	
CGI–S				
Baseline	2.88 (0.050)	2.87 (0.071)	3.12 (0.050)	3.09 (0.049)
Change from baseline	0.14 (0.051)	0.66 (0.073)	−0.13 (0.049)	0.05 (0.049)
Between-group difference in changes from baseline	−0.52 (−0.70 to −0.35), *P* < 0.0001		−0.17 (−0.31 to −0.04) *P* = 0.0123	
Personal and Social Performance Scale				
Baseline	[redacted]		[redacted]	
Change from baseline	[redacted]		[redacted]	
P value for between-group difference in changes from baseline	[redacted]		[redacted]	

AE = adverse event; ARD = absolute risk difference; ARIP = aripiprazole; CGI–S = Clinical Global Impressions–Severity of illness; CI = confidence interval; EPS = extrapyramidal symptoms; HR = hazard ratio; IM = intramuscular; n = number of patients with the events; N = total number of patients evaluated; NE = not estimable because there is no statistically significant absolute between-risk difference; NNH = number needed to harm; NNT = number needed to treat; PANSS = Positive and Negative Syndrome Scale; PBO = placebo; RR = relative risk; SAE = serious adverse event; SE = standard error; MD = mean difference; WDAE = withdrawal due to adverse events.

[a] Remission included only those patients who stayed in the study for 6 months.

Note: ARD, NNT, and NNH were calculated by CADTH.

3.7 Harms

Only those harms identified in the review protocol (see Section 2.2.1, Protocol) are reported below. Also see APPENDIX 4: DETAILED OUTCOME DATA for detailed harms data.

3.7.1 Adverse events

The main AEs are presented in Table 9. In Study 246, overall, during the RCT phase, 63.2% patients with aripiprazole IM and 61.9% patients with placebo experienced treatment-emergent adverse events (TEAEs). TEAEs with an incidence of ≥ 2% in either treatment group are shown in Table 29. TEAEs occurred at a similar incidence in the aripiprazole IM and placebo groups, or occurred more frequently in the placebo group except for arthralgia, fatigue, sedation, and tremor, which occurred more frequently (with at least twice the incidence) in the aripiprazole IM group. The only TEAE reported by ≥ 5% of aripiprazole patients and with at least twice the incidence among the placebo group was tremor (aripiprazole IM versus placebo, 5.9% versus 1.5%). In Study 247, 83% patients on aripiprazole IM and 80% on oral aripiprazole reported TEAEs. The incidence of TEAEs reported for ≥ 5% of aripiprazole IM patients was comparable to or less than that reported for patients treated with oral aripiprazole with

the exception of akathisia (aripiprazole IM versus aripiprazole oral: 10.6% versus 6.8%), injection-site pain (7.5% versus 2.3%), and infection (6.8% versus 4.1%) (see Table 29). TEAEs related to akathisia, injection-site pain, and infection were generally mild in severity; none were considered to be a serious TEAE or associated with discontinuation of treatment. Other TEAEs that occurred at ≥ 5% incidence in any treatment group were insomnia (aripiprazole IM versus oral: 11.7% versus 13.9%), headache (9.8% versus 11.3%), nasopharyngitis (7.9% versus 9.4%), anxiety (7.2% versus 4.9%), influenza (4.2% versus 4.1%), and back pain (3.8% versus 5.3%) (see Table 29).

3.7.2 Serious adverse events

In Study 246, 4.1% of patients with aripiprazole IM and 6.7% patients in placebo reported SAEs. The only serious TEAE reported for ≥ 1% was psychotic disorder (1.5% in aripiprazole IM versus 3.0% in placebo). Serious TEAEs that were considered to be possibly related to trial medication included psychotic disorder, diabetes mellitus, hyperglycemia, suicidal ideation, sinus bradycardia, and schizophrenia. In Study 247, 5.7% patients on aripiprazole IM and 5.6% on oral aripiprazole reported SAEs. The serious TEAEs reported for ≥ 1% patients were schizophrenia (1.9% in aripiprazole IM versus 0.8% oral aripiprazole) and psychotic disorder (1.5% versus 0.8%; see Table 9). The only serious TEAE considered to be possibly related to trial medication was fatigue (see Table 30).

3.7.3 Withdrawals due to adverse events

In both studies, the most frequently reported AE that led to discontinuation was psychotic disorder. In Study 246, there were 4.1% patients on aripiprazole IM and 9.7% on placebo who withdrew from the study because of an AE. The TEAEs resulting in trial medication discontinuation that were reported by ≥ 1% of patients in either treatment group were psychotic disorder (aripiprazole IM versus placebo, 2.6% versus 6.0%) and schizophrenia (0.7% versus 3.7%). In Study 247, 4.9% patients with aripiprazole IM and 4.5% with aripiprazole oral withdrew from the study due to an AE. TEAEs resulting in trial medication discontinuation that were reported by ≥ 1% of patients in either treatment group were psychotic disorder (aripiprazole IM versus oral, 1.5% versus 1.9%) and schizophrenia (3.0% versus 1.9%). A summary of the TEAEs resulting in discontinuation of trial medication is presented in Table 31.

3.7.4 Notable harms

After consultation with the clinical expert involved in the review, the following notable harms (i.e., AEs with special interest clinically) were identified: movement disorders (EPS, tardive dyskinesia, etc.), weight gain, sexual dysfunction, and metabolic syndrome.

a) Extrapyramidal Symptoms–Related Adverse Events

In Study 246, more patients who received aripiprazole IM (15%) experienced EPS-related AEs than did those in the placebo group (10%) (Table 32). In Study 247, more patients who received aripiprazole IM (21%) experienced EPS-related AEs than did those in the oral aripiprazole group (11.7%). The most common EPS-related event was akathisia (6% in both groups in Study 246; 11% in aripiprazole IM and 7% in oral aripiprazole in Study 247). In terms of EPS symptom rating scales, such as AIMS, BARS, or SAS, there was no statistically significant between-group difference in change from baseline in either of the studies, although a minimal variation from baseline in EPS symptoms was observed (Table 33).

b) Weight Gain

In Study 246, numerically more patients on aripiprazole IM (6.4%) experienced potentially clinically important weight gain (≥ 7% body weight gain) than did those who received placebo (5.2%), while in Study 247, numerically more patients treated with oral aripiprazole (11.7%) experienced potentially

clinically important weight gain than did those who received aripiprazole IM (9.5%). Neither sexual dysfunction nor metabolic syndrome was reported in either of the studies.

TABLE 9: HARMS

Outcome	Study 246		Study 247	
	ARIP IM (N = 269)	**PBO (N = 134)**	**ARIP IM (N = 265)**	**Oral ARIP (N = 266)**
TEAEs				
Patients with > 0 TEAEs, N (%)	170 (63.2)	83 (61.9)	219 (82.6)	213 (80.1)
Most Common TEAEs				
Insomnia	27 (10.0)	12 (9.0)	31 (11.7)	37 (13.9)
Weight gain	26 (9.7)	13 (9.7)	24 (9.1)	35 (13.2)
Nasopharyngitis	10 (3.7)	7 (5.2)	21 (7.9)	25 (9.4)
Headache	16 (5.9)	7 (5.2)	26 (9.8)	30 (11.3)
Anxiety	16 (5.9)	10 (7.5)	19 (7.2)	13 (4.9)
Injection-site pain	8 (3.0)	5 (3.7)	20 (7.5)	6 (2.3)
Serious TEAEs				
Patients with ≥ 1 Serious TEAEs, N (%)	11/269 (4.1)	9/134 (6.7)	15/264 (5.7)	15/266 (5.6)
Psychotic disorder	4 (1.5)	4 (3.0)	4 (1.5)	2 (0.8)
Schizophrenia	2 (0.7)	2 (1.5)	5 (1.9)	2 (0.8)
Suicidal ideation	2 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)
Suicide attempt	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.4)
Withdrawals				
Total, N (%)	246/269 (91.4)	131/134 (97.8)	69/265 (26.0)	88 /266 (33.1)
Most Common Reasons				
Sponsor discontinued	179 (66.5)	58 (43.3)	NA	NA
Withdrew consent	14 (5.2)	4 (3.0)	21 (7.9)	29 (10.9)
WDAEs				
n, N (%)	11/269 (4.1)	13/134 (9.7)	13 /265(4.9)	12/266 (4.5)
Most common reasons				
Relapse with AE	11 (4.1)	13 (9.7)	[redacted]	[redacted]
Psychotic disorder	[redacted]	[redacted]	[redacted]	[redacted]
Notable harms(s) n, N (%)				
EPS or EPS-Related Events	40/269 (14.9)	13/134 (9.7)	58/265 (21.9)	31/266 (11.7)
Akathisia	15 (5.6)	8 (6.0)	28 (10.6)	18 (6.8)

Outcome	Study 246		Study 247	
	ARIP IM (N = 269)	PBO (N = 134)	ARIP IM (N = 265)	Oral ARIP (N = 266)
Parkinsonism	[redacted]	[redacted]	[redacted]	[redacted]
Tremor	16 (5.9)	2 (1.5)	8 (3.0)	9 (3.4)
Weight gain (7% gain)				
n, N (%)	17/267 (6.4)	7/134 (5.2)	25/264 (9.5)	31/266 (11.7)

AE = adverse event; ARIP = aripiprazole; EPS = extrapyramidal symptoms; n = number of patients with the events; N = total number of patients evaluated; PBO = placebo; SAE = serious adverse event; TEAE = treatment-emergent AE; WDAE = withdrawal due to adverse events.

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence for this review was derived from two double-blind, randomized trials, Study 246 and Study 247. Study 246 evaluated the efficacy and safety of aripiprazole IM compared with placebo (i.e., withdrawal from aripiprazole IM) as maintenance treatment in stabilized schizophrenia patients on aripiprazole IM. Study 247 evaluated the efficacy and safety of aripiprazole IM compared with oral aripiprazole as maintenance treatment in oral aripiprazole stabilized patients with schizophrenia. Overall, the important patient demographic and baseline psychiatric characteristics were similar between treatment groups in both studies. The dropout rates were also comparable between the two treatment arms in both studies, although they were numerically higher for the oral aripiprazole group in Study 247. Patient-reported outcomes and valid symptom severity scales were evaluated; however, MCIDs have not been reported for most of the measures, making interpretation of the findings with respect to clinical relevance challenging.

While the two included studies were double-blinded RCTs, several limitations potentially limiting the internal validity or generalizability of the findings from these studies include the following. The populations of the two studies consisted of highly selected, stabilized patients. Study 246 was a "withdrawal" design and terminated early, a drawback of which is that patients may have experienced symptoms provoked by the withdrawal of stabilized active treatment (i.e., the placebo group discontinued aripiprazole IM). The comparative between-groups differences (aripiprazole IM versus placebo) observed may represent maintenance versus provoked relapse, but not the actual effect for the treatment of schizophrenia. No studies were identified comparing aripiprazole IM with other antipsychotic IM comparators. Two other atypical IM antipsychotics (paliperidone palmitate[17] and risperidone IM[16]) marketed in Canada would be the optimal comparators for the purpose of formulary review. Finally, the duration of Study 247 may not have been long enough to fully detect potential differences between aripiprazole IM and oral aripiprazole in terms of efficacy and safety.

4.2 Interpretation of Results

4.2.1 Efficacy

The evidence reviewed comes from two double-blinded RCTs, Study 246 and Study 247. Study 246 was a placebo-controlled RCT; Study 247 compared aripiprazole IM with oral aripiprazole. The comparative effectiveness of aripiprazole IM versus other active IM antipsychotics in the maintenance treatment of schizophrenia is unknown due to a lack of head-to-head studies.

In terms of mortality, hospitalization, and suicidality, very few events were observed in the two studies, and there was no obvious difference between treatment groups (aripiprazole IM versus placebo in Study 246 or aripiprazole IM versus oral aripiprazole in Study 247). However, because these were not primary outcomes and there were very few events, the findings on these outcomes are inconclusive.

Although quality of life as an important outcome, it was not assessed in either of the included studies. Thus, the impact of aripiprazole IM on this outcome remains unknown.

Regarding functional capacity as measured by PSP total scores, a statistically significantly greater decrease in social functioning from baseline was observed in the placebo group than that in the aripiprazole IM group (–6.2 versus –1.7; $P = 0.0002$) in Study 246. However, the difference is not considered clinically meaningful because it accounts for only half of the MCID of 10 points for PSP. In Study 247, no statistically significant difference was observed between aripiprazole IM and oral aripiprazole in terms of changes from baseline.

Relapse rate was the key secondary outcome in Study 246, but was the primary outcome in Study 247. Time to relapse was the primary outcome in Study 246, but was the secondary outcome in Study 247. In Study 246, both the interim and final analyses showed a significantly lower relapse rate (final analysis: ARD –0.30; 95% CI, –0.39 to –0.20; $P < 0.0001$) and delayed time to relapse (hazard ratio 0.199; 95% CI, 0.13 to 0.32; $P < 0.0001$) with aripiprazole IM compared with placebo. For both treatment groups, the most common criteria for relapse were the CGI–I + PANSS scores criteria. However, due to the nature of the withdrawal RCT design in Study 246, randomization to placebo may in fact provoke the relapse that is theoretically delayed by aripiprazole. It is impossible to rule out the effect of withdrawal and hence draw conclusions as to whether the treatment benefit reported for aripiprazole is overestimated. In Study 247, the between-group difference in relapse rates was −0.64% (95% CI, −5.26 to 3.99) by the end of week 26, which was below the predefined noninferiority margin, 11.5%. Therefore, based on the pre-specified criteria, noninferiority of aripiprazole IM to the aripiprazole oral was claimed. However, the noninferiority analysis was conducted using the ITT population alone, without comparison to findings in the PP set, which was not reported. Typically, a claim of noninferiority cannot be established without examining whether the 95% CI bounds for the effect estimate are within the noninferiority margin in both the ITT and PP datasets.[31,32] In addition, the clinical expert involved in this review pointed out that relapse should be monitored over multiple visits because schizophrenic patients' symptoms often fluctuate. Furthermore, whether the relapse based on symptom scores was determined based on a single visit or multiple visits was not clearly addressed in the trial; therefore, the findings on relapse should be interpreted with reservation.

Symptoms were measured with PANSS or CGI–S. In Study 246, the adjusted mean change from baseline at week 52 for the PANSS total score was statistically significantly lower in the aripiprazole IM group than in the placebo group (1.43 versus 11.55; $P < 0.0001$). Because the MCID for PANSS was unspecified, the clinical significance of the difference between treatment groups observed above remains uncertain. In Study 247, the mean PANSS total score remained relatively stable across the RCT phase in both groups.

There were no statistically or clinically relevant between-group differences in changes from baseline in terms of cognition measured with the Trail A score, TOL Item Scores, and University of Maryland: Letter–Number Span Total Score in either of the studies. However, based on discussion with the clinical expert involved in this review, cognition should have been monitored in a more comprehensive way (such as with MCCB).

Findings on patient satisfaction were similar in all categories of patient satisfaction between the two treatment groups in both Study 246 and Study 247.

There was no statistically significant difference observed in MAQ Total Score, DAI Score, and IAQ Total Score. It is not certain whether these scales used to measure medication adherence are reliable or not.[33-35]

Based on a 52-week, single-arm extension study,[9] the effect of monthly administration of aripiprazole IM achieved in the RCT phase appeared to be maintained at 52 weeks (Appendix 6).

In the absence of a head-to-head comparison of aripiprazole IM with other IMs, the manufacturer submitted an indirect comparison of IM antipsychotics. In terms of relapse and discontinuation from treatment, the mixed treatment comparison (MTC) submitted by the manufacturer reported that aripiprazole IM showed similar efficacy to other IM antipsychotics, including AAP IM or TAP IM. However, the findings should be interpreted with caution, because the key limitation of the MTC was that the efficacy of different doses of different drugs (e.g., olanzapine IM, haloperidol IM) was assumed to be equal; therefore, they were considered as a single treatment category; the efficacy of the sub-therapeutic dose was considered equal to that of placebo. (See Appendix 7.)

4.2.2 Harms

There was one death reported in each trial. Overall, TEAEs were similar between aripiprazole IM and placebo (80.7% to 82.0%) and between IM and oral aripiprazole (62.5% to 63.2%). In Study 246, the most common TEAE was tremor (aripiprazole IM versus placebo, 5.9% versus 1.5%). In Study 247, the most common TEAEs (≥ 5%) in aripiprazole were comparable to those of oral aripiprazole, with the exception of akathisia (aripiprazole IM versus aripiprazole oral, 10.6% versus 6.8%), injection-site pain (7.5% versus 2.3%), and infection (6.8% vs 4.1%). More patients in aripiprazole IM experienced EPS-related AEs than those in the placebo group in Study 246 (15% versus 10%). Interestingly, patients on aripiprazole IM reported more EPS-related AEs than those on oral aripiprazole in Study 247 (21% versus 11.7%). The clinical expert involved in this review indicated that more EPS associated with aripiprazole IM, compared with oral aripiprazole, may be due to non-equivalent doses. The most common EPS-related event was akathisia (6% in both groups in Study 246 and 11% in aripiprazole IM and 7% in oral aripiprazole in Study 247). Clinically meaningful weight gain (7% body weight gain) was also comparable between aripiprazole IM and placebo (6.4% versus 5.2%) or oral aripiprazole (11.7% versus 9.5%) Neither sexual dysfunction nor metabolic syndrome was reported in either of the studies.

Overall, the incidence of serious TEAEs was infrequent and comparable in both groups in both studies. The only serious TEAEs reported for ≥ 1% of aripiprazole IM patients were schizophrenia and psychotic disorder.

In Study 246, more patients in placebo than in aripiprazole IM (13.4% versus 7.4%) discontinued use because of an AE. In Study 247, discontinuation due to AEs was similar between IM and oral aripiprazole (7.9% versus 7.1%). In both studies, psychotic disorder was the most common (≥ 2% of patients) AE that led to discontinuation.

In summary, the general safety profile of aripiprazole IM is similar to that of oral aripiprazole. No new safety concerns were detected in the two included RCTs. Injection-site AEs were mild, and diminished between first and last injection. Since more patients used benzodiazepines and anticholinergics in the aripiprazole group compared with the placebo or oral aripiprazole groups, the actual EPS-related AEs in

the aripiprazole IM group could be higher in reality. The clinical expert mentioned that head-to-head comparison versus other IM antipsychotics would be useful to compare SAEs; however, based on a manufacturer-submitted systematic review and MTC, aripiprazole IM also presented the lowest risk of clinically relevant weight gain among the IM antipsychotics. No new obvious harms arose in the single-arm extension study.[9] Again, due to the potential limitations of the MTC — such as the fact that the efficacy of different doses of different drugs (e.g., olanzapine IM and haloperidol IM) was assumed to be equal, leading them to be considered as a single treatment category — the efficacy of the sub-therapeutic dose was considered equal to that of placebo. The findings on the comparative safety should be interpreted with caution.

5. CONCLUSIONS

Findings in this review suggest that switching from oral aripiprazole (10 mg to 30 mg) to aripiprazole IM (400 mg or 300 mg) was noninferior to continuing oral aripiprazole in terms of the relapse rate at week 26 in the maintenance treatment of adult patients with schizophrenia stabilized on oral aripiprazole. In addition, for patients stabilized on aripiprazole IM, aripiprazole IM maintenance treatment significantly delayed the time to relapse compared with those who discontinued the treatment. The general safety profile of aripiprazole IM is similar to that of oral aripiprazole. A manufacturer-submitted MTC suggested no significant differences with respect to efficacy and safety between aripiprazole IM and other IM antipsychotics. However, the body of evidence for aripiprazole IM used in maintenance treatment of schizophrenia is limited by a highly restricted study population; no evidence for patients who stabilized with other non-aripiprazole AAPs, or who were inadequately controlled with oral or existing IM antipsychotics; the withdrawal design and early termination of the placebo-controlled study (Study 246); the absence of a PP analysis in the noninferiority study; and lack of head-to-head IM comparisons. As well, the included studies were not designed to adequately assess key outcomes, including mortality, hospitalization, suicidality, quality of life, functional capacity, and cognition.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review (CDR) staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

1. Brief Description of Patient Group(s) Supplying Input

The Schizophrenia Society of Canada (SSC) is a non-profit incorporated charity serving people with schizophrenia and their families. Its mission is to improve the quality of life of those affected by schizophrenia and psychosis through public education, support programs, advocacy, and research. The SSC received a grant from Otsuka Pharmaceuticals this year. It did not declare whether it had a conflict of interest in the compilation of the submission.

The Schizophrenia Society of Ontario (SSO) is a non-profit charitable organization dedicated to making a positive difference in the lives of people, families, and communities affected by schizophrenia and psychotic illnesses. It provides assistance, information and support to individuals and families living with schizophrenia. The SSO receives funding from Janssen, Novartis, Otsuka, Hoffman–La Roche, Bristol–Myers Squibb, Lundbeck, and Sunovion. It declared no conflict of interest in the compilation of the submission.

2. Condition- and Current Therapy-Related Information

The SSC obtained information through an online survey of provincial schizophrenia societies and their members, a quality of life survey of more than 1,000 respondents, focus groups, and one-on-one discussions. It recently conducted a survey of 40 individuals living with schizophrenia, a survey of 56 caregivers, and two focus groups. Both surveys covered respondents' experiences with the illness, medications, and treatments. The focus groups covered treatment and quality of life.

Schizophrenia interferes with the ability to live a normal life. Symptoms include hallucinations; delusions; confusion; difficulty sleeping, thinking, communicating, and socializing; fear of others due to paranoia; lack of energy; poor concentration; memory problems; hopelessness; depression; anxiety; suicidal thoughts; appetite problems; and lack of insight into their own condition. Schizophrenia leads to disengagement from life, lack of purpose and hope, communication problems, poverty, and the loss of friends as well as educational and job opportunities. The condition has a disabling effect, impairing people's ability to engage in basic functions such as making friends, taking public transit, completing cognitive challenges, caring for themselves, and pursuing hopes and dreams. Sometimes alcohol and drugs replace medication, with disastrous effects. Many patients have more than one mental health issue. Patients with schizophrenia experience social prejudice and discrimination, and are socially isolated due to both stigma and the illness itself. They often experience major difficulties accessing employment (with many relying on social assistance or working part-time and with a family income of $25,000 or less), adequate housing, medical treatment, and support. Severe schizophrenia often leads to homelessness and incarceration. Cardiovascular and metabolic issues result in some patients dying 20 years earlier than the rest of the population on average. However, with early access to treatment, some patients can recover some degree of quality of life.

Ninety-five per cent of patients in the SSC survey are using medication notwithstanding the side effects; those who stopped their medication did so because of side effects. In the SSO survey, 82% of patients were on antipsychotic treatment, but many of their symptoms were not fully controlled. Reported side

effects include inability to concentrate, tiredness, interruption of sleep, weight gain, loss of sex life, restlessness, and muscle spasms. Because the response to medication is unique for each patient, most have tried many medications, trying to find an effective treatment for their symptoms that is convenient and has minimal side effects. Some patients reported a lack of accessible and transparent information about side effects. Self-help groups, spirituality, and family support may also be part of the therapy. The SSO survey found that a majority of patients believed psychosocial treatments are more effective than pharmacological ones and pharmacological treatments are most effective in conjunction with psychosocial ones.

Respondents noted that medication options are restricted by provincial drug plans and by the lack of training for general practitioners to prescribe. Individuals and caregivers reported serious concerns about the costs of medications. Patients reported barriers to accessing psychiatrists and professional help in terms of both availability and costs.

Family are the primary caregivers of those living with schizophrenia, and carry a significant burden because of the social perception of mental illness. There is no respite for them. They feel frustrated by the difficulties they experience accessing treatment and information and navigating the mental health system. Persistence of symptoms leads to hopelessness: this often increases caregiver burnout, creates tension between family members, and increases stress. Families worry about side effects and note the need for adherence. They are looking for better medications to improve patients' quality of life.

3. Related Information About the Drug Being Reviewed

Patients have the expectation that Abilify Maintena will have fewer side effects; will improve adherence because it is injected once a month; and will improve their quality of life.

The SSO surveys reported that 14 patients had experience with Abilify Maintena and that 17 caregivers had relatives or friends who had used it. Half of the respondents reported an improvement in symptoms; half reported that there was no change or that some symptoms improved while others worsened; and one patient reported that symptoms only worsened. Compared with other medications, some respondents reported an improvement in side effects, some noted no change, and some noted a worsening. Side effects included weight gain, dry mouth, restlessness, anxiety, dizziness, muscle spasms, and sexual dysfunction. A majority of respondents reported an increase of adherence to medication treatment, keeping in greater contact with their doctor, an increase in physical activity, and improvement or no change in quality of life, cognitive abilities, mood, self-esteem, and engagement in activities. Advantages of Abilify Maintena included symptom control, fewer episodes of psychosis, decreased hospitalization, and fewer side effects. Disadvantages included the following: not all symptoms were well controlled and, according to caregivers, the injections made individual patients feel uncomfortable. When asked what would make the medication better, the majority answered "reducing side effects" and "increasing ability to control symptoms." Respondents would like medications to be easier to access. They have concerns about the costs of medications, which they see as a major financial burden.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 29, 2014
Alerts:	Biweekly search updates until CDEC meeting
Study Types:	No search filters were applied.
Limits:	No date or language limits were used. Conference abstracts were excluded.

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
	MEDLINE Search
1	(Abilify Maintena or aripiprazole LAI or aripiprazole IM).ti,ab,ot,sh,hw,rn,nm.
2	(aripiprazole adj (LAI or IM)).ti,ab,ot,sh,hw,rn,nm.
3	or/1-2
4	(aripiprazol* or Abilify* or Abilitat or HSDB7320 or HSDB-7320 or OPC31 or OPC-31 or OPC14597 or OPC-14597 or BMS337039 or BMS-337039).ti,ab,ot,sh,hw,rn,nm.
5	129722-12-9.rn,nm.
6	or/4-5
7	exp Injections/
8	Delayed-Action Preparations/
9	long acting drug/
10	injection/
11	sustained release preparation/
12	(once-monthly or long-acting or prolonged-release or extended-release or sustained-release or delayed-action or slow-acting or slow-release or injectable or injectables or injection or injections or intramuscular or intra-muscular).ti,ab.
13	or/7-12
14	and/6,13
15	or/3,14
16	15 use pmez
	Embase search
17	(Abilify Maintena or aripiprazoleLAI or aripiprazoleIM).ti,ab.
18	(aripiprazole adj (LAI or IM)).ti,ab.
19	or/17-18
20	*aripiprazole/
21	(aripiprazol* or Abilify* or Abilitat or HSDB7320 or HSDB-7320 or OPC31 or OPC-31 or OPC14597 or OPC-14597 or BMS337039 or BMS-337039).ti,ab.
22	or/20-21
23	and/13,22
24	or/19,23
25	24 use oemezd
26	conference abstract.pt.
27	25 not 26
	Combine MEDLINE and Embase results
28	or/16,27
29	remove duplicates from 28

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	July 23, 2014
Keywords:	Abilify Maintena, aripiprazole, schizophrenia
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
None	

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 10: PATIENT DISPOSITION (INTERIM PHASE) IN STUDY 246

Patients	ARIP IM	PBO	Total
	n (%)		
Screen	-	-	1,025
Conversion Phase (I)	-	-	567 (100)
Oral Stabilization Phase (I)	-	-	668 (100)
ARIP IM Stabilization Phase (I)	-	-	548 (100)
Randomized (I)	230 (100)	114 (100)	344 (100)
Discontinued	57 (24.8)	62 (54.4)	119 (34.6)
Sponsor Discontinued Study	0 (0.0)	0 (0.0)	0 (0.0)
Other Reasons			
Lost to Follow-up	6 (2.6)	3 (2.6)	9 (2.6)
Met Withdrawal Criteria	3 (1.3)	2 (1.8)	5 (1.5)
Withdrawn by Investigator	6 (2.6)	6 (5.3)	12 (3.5)
Withdrew Consent	12 (5.2)	4 (3.5)	16 (4.7)
Protocol Deviation	1 (0.4)	0 (0.0)	1 (0.3)
AE Without Impending Relapse	7 (3.0)	5 (4.4)	12 (3.5)
Impending Relapse With AE	9 (3.9)	11 (9.6)	20 (5.8)
Impending Relapse Without AE	13 (5.7)	31 (27.2)	44 (12.8)
Completed[a]	16 (7.0)	2 (1.8)	18 (5.2)
Continuing	157 (68.3)	50 (43.9)	207 (60.2)
Analyzed for Safety[b]	230 (100)	114 (100)	344 (100)
Analyzed for Efficacy[c]	230 (100)	114 (100)	344 (100)

AE = adverse events; ARIP = aripiprazole; I = interim analysis; IM = intramuscular; n = number of patients with the events; N = total number of patients evaluated; PBO = placebo.
[a] Patients completing the RCT phase, week 52 visit.
[b] Patients receiving at least one dose of trial medication in the RCT phase were included in the safety analysis.
[c] Patients evaluated for at least one efficacy end point in the RCT phase were included in the efficacy analysis.
Source: Clinical Study Report Study 246, Table 8.1–3, p. 193.

TABLE 11: EXTENT OF EXPOSURE TO ARIPIPRAZOLE ORAL BY PHASE

	Study 246				Study 247			
	n (%)	MEAN (SD) mg	Median (mg)	Range, (mg)	n (%)	MEAN (SD), mg	Median (mg)	Range (mg)
Conversion Phase	632 (99.8)	12.5 (4.3)	11.9	1.1 to 30	709 (100)	13.7 (5.0)	12.5	3.4 to 30
Oral Stabilization Phase	709 (99.9)	19.2 (6.7)	17.7	7.5 to 32.3	842 (100)	19.6 (6.8)	18.8	1.7 to 56.7
RCT Phase	NA	NA	NA	NA	266 (100)	20 (0.6)	19.9	4.8 to 30.1

n = number of patients with the events; NA = not applicable; RCT = randomized controlled trial; SD = standard deviation.
Source: Study 246 Clinical Study Report CT-20.1.1 p. 1395–1397; Study 247 Clinical Study Report, CT-20.1 p.1989–1992, CT-7.1 p. 722.

TABLE 12: EXTENT OF EXPOSURE TO ARIPIPRAZOLE IM

No. of Injections	Study 246		Study 247	
	ARIP IM		ARIP IM	
	n (%)	MEAN[a] (SD)	n (%)	MEAN (SD)
1st	[redacted]	[redacted]	[redacted]	[redacted]
2nd	[redacted]	[redacted]	[redacted]	[redacted]
3rd	[redacted]	[redacted]	[redacted]	[redacted]
4th	[redacted]	[redacted]	[redacted]	[redacted]
5th	[redacted]	[redacted]	[redacted]	[redacted]
6th	[redacted]	[redacted]	[redacted]	[redacted]
7th	[redacted]	[redacted]	[redacted]	[redacted]
8th	[redacted]	[redacted]	[redacted]	[redacted]
9th	[redacted]	[redacted]	[redacted]	[redacted]
10th	[redacted]	[redacted]	[redacted]	[redacted]
11th	[redacted]	[redacted]	[redacted]	[redacted]
12th	[redacted]	[redacted]	[redacted]	[redacted]
13th	[redacted]	[redacted]	[redacted]	[redacted]

ARIP = aripiprazole; IM = intramuscular; n = number of patients with the events; SD = standard deviation.
[a] Median 400 mg, range 300 to 400 mg except for all time points in both ARIP IM and placebo.
[b] Range: 400 mg to 400 mg.
Source: Study 246 Clinical Study Report CT-7.2.1, p. 804–805; Study 247 Clinical Study Report CT-7.2.1, p. 724.

TABLE 13: CONCOMITANT MEDICATIONS USED BY 3% OR MORE OF PATIENTS

Medication[a]	Study 246		Study 247	
	ARIP IM (N = 269) n (%)[b]	PBO (N = 134) n (%)[b]	ARIP IM (N = 265) n (%)[b]	ARIP Oral (N = 266) n (%)[b]
Any concomitant medication use	[redacted]	[redacted]	[redacted]	[redacted]
Lorazepam	[redacted]	[redacted]	[redacted]	[redacted]
Ibuprofen	[redacted]	[redacted]	[redacted]	[redacted]
Benztropine mesilate	[redacted]	[redacted]	[redacted]	[redacted]
Paracetamol	[redacted]	[redacted]	[redacted]	[redacted]
Clonazepam	[redacted]	[redacted]	[redacted]	[redacted]
Diazepam	[redacted]	[redacted]	[redacted]	[redacted]
Simvastatin	[redacted]	[redacted]	[redacted]	[redacted]
Zolpidem tartrate	[redacted]	[redacted]	[redacted]	[redacted]
Trihexyphenidyl	[redacted]	[redacted]	[redacted]	[redacted]
Metformin	[redacted]	[redacted]	[redacted]	[redacted]
Multivitamin	[redacted]	[redacted]	[redacted]	[redacted]
Zolpidem	[redacted]	[redacted]	[redacted]	[redacted]
Propranolol	[redacted]	[redacted]	[redacted]	[redacted]
Alprazolam	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]	[redacted]	[redacted]
Vicodin	[redacted]	[redacted]	[redacted]	[redacted]

Medication[a]	Study 246		Study 247	
	ARIP IM (N = 269) n (%)[b]	PBO (N = 134) n (%)[b]	ARIP IM (N = 265) n (%)[b]	ARIP Oral (N = 266) n (%)[b]
Omeprazole	[redacted]	[redacted]	[redacted]	[redacted]
Acetylsalicylic acid	[redacted]	[redacted]	[redacted]	[redacted]
Hydrochlorothiazide	[redacted]	[redacted]	[redacted]	[redacted]
Salbutamol	[redacted]	[redacted]	[redacted]	[redacted]
Levothyroxine	[redacted]	[redacted]	[redacted]	[redacted]
Aripiprazole[c]	[redacted]	[redacted]	[redacted]	[redacted]
Paracetamol	[redacted]	[redacted]	[redacted]	[redacted]
Ascorbic Acid	[redacted]	[redacted]	[redacted]	[redacted]
Amoxicillin	[redacted]	[redacted]	[redacted]	[redacted]
Biperiden	[redacted]	[redacted]	[redacted]	[redacted]
Naproxen	[redacted]	[redacted]	[redacted]	[redacted]
Eszopiclone	[redacted]	[redacted]	[redacted]	[redacted]
Acetylsalicylic Acid (Analgesic)	[redacted]	[redacted]	[redacted]	[redacted]
Ciprofloxacin	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]

ARIP = aripiprazole; IM = intramuscular; n = number of patients with the events; N = total number of patients evaluated; PBO = placebo; RCT = randomized controlled trial; WHO = World Health Organization.
[a] Medications were coded using the WHO Drug Dictionary (WHO–DRL).
[b] Percentages are based on the number of patients in RCT phase.
[c] Represents disallowed use of oral aripiprazole. All of these incidences were captured as protocol deviations.
Source: Study 246 Clinical Study Report, p. 333; Study 247 Clinical Study Report, p. 325.

TABLE 14: CONCOMITANT BENZODIAZEPINES AND ANTICHOLINERGICS USE

Medication	Treatment	N[a]	n (%)[b]	Average Daily Dose (mg) During Phase[a]		
				Ne[c]	Mean (SD)	Median
Study 246						
Anticholinergic drugs	ARIP IM	269	45 (16.7)	[redacted]	[redacted]	[redacted]
	PBO	134	14 (10.4)	[redacted]	[redacted]	[redacted]
Benzodiazepine derivatives	ARIP IM	269	87 (32.3)	[redacted]	[redacted]	[redacted]
	PBO	134	46 (34.3)	[redacted]	[redacted]	[redacted]
Study 247						
Anticholinergic drugs	ARIP IM	265	52 (19.6)	[redacted]	[redacted]	[redacted]
	ARIP oral	266	46 (17.3)	[redacted]	[redacted]	[redacted]
Benzodiazepine derivatives	ARIP IM	265	103 (38.9)	[redacted]	[redacted]	[redacted]
	ARIP oral	266	88 (33.1)	[redacted]	[redacted]	[redacted]

ARIP = aripiprazole; IM = intramuscular; n = number of patients with the events; N = total number of patients evaluated; Ne = number of randomized patients taking the medication during RCT with available daily dosage; PBO = placebo; RCT = randomized controlled trial; SD = standard deviation.
[a] Average daily dose (mg) during RCT = (total mg taken during the phase)/(number of days from entry to the end of the phase).
Source: Study 246 Clinical Study Report, p. 334; Study 247 Clinical Study Report, p. 326.

TABLE 15: PROPORTION OF PATIENTS WITH HOSPITALIZATION

	Study 246		Study 247	
	ARIP IM (N = 269)	PBO (N = 134)	ARIP IM (N = 265)	ARIP oral (N = 266)
Hospitalization?	n (%)[a]			
No	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalization (reason)				
Substance Abuse	[redacted]	[redacted]	[redacted]	[redacted]
Other Psychiatric or Mental Health Problem	[redacted]	[redacted]	[redacted]	[redacted]
Other, Non-Psychiatric Problem	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation of Psychotic Symptoms/Impending Relapse	[redacted]	[redacted]	[redacted]	[redacted]
Day Hospital/Partial Hospitalization	[redacted]	[redacted]	[redacted]	[redacted]

ARIP = aripiprazole; IM = intramuscular; n = number of patients with the events; N = total number of patients evaluated; PBO = placebo.
[a] Percentages are based on the number of patients randomly assigned to treatment.
Source: Study 246, p. 251; Study 247, p. 238.

TABLE 16: TREATMENT-EMERGENT POSSIBLE SUICIDAL EVENTS — C–CASA/C–SSRS IN STUDY 246

	ARIP IM (N = 269) n (%)	PBO (N = 134) n (%)
Primary Analysis		
Suicidal	[redacted]	[redacted]
Completed Suicide	[redacted]	[redacted]
Suicide Attempt	[redacted]	[redacted]
Preparatory Actions Toward Imminent Suicidal Behaviour	[redacted]	[redacted]
Suicidal Ideation	[redacted]	[redacted]
Sensitivity Analysis		
Potential Suicidal	[redacted]	[redacted]
Completed Suicide	[redacted]	[redacted]
Suicide Attempt	[redacted]	[redacted]
Preparatory Actions Toward Imminent Suicidal Behaviour	[redacted]	[redacted]
Suicidal Ideation	[redacted]	[redacted]
Self-Injurious Behaviour, Intent Unknown	[redacted]	[redacted]

ARIP = aripiprazole; C–CASA = Columbia Classification Algorithm of Suicide Assessment; C–SSRS = Columbia–Suicide Severity Rating Scale; IM = intramuscular; n = number of patients with event; N = total number of patients evaluated; PBO = placebo.
Note: Patients with multiple ratings within the same category were counted once toward the total.
Source: Study 246, p. 362.

TABLE 17: TREATMENT-EMERGENT POSSIBLE SUICIDAL EVENTS — C–SSRS IN STUDY 247

	ARIP IM (N = 265)		ARIP Oral (N = 266)	
	Ne	n (%)	Ne	n (%)
Suicidality				
Completed Suicide[a]	[redacted]	[redacted]	[redacted]	[redacted]
Suicidality[a]	[redacted]	[redacted]	[redacted]	[redacted]
Suicidal Behaviour[b]	[redacted]	[redacted]	[redacted]	[redacted]
Emergence of Suicidal Behaviour[c]	[redacted]	[redacted]	[redacted]	[redacted]
Suicidal Ideation[d]	[redacted]	[redacted]	[redacted]	[redacted]
Emergence of Suicidal Ideation[e]	[redacted]	[redacted]	[redacted]	[redacted]
Emergence of Serious Suicidal Ideation[f]	[redacted]	[redacted]	[redacted]	[redacted]
Worsening of Suicidal Ideation[g]	[redacted]	[redacted]	[redacted]	[redacted]

ARIP = aripiprazole; C–CASA = Columbia Classification Algorithm of Suicide Assessment; C–SSRS = Columbia–Suicide Severity Rating Scale; IM = intramuscular; n = number of patients with events; N = total number of patients evaluated; Ne = total number of patients with available data.

[a] Suicidality: defined as reporting any suicidal ideation or behaviour.

[b] Suicidal behaviour only: defined as reporting any type of suicidal behaviours (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behaviour) throughout the assessment period.

[c] Emergence of suicidal behaviour: defined as having no suicidal behaviour at baseline and reporting any type of behaviour at post-baseline.

[d] Suicidal ideation only: defined as reporting any type of suicidal ideation.

[e] Emergence of suicidal ideation: defined as having no suicidal ideation at baseline and reporting any type of ideation during treatment.

[f] Emergence of serious suicidal ideation: defined as having no suicidal ideation at baseline and reporting serious suicidal ideation with a score of 4 or 5 on the suicidal ideation severity rating during treatment.

[g] Worsening of suicidal ideation: defined as having a more severe rating post-baseline than at baseline in the suicidal ideation rating assessment.

Source: Study 247, p. 352.

TABLE 18: RESPONSE AND REMISSION

	Study 246		Study 247	
	ARIP IM	Placebo	ARIP IM	Oral ARIP
Remission, n/N[a] (%)				
Remission Achieved	[redacted]	[redacted]	[redacted]	[redacted]
Response n/N (%)[b]				
Response Rate	[redacted]	[redacted]	[redacted]	[redacted]

ARIP = aripiprazole; IM = intramuscular; n = number of patients with event; N = total number of patients evaluated; NR = not reported.

[a] Remission was defined as patients who achieved a score of ≤ 3 on each of the following specific PANSS items: delusions (P1), unusual thought content (G9), hallucinatory behaviour (P3), conceptual disorganization (P2), mannerisms/posturing (G5), blunted affect (N1), social withdrawal (N4), and lack of spontaneity (N6), and maintained this for a period of six months.

[b] Response was defined as patients who met all of the stability criteria.

Note: *P* value was derived using the chi-square test.

Source: Study 246 Clinical Study Report CT-5.2.1 and CT-5.2.2, p. 552–557; Study 247 Clinical Study Report CT-5.2.2 and CT-5.2.3, p. 529–533.

TABLE 19: PERCENTAGE OF RELAPSE CRITERIA — INTERIM AND FINAL ANALYSES (BY SYMPTOMS SCALE)

Criteria of Relapse[a]	Study 246					Study 247				
	ARIP IM		PBO		*P* value	ARIP IM		PBO		*P* value
	N	n (%)	N	n (%)		N	n (%)	N	n (%)	
Interim Analysis										
At least one of the criteria	[redacted]									
CGI–I + PANSS	[redacted]									
Hospitalization	[redacted]									
CGI–SS	[redacted]									
Violent Behaviour	[redacted]									
Final Analysis										
At least one of the criteria	[redacted]									
CGI–I + PANSS	[redacted]									
Hospitalization	[redacted]									
CGI–SS	[redacted]									
Violent Behaviour	[redacted]									

ARIP = aripiprazole; IM = intramuscular; n = number of patients with event; N = total number of patients evaluated; NR = not reported; PBO = placebo.
[a] Patients could meet more than one of the criteria; *P* value was derived from the chi-square test.
Source: Study 246 Clinical Study Report, Table 9.4-1, p. 216; Study 247 Clinical Study Report, CT-5.2.1.4, p. 528.

TABLE 20: ANALYSIS OF ESTIMATED PROPORTION OF PATIENTS WITH RELAPSE BY END OF WEEK 26 IN STUDY 247

Study 247	Treatment	Relapse (n/N)	Overall Relapse Rate(%)[a]	Week 26	
				Relapse Rate (%) (SE)[b]	Difference (%)[c] 95% CI, *P* Value[d]
Noninferiority	[redacted]				

ARIP = aripiprazole; CI = confidence interval; IM = intramuscular; n = number of patients with event; N = total number of patients evaluated; SE = standard error.
[a] The summary statistics are based on all available relapse data for all patients in the efficacy sample.
[b] Relapse rates are estimated from the Kaplan–Meier curves for time to impending relapse at day 182 (week 26); SEs were calculated using Greenwood's formula.
[c] Difference = estimated relapse rate for ARIP IM group minus oral ARIP group in the noninferiority test.
[d] *P* values were derived using z-statistics.
Source: Study 247 Clinical Study Report, T 9.3-1, p. 196.

TABLE 21: ANALYSIS OF TIME TO RELAPSE IN STUDY 246

	Randomized (N)	Relapse (n)	Relapse Rate (%)	Median Time to Event (days)	HR (95% CI)	*P* Value[a]
Study 246						
Interim Analysis						
ARIP IM	230	22	9.6	NE	0.212[b] (0.13 to 0.36)	< 0.0001
Placebo	114	42	36.8	212	4.72[c] (2.81 to 7.94[c])	
Final Analysis						
ARIP IM	269	27	10.0	NE	0.199[b] (0.13 to 0.32[b])	< 0.0001
Placebo	134	53	39.6	209	5.029[c] (3.15 to 8.02[c])	
Study 247						
ARIP IM	265	22	8.30	NR	0.991 (0.545 to 1.803)[d]	0.9920
ARIP Oral	266	21	7.89	NR	1.009 (0.555 to 1.834)[e]	

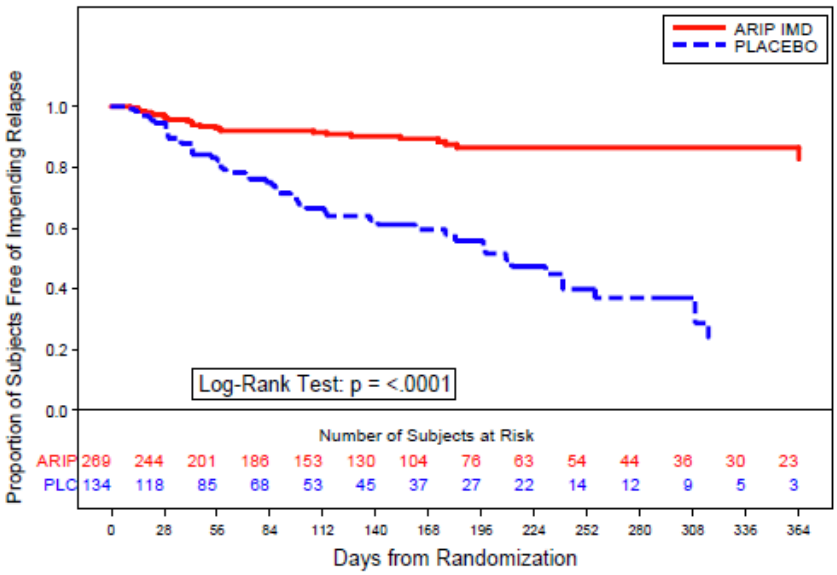
ARIP = aripiprazole; CI = confidence interval; HR = hazard radio; IM = intramuscular; n = number of patients with event; N = total number of patients evaluated; NR = not reported; NE = not estimable.
Note: The median time to impending relapse was not estimable because the percentage of patients relapsed was too low.
[a] *P* value was derived from the log-rank test for time to impending relapse.
[b] ARIP IM/placebo. HR and its 95% CI were derived from the Cox proportional hazard model with treatment as a term. HR < 1 is in favour of ARIP IM group.
[c] Placebo/ARIP IM HR and its 95% CI were derived from the Cox proportional hazard model with treatment as a term. HR > 1 is in favour of ARIP IM group.
[d] ARIP IM /ARIP oral: HRs and their 95% CIs were derived from the Cox proportional hazard model with treatment as term. HR < 1 is in favour of ARIP IM.
[e] ARIP/ARIP IM. HR and its 95% CI were derived from the Cox proportional hazard model with treatment as a term. HR > 1 is in favour of ARIP IM.
Source: Clinical Study Report 246, Table 9.3-1, p. 214.

FIGURE 6: KAPLAN–MEIER PRODUCT LIMIT PLOT OF TIME TO RELAPSE — INTERIM ANALYSIS IN STUDY 246

Figure 6 contained confidential information and was removed at the request of the manufacturer.

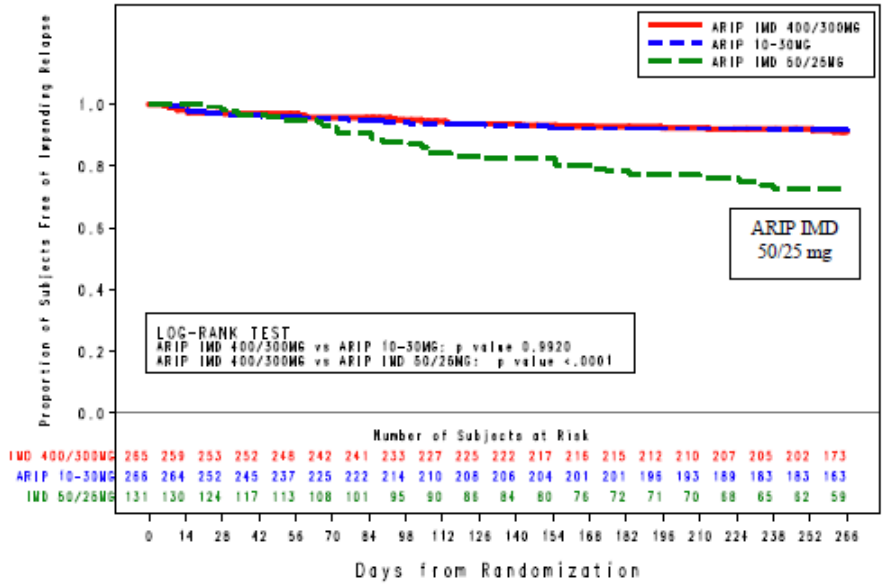
Relapse — Interim Analysis (64 events).
ARIP IMD = aripiprazole intramuscular depot.
Note: *P* value in legend represents *P* value < 0.0001.
Source: Study 246 Clinical Study Report, F 9.3-1, p. 212.

FIGURE 7: KAPLAN–MEIER PRODUCT LIMIT PLOT OF TIME TO RELAPSE — FINAL ANALYSIS IN STUDY 246



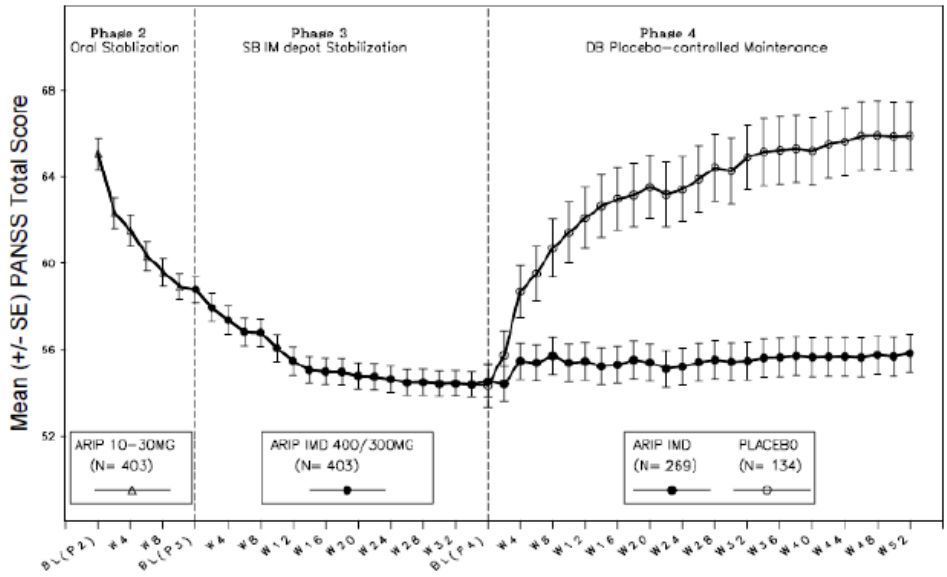
Relapse (RCT) – Final Analysis (80 events).
ARIP IMD = aripiprazole intramuscular depot; PLC = placebo; RCT = randomized controlled trial.
Source: Study 246 Clinical Study Report, F 9.3-2, p. 213.

FIGURE 8: KAPLAN–MEIER PRODUCT LIMIT PLOT OF TIME TO RELAPSE IN STUDY 247



ARIP = aripiprazole; IMD = IM depot.
Source: Study 247 Clinical Study Report, F 9.4.1-1, p. 200.

FIGURE 9: MEAN POSITIVE AND NEGATIVE SYNDROME SCALE TOTAL SCORE OVER TIME (LAST OBSERVATION CARRIED FORWARD) (RANDOMIZED CONTROLLED TRIAL, EFFICACY SAMPLE) IN STUDY 246



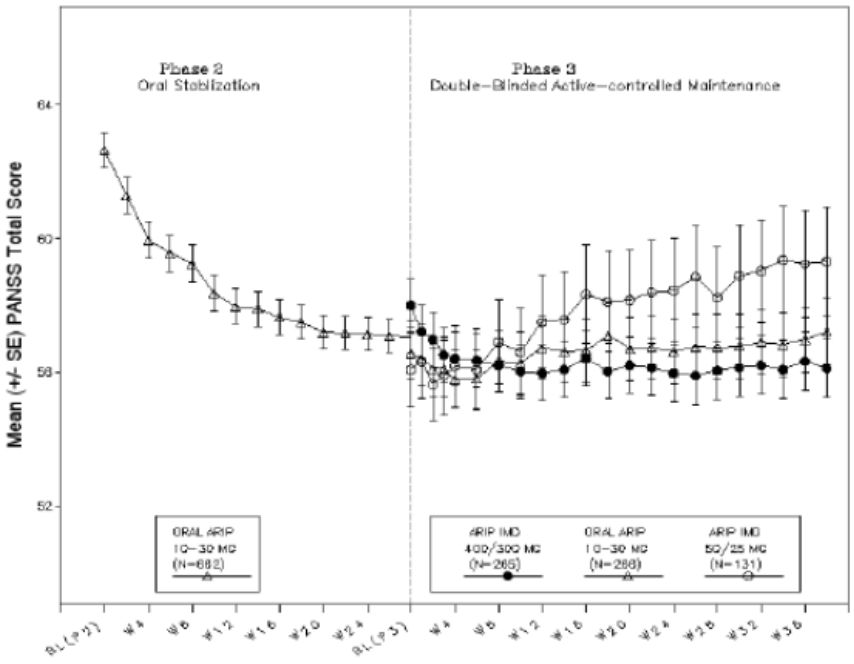
BL = baseline; DB = double-blind; SB = single-blind; P = phase; W = week.
Source: Study 246, Figure 9.5.2.1-1, p. 219.

TABLE 22: MEAN CHANGE FROM BASELINE IN SYMPTOM SCORES IN STUDY 246

Study 246	ARIP IM		PBO		Comparison (ARIP IM vs. PBO)
	N	LSM (SE)[a]	N	LSM(SE)[a]	Difference (95% CI), *P* Value
PANSS Total					
Baseline	266	54.41 (0.73)	134	54.35 (1.02)	0.06 (−2.40 to 2.53); *P* = 0.9601
Changes Week 52	266	1.43 (0.76)	134	11.55 (1.07)	**−10.11 (−12.68 to −7.54); *P* < 0.0001**
PANSS Positive Subscale Score					
Baseline	266	11.94 (0.21)	134	11.79 (0.29)	0.15 (−0.55 to 0.84); *P* = 0.6825
Changes Week 52	266	0.44 (0.27)	134	4.25 (0.37)	**−3.82 (−4.72 to −2.91); *P* < 0.0001**
PANSS Negative Subscale Score					
Baseline	266	15.82 (0.26)	134	15.72 (0.36)	0.10 (−0.78 to 0.97); *P* = 0.8306
Changes Week 52	266	0.19 (0.201)	134	1.55 (0.284)	**−1.36 (−2.04 to −0.67); *P* = 0.0001**
CGI–S					
Baseline	266	2.88 (0.050)	134	2.87 (0.071)	0.01(−0.16 to 0.19); *P* = 0.8723
Changes Week 52	266	0.14 (0.051)	134	0.66 (0.073)	**−0.52 (−0.70 to −0.35); *P* < 0.0001**
CGI–I					
Baseline		NA			
Changes Week 52	266	3.70 (1.05)	133	4.53(1.23)	***P* < 0.0001**

ARIP = aripiprazole; CGI–S = Clinical Global Impressions — Severity of illness; CGI–I = Clinical Global Impressions–Improvement; CI = confidence interval; IM = intramuscular; LSM = least squares means; N = total number of patients evaluated; NA = not applicable; PANSS = Positive and Negative Syndrome Scale; PBO = placebo; SE = standard error.
Note: Patients with baseline and at least one post-baseline assessment are included.
[a] LSM (adjusted mean), SE, difference, CI, and *P* values are derived from analysis of variance model with treatment as a term for baseline value and analysis of covariance model with treatment as a term and baseline as a covariate for change from baseline.
Source: Study 246 Clinical Study Report, p. 218–230.

FIGURE 10: MEAN POSITIVE AND NEGATIVE SYNDROME SCALE TOTAL SCORE OVER TIME IN STUDY 247



BL = baseline; P = phase; W = week.
Source: Clinical Study Report 247, Figure 9.5.1.1-1, p. 205.

TABLE 23: MEAN CHANGE FROM BASELINE IN SYMPTOM SCORES IN STUDY 247

Study 247	ARIP IM		ARIP Oral		Comparison (ARIP IM Versus ARIP Oral)
	N	LSM (SE)[a]	N	LSM (SE)[a]	Difference (95% CI), *P* Value
PANSS Total					
Baseline	263	57.94 (0.786)	266	56.57 (0.782)	1.37 (−0.81 to 3.55); *P* = 0.2179
Changes at Week 38	263	−1.66 (0.718)	266	0.58 (0.714)	**−2.24 (−4.23 to −0.25); *P* = 0.0272**
PANSS Positive Subscale Score					
Baseline	263	12.76 (0.230)	263	12.15 (0.228)	0.60 (−0.03 to 1.24); *P* = 0.0634
Changes at Week 38	263	−0.12 (0.249)	266	0.52 (0.247)	−0.64 (−1.33 to 0.05); *P* = 0.0675
PANSS Negative Subscale Score					
Baseline	263	16.79 (0.312)	266	16.93 (0.31)	−0.14 (−1.00 to 0.73); *P* = 0.7544
Changes at Week 38	263	−0.74 (0.220)	266	−0.15 (0.219)	−0.59 (−1.20 to 0.02); *P* = 0.0572
CGI–S					
Baseline	259	3.12 (0.050)	263	3.09 (0.049)	0.02 (−0.11 to 0.16); *P* = 0.7262
Changes at Week 38	259	−0.13 (0.049)	263	0.05 (0.049)	**−0.17 (−0.31 to −0.04); *P* = 0.0123**
CGI–I					
Baseline		NA		NA	NA
Changes at Week 38	263	3.27 (1.16)	266	3.66 (1.16)	***P* = 0.0002**

ARIP = aripiprazole; CGI–S = Clinical Global Impressions — Severity of illness; CGI–I = Clinical Global Impressions — Improvement; CI = confidence interval; IM = intramuscular; LSM = least squares means; N = total number of patients evaluated; NA = not applicable; PANSS = Positive and Negative Syndrome Scale; PBO = placebo; SE = standard error.
Note: Patients with baseline and at least one post-baseline assessment are included.
[a] LSM (adjusted mean), SE, difference, CI, and *P* values are derived from analysis of variance model with treatment as a term for baseline value and analysis of covariance model with treatment as a term and baseline as a covariate for change from baseline.
Source: Study 247 Clinical Study Report, p. 204–217.

TABLE 24: PERSONAL AND SOCIAL PERFORMANCE SCALE AND COGNITION ASSESSMENT

Study Visit	Study 246				Study 247			
	ARIP IM		PBO		ARIP IM		ARIP Oral	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
PSP TOTAL SCORE								
Baseline	264	67.95 (12.34)	130	69.42 (11.04)	260	65.32 (11.27)	257	66.89 (12.06)
Last Visit	258	66.58 (14.33)	127	63.22 (15.48)	257	65.88 (13.07)	248	66.82 (13.09)
Change From Baseline	253	−1.74 (10.37)	123	−6.20 (10.83)	252	0.45 (11.20)	240	0.08 (9.37)
P Value (ARIP IM vs. Placebo or ARIP Oral)	*P* = 0.0002				*P* = 0.9946			
Cognition Assessment								
Trail A Score								
Baseline	261	54.60 (30.55)	133	54.11 (31.63)	255	54.81 (32.00)	251	52.34 (37.65)
Last Visit	252	52.71 (28.57)	122	56.11 (31.49)	255	51.80 (28.18)	245	51.68 (29.20)
Change From Baseline	247	−1.55 (16.46)	122	0.87 (16.88)	246	−3.16 (22.78)	231	−2.16 (23.49)
P Value (ARIP IM vs. Placebo or ARIP Oral)	*P* = 0.1435				*P* = 0.9025			
Tower of London Item Scores								
Total Move Score								
Baseline	253	36.02 (27.17)	128	31.62 (24.43)	252	36.32 (22.50)	247	37.06 (24.16)
Last Visit	242	33.94 (23.61)	119	32.86 (22.89)	249	33.20 (23.52)	242	36.24 (25.47)
Change From Baseline	119	229.75 (121.14)	118	2.42 (16.21)	241	−2.79 (20.56)	127	−0.93 (19.41)
P Value (ARIP IM vs. Placebo or ARIP Oral)	*P* = 0.3388				*P* = 0.2350			
Execution Time								
Baseline	253	263.41 (166.31)	128	223.19 (116.31)	252	254.13 (158.57)	247	268.43 (178.87)
Last Visit	242	254.37 (149.48)	119	229.75 (121.14)	249	227.53 (157.94)	242	251.87 (170.60)
Change From Baseline	235	−6.14 (102.92)	118	9.47 (78.55)	241	−25.73 (115.08)	225	−29.71 (114.12)
P Value (ARIP IM vs. Placebo or ARIP Oral)	*P* = 0.5410				*P* = 0.8604			
University of Maryland: Letter–Number Span Total Score								
Baseline	240	13.18 (4.53)	126	13.13 (4.18)	239	12.22 (4.20)	235	12.08 (4.60)
Last Visit	233	13.06 (4.35)	115	11.97 (3.95)	227	12.04 (4.00)	227	11.93 (4.58)
Change From Baseline	226	−0.10 (2.58)	115	−1.31 (2.86)	219	−0.18 (2.76)	213	−0.13 (3.02)
P Value (ARIP	*P* < 0.0001				*P* = 0.9597			

Study Visit	Study 246				Study 247			
	ARIP IM		PBO		ARIP IM		ARIP Oral	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
IM vs. Placebo or ARIP Oral)								
Drug Attitude Inventory Score								
Baseline	266	21.06 (8.39)	130	22.18 (8.10)	254	20.69 (8.38)	254	20.75 (8.38)
Last Visit	252	21.06 (8.74)	124	22.21 (8.35)	253	20.05 (9.21)	245	20.41 (8.30)
Change From Baseline	249	−0.38 (6.36)	120	−0.10 (7.13)	245	−0.53 (7.33)	235	−0.27 (6.96)
P Value (ARIP IM vs. Placebo or ARIP Oral)	*P* = 0.4019				*P* = 0.6034			
MAQ Total Score								
Baseline	264	0.58 (0.93)	131	0.37 (0.73)	257	0.72 (0.96)	253	0.64 (0.91)
Last Visit	258	0.53 (0.91)	126	0.49 (0.94)	256	0.66 (0.91)	247	0.64 (0.87)
Change From Baseline	253	−0.04 (0.80)	123	0.12 (0.90)	248	−0.08 (0.99)	236	−0.02 (0.94)
P Value (ARIP IM vs. Placebo or ARIP Oral)	*P* = 0.3341				*P* = 0.8793			
IAQ Total Score								
Baseline	264	30.24 (4.70)	127	31.23 (4.74)	215	31.90 (3.91)	228	31.78 (4.38)
Last Visit	261	31.52 (5.59)	122	35.08 (5.60)	259	31.97 (4.43)	252	32.51 (5.05)
Change From Baseline	256	1.32 (4.74)	121	3.78 (5.34)	210	0.08 (4.45)	217	0.35 (4.35)
P Value (ARIP IM vs. Placebo or ARIP Oral)	*P* < 0.0001				*P* = 0.5007			

ARIP = aripiprazole; IAQ = Investigator's Assessment Questionnaire; IM = intramuscular; PBO = placebo; SD = standard deviation.
Note: Patients with baseline or at least one post-baseline assessment are included. Baseline is the value at the end of the preceding phase; last visit = last post-baseline evaluation in the phase; for last visit, data are equivalent to week 52 LOCF data in Study 246 or week 38 LOCF data in Study 247; *P* values are derived from comparison within analysis of covariance (ANCOVA) model with treatment as term and baseline as covariate.
Source: Study 246 Clinical Study Report, p. 234–245; Study 247 Clinical Study Report, Table 9.5.2.1-1, p. 222–231.

TABLE 25: PROPORTION OF PATIENTS WITH EACH LEVEL OF TREATMENT SATISFACTION IN PSMQ–MODIFIED

Visit	Level	Study 246				Study 247			
		ARIP IM		PBO		ARIP IM		ARIP oral	
		Ne	n (%)	Ne	n (%)	Ne	n (%)	Ne	n (%)
Baseline	Extremely satisfied	268	91 (34.0)	134	55 (41.0)	257	68 (26.5)	254	73 (28.7)
	Very satisfied	268	129 (48.1)	134	54 (40.3)	257	130 (50.6)	254	127 (50.0)
	Somewhat satisfied	268	40 (14.9)	134	20 (14.9)	257	49 (19.1)	254	47 (18.5)
	Somewhat unsatisfied	268	5 (1.9)	134	4 (3.0)	257	5 (1.9)	254	5 (2.0)
	Very unsatisfied	268	3 (1.1)	134	1 (0.7)	257	5 (1.9)	254	1 (0.4)
	Extremely unsatisfied	268	0 (0.0)	134	0 (0.0)	257	0	254	1 (0.4)
Last Visit[a]	Extremely satisfied	261	89 (34.1)	127	32 (25.2)	258	97 (37.6)	253	88 (34.8)
	Very satisfied	261	111 (42.5)	127	52 (40.9)	258	106 (41.1)	253	112 (44.3)
	Somewhat satisfied	261	42 (16.1)	127	24 (18.9)	258	40 (15.5)	253	41 (16.2)
	Somewhat unsatisfied	261	10 (3.8)	127	12 (9.4)	258	11 (4.3)	253	6 (2.4)
	Very unsatisfied	261	3 (1.1)	127	4 (3.1)	258	1 (0.4)	253	3 (1.2)
	Extremely unsatisfied	261	6 (2.3)	127	3 (2.4)	258	3 (1.2)	253	3 (1.2)

ARIP = aripiprazole; IM = intramuscular; n = number of events; Ne = total number of patients evaluated at the specified visit; PBO = placebo; PSMQ–Modified = Patient Satisfaction with Medication Questionnaire — Modified.
[a] For last visit, data are equivalent to week 52 LOCF data in Study 246 and to week 38 LOCF data in Study 247.
Source: Study 246, p. 247, Study 247, p. 233.

TABLE 26: PROPORTION OF PATIENTS WITH EACH DEGREE OF TREATMENT SIDE EFFECT IN PSMQ–MODIFIED

	Level	Study 246				Study 247			
		ARIP IM		PBO		ARIP IM		ARIP Oral	
		Ne	n (%)	Ne	n (%)	Ne	n (%)	Ne	n (%)
Baseline	No side effects	268	146 (54.5)	134	73 (54.5)	256	117 (45.7)	254	118 (46.5)
	Much less side effects	268	59 (22.0)	134	26 (19.4)	256	60 (23.4)	254	62 (24.4)
	Fewer side effects	268	37 (13.8)	134	25 (18.7)	256	41 (16.0)	254	49 (19.3)
	The same as previous	268	19 (7.1)	134	9 (6.7)	256	25 (9.8)	254	14 (5.5)
	A little more side effects	268	4 (1.5)	134	1 (0.7)	256	11 (4.3)	254	10 (3.9)
	Many more side effects	268	3 (1.1)	134	0 (0.0)	256	2 (0.8)	254	1 (0.4)
Last Visit[a]	No side effects	261	144 (55.2)	127	67 (52.8)	258	124 (48.1)	253	129 (51.0)
	Much less side effects	261	47 (18.0)	127	24 (18.9)	258	65 (25.2)	253	62 (24.5)
	Less side effects	261	41 (15.7)	127	22 (17.3)	258	38 (14.7)	253	36 (14.2)
	The same as previous	261	11 (4.2)	127	7 (5.5)	258	18 (7.0)	253	12 (4.7)
	A little more side effects	261	12 (4.6)	127	7 (5.5)	258	7 (2.7)	253	9 (3.6)
	Much more side effects	261	6 (2.3)	27	0 (0.0)	258	6 (2.3)	253	5 (2.0)

ARIP = aripiprazole; IM = intramuscular; n = number of events; Ne = total number of patients evaluated at the specified visit; PBO = placebo; PSMQ–Modified = Patient Satisfaction with Medication Questionnaire — Modified.

[a] For last visit, data are equivalent to week 52 LOCF data in Study 246 and to week 38 LOCF data in Study 247.

Source: Study 246, p. 248; Study 247, p. 234.

TABLE 27: CURRENT OR PREVIOUS MEDICATION SATISFACTION IN PSMQ–MODIFIED

	Question — Response	Study 246				Study 247			
		ARIP IM		PBO		ARIP IM		ARIP Oral	
		Ne	n (%)	Ne	n (%)	Ne	n (%)	Ne	n (%)
Baseline	Patient — current	268	254 (94.8)	133	130 (97.7)	246	226 (91.9)	253	235 (92.9)
	Patient — previous	268	14 (5.2)	133	3 (2.3)	246	20 (8.1)	253	18 (7.1)
	Caretaker comment[a] — yes	268	140 (52.2)	134	52 (38.8)	252	100 (39.7)	250	103 (41.2)
	Caretaker comment[b] — no	268	128 (47.8)	134	82 (61.2)	252	152 (60.3)	250	147 (58.8)
Last Visit[b]	Patient — current	261	225 (86.2)	126	108 (85.7)	255	232 (91.0)	252	231 (91.7)
	Patient — previous	261	36 (13.8)	126	18 (14.3)	255	23 (9.0)	252	21 (8.3)
	Caretaker comment[b] — yes	261	126 (48.3)	127	64 (50.4)	258	127 (49.2)	252	115 (45.6)
	Caretaker comment[b] — no	261	135 (51.7)	127	63 (49.6)	258	131 (50.8)	252	137 (54.4)

ARIP = aripiprazole; IM = intramuscular; n = number of events; Ne = total number of patients evaluated at the specified visit; PBO = placebo; PSMQ–Modified = Patient Satisfaction with Medication Questionnaire — Modified.
[a] "Has any caretaker made any comments on any differences between you being on your current medication and previous medication?"
[b] For last visit, data are equivalent to week 52 LOCF data in Study 246 or to week 38 LOCF data in Study 247.
Source: Study 246, p. 249; Study 247, p. 235.

TABLE 28: SUMMARY OF ADVERSE EVENTS

	Study 246		Study 247	
	ARIP IM n (%)	PBO n (%)	ARIP IM n (%)	ARIP Oral n (%)
Patients Treated	269 (100)	134 (100)	264 (99.6)	266 (100.0)
Patients With AEs	170 (63.2)	83 (61.9)	219 (82.6)	213 (80.1)
Patients With TEAEs	170 (63.2)	83 (61.9)	219 (82.6)	213 (80.1)
Patients With Serious TEAEs	11 (4.1)	9 (6.7)	15 (5.7)	15 (5.6)
Patients Discontinued Medication Due to TEAEs	19 (7.1)	18 (13.4)	21 (7.9)	19 (7.1)
Patients Who Died Due to TEAEs	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)

AE = adverse event; ARIP = aripiprazole; IM = intramuscular; n = number of events; TEAE = treatment-emergent AE; PBO = placebo.
Note: TEAE is defined as an AE that began after the start of trial medication treatment; or if the event was continuous from baseline and was serious, trial medication-related, or resulted in death, discontinuation, or interruption or reduction of trial therapy. Patients with multiple occurrences of TEAEs are counted only once per specific category.
Note: Percentages are based on the number of treated randomized patients.
Source: Study 246, p. 283; Study 247, p. 279.

TABLE 29: TREATMENT-EMERGENT ADVERSE EVENTS REPORTED FOR ≥ 2% PATIENTS IN ANY TREATMENT GROUP IN THE RANDOMIZED CONTROLLED TRIAL SAFETY SAMPLE

	Study 246		Study 247	
	ARIP IM (N = 269) n (%)	PBO (N = 134) n (%)	ARIP IM (N = 265) n (%)	ARIP Oral (N = 266) n (%)
Any TEAE[a]	269 (100)	134 (100)	219 (82.6)	213 (80.1)
Diarrhea	6 (2.2)	3 (2.2)	9 (3.4)	9 (3.4)
Toothache	7 (2.6)	3 (2.2)	7 (2.6)	13 (4.9)
Vomiting/nausea	8 (3.0)	3 (2.2)	6 (2.3)	4 (1.5)
Abdominal pain upper	NR	NR	3 (1.1)	4 (1.5)
Fatigue	6 (2.2)	1 (0.7)	5 (1.9)	9 (3.4)
Injection-site pain	8 (3.0)	5 (3.7)	20 (7.5)	6 (2.3)
Edema peripheral	1 (0.4)	3 (2.2)	3 (1.1)	3 (1.1)
Nasopharyngitis	10 (3.7)	7 (5.2)	21 (7.9)	25 (9.4)
Infection	NR	NR	18 (6.8)	11 (4.1)
Influenza	NR	NR	11 (4.2)	11 (4.1)
Upper respiratory tract infection	7 (2.6)	3 (2.2)	6(2.3)	5(1.9)
Blood pressure increased	2 (0.7)	3 (2.2)	NR	NR
Blood creatinine phosphokinase increased	NR	NR	7 (2.6)	6 (2.3)
Decreased appetite	NR	NR	5 (1.9)	1 (0.4)
Arthralgia	6 (2.2)	1 (0.7)	9 (3.4)	4 (1.5)
Back pain	6 (2.2)	3 (2.2)	10 (3.8)	14 (5.3)
Pain in extremity	5 (1.9)	6 (4.5)	6 (2.3)	7 (2.6)
Muscle spasms	NR	NR	6 (2.3)	4 (1.5)
Akathisia	15 (5.6)	8 (6.0)	28 (10.6)	18 (6.8)
Dizziness	5 (1.9)	4 (3.0)	9 (3.4)	6 (2.3)
Headache	16 (5.9)	7 (5.2)	26 (9.8)	30 (11.3)
Sedation	7 (2.6)	1 (0.7)	6 (2.3)	3 (1.1)
Tremor	16 (5.9)	2 (1.5)	8 (3.0)	9 (3.4)
Agitation	2 (0.7)	3 (2.2)	6 (2.3)	2 (0.8)
Anxiety	16 (5.9)	10 (7.5)	19 (7.2)	13 (4.9)
Depression	5 (1.9)	3 (2.2)	NR	NR
Insomnia	27 (10.0)	12 (9.0)	31 (11.7)	37 (13.9)
Somnolence	NR	NR	9 (3.4)	12 (4.5)
Psychotic disorder	8 (3.0)	9 (6.7)	8 (3.0)	8 (3.0)
Restlessness	6 (2.2)	3 (2.2)	10 (3.8)	4 (1.5)
Schizophrenia	2 (0.7)	5 (3.7)	8 (3.0)	5 (1.9)
Agitation	NR	NR	7 (2.6)	2 (0.8)
Cough	6 (2.2)	4 (3.0)	8 (3.0)	7 (2.6)
Rash	NR	NR	0 (0.0)	4 (1.5)

	Study 246		Study 247	
	ARIP IM (N = 269) n (%)	**PBO (N = 134) n (%)**	**ARIP IM (N = 265) n (%)**	**ARIP Oral (N = 266) n (%)**
Nasal congestion	1 (0.4)	3 (2.2)	NR	NR
Hypertension	4 (1.5)	3 (2.2)	3 (1.1)	4 (1.5)

AE = adverse event; ARIP = aripiprazole; IM = intramuscular; n = number of events; N = number of evaluated; NR = not reported; PBO = placebo;
TEAE = treatment-emergent AE.
[a] TEAE is defined as an AE that began after the start of trial medication treatment; or if the event was continuous from baseline and was serious, trial medication-related, or resulted in death, discontinuation, or interruption or reduction of trial therapy. Patients with multiple occurrences of TEAEs are counted only once per specific category.
Source: Study 246, p. 287; Study 247, p. 283.

TABLE 30: SERIOUS TREATMENT-EMERGENT ADVERSE EVENTS

	Study 246		Study 247	
	ARIP IM (N = 269), n (%)	**PBO (N = 134), n (%)**	**ARIP IM (N = 265), n (%)**	**ARIP Oral (N = 266), n (%)**
Any serious TEAE[a]	11 (4.1)	9 (6.7)	15 (5.7)	15 (5.6)
Sinus bradycardia	0 (0.0)	1 (0.7)	NR	NR
Acute myocardial infarction	NR	NR	1 (0.4)	1 (0.4)
Cardiac arrest	NR	NR	0 (0.0)	1 (0.4)
Cardiac failure congestive	NR	NR	1 (0.4)	0 (0.0)
Diarrhea	0 (0.0)	1 (0.7)	NR	NR
Biliary colic	0 (0.0)	1 (0.7)	NR	NR
Gunshot wound[b]	1 (0.4)	0 (0.0)	NR	NR
Injury	1 (0.4)	0 (0.0)	NR	NR
Multiple injuries	1 (0.4)	0 (0.0)	NR	NR
Diabetes mellitus	1 (0.4)	0 (0.0)	NR	NR
Hyperglycemia	1 (0.4)	0 (0.0)	NR	NR
Pancreatic carcinoma	1 (0.4)	0 (0.0)	NR	NR
Grand mal convulsion	0 (0.0)	1 (0.7)	NR	NR
Hallucination, auditory	1 (0.4)	0 (0.0)	NR	NR
Psychotic disorder	4 (1.5)	4 (3.0)	4 (1.5)	2 (0.8)
Schizophrenia	2 (0.7)	2 (1.5)	5 (1.9)	2 (0.8)
Suicidal ideation	2 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)
Suicide attempt	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.4)
Chest pain	NR	NR	0 (0.0)	1 (0.4)
Fatigue	NR	NR	0 (0.0)	1 (0.4)
Cholecystitis, chronic	NR	NR	1 (0.4)	0 (0.0)
Appendicitis, perforated	NR	NR	1 (0.4)	0 (0.0)
Pneumonia	NR	NR	1 (0.4)	1 (0.4)
Ankle fracture	NR	NR	0 (0.0)	1 (0.4)
Radius fracture	NR	NR	1 (0.4)	0 (0.0)
Ovarian epithelial cancer	NR	NR	0 (0.0)	1 (0.4)
Ovarian fibroma	NR	NR	0 (0.0)	1 (0.4)

	Study 246		Study 247	
	ARIP IM (N = 269), n (%)	PBO (N = 134), n (%)	ARIP IM (N = 265), n (%)	ARIP Oral (N = 266), n (%)
Agitation	NR	NR	1 (0.4)	0 (0.0)
Drug abuse	NR	NR	0 (0.0)	1 (0.4)
Schizophrenia, paranoid type	NR	NR	0 (0.0)	2 (0.8)
Acute respiratory distress syndrome	NR	NR	1 (0.4)	0 (0.0)
Asthma	NR	NR	0 (0.0)	1 (0.4)

AE = adverse event; ARIP = aripiprazole; IM = intramuscular; n = number of events; N = number of evaluated; NR = not reported; PBO = placebo;
TEAE = treatment-emergent AE.
[a] TEAE is defined as an AE that began after the start of trial medication treatment; or if the event was continuous from baseline and was serious, trial medication-related, or resulted in death, discontinuation, or interruption or reduction of trial therapy. Patients with multiple occurrences of TEAEs are counted only once per specific category.
[b] Occurred during a robbery.
Source: Study 246, p. 297; Study 247, p. 292–293.

TABLE 31: TREATMENT-EMERGENT ADVERSE EVENTS LEADING TO DISCONTINUATION OF TRIAL MEDICATION

	Study 246		Study 247	
	ARIP IM (N = 269), n (%)	PBO (N = 134), n (%)	ARIP IM (N = 265), n (%)	ARIP Oral (N = 266), n (%)
Any TEAE leading to discontinuation of trial medication[a]	19 (7.1)	18 (13.4)	21 (7.9)	19 (7.1)
Injection-site pain	1 (0.4)	0 (0.0)	NR	NR
Irritability	0 (0.0)	1 (0.7)	NR	NR
Drug hypersensitivity	1 (0.4)	0 (0.0)	NR	NR
Gunshot wound[b]	1 (0.4)	0 (0.0)	NR	NR
Diabetes mellitus	1 (0.4)	0 (0.0)	NR	NR
Arthralgia	1 (0.4)	0 (0.0)	NR	NR
Tardive dyskinesia	0 (0.0)	1 (0.7)	1 (0.4)	0 (0.0)
Abnormal dreams	1 (0.4)	0 (0.0)	NR	NR
Aggression	0 (0.0)	1 (0.7)	NR	NR
Agitation	0 (0.0)	1 (0.7)	1 (0.4)	0 (0.0)
Anxiety	1 (0.4)	0 (0.0)	NR	NR
Paranoia	0 (0.0)	1 (0.7)	NR	NR
Psychotic disorder	7 (2.6)	8 (6.0)	4 (1.5)	5 (1.9)
Schizophrenia	2 (0.7)	5 (3.7)	8 (3.0)	5 (1.9)
Suicidal ideation	2 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)
Suicidal attempt	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)
Cardiac arrest	NR	NR	0 (0.0)	1 (0.4)
Chest pain	NR	NR	0 (0.0)	1 (0.4)
Liver function test, abnormal	NR	NR	1 (0.4)	0 (0.0)
Dystonia	NR	NR	1 (0.4)	0 (0.0)
Tremor	NR	NR	2 (0.8)	0 (0.0)
Depression	NR	NR	0 (0.0)	1 (0.4)

	Study 246		Study 247	
	ARIP IM (N = 269), n (%)	PBO (N = 134), n (%)	ARIP IM (N = 265), n (%)	ARIP Oral (N = 266), n (%)
Drug abuse	NR	NR	0 (0.0)	1 (0.4)
Hallucinations, visual	NR	NR	0 (0.0)	1 (0.4)
Insomnia	NR	NR	1 (0.4)	0 (0.0)
Schizophrenia, paranoid type	NR	NR	0 (0.0)	3 (1.1)
Acute respiratory distress syndrome	NR	NR	1 (0.4)	0 (0.0)

AE = adverse event; ARIP = aripiprazole; IM = intramuscular; n = number of events; N = number of evaluated; NR = not reported; PBO = placebo;
TEAE = treatment-emergent AE.
[a] A TEAE is defined as an AE that began after the start of trial medication treatment; or if the event was continuous from baseline and was serious, trial medication-related, or resulted in death, discontinuation, or interruption or reduction of trial therapy. Patients with multiple occurrences of TEAEs are counted only once per specific category.
[b] Occurred during a robbery.
Source: Study 246, p. 302; Study 247, p. 297.

TABLE 32: TREATMENT-EMERGENT EXTRAPYRAMIDAL SYMPTOMS–RELATED ADVERSE EVENTS

	Study 246		Study 247	
	ARIP IM (N = 269), n (%)	PBO (N = 134), n (%)	ARIP IM (N = 265), n (%)	ARIP Oral (N = 266), n (%)
Any EPS or EPS-related event[a]	40 (14.9)	13 (9.7)	58 (21.9)	31 (11.7)
Akathisia event[a]	15 (5.6)	8 (6.0)	29 (10.9)	18 (6.8)
Akathisia	15 (5.6)	8 (6.0)	28 (10.6)	18 (6.8)
Psychomotor hyperactivity	NR	NR	1 (0.4)	0 (0.0)
Dyskinetic event[a]	2 (0.7)	2 (1.5)	7 (2.6)	3 (1.1)
Dyskinesia	2 (0.7)	1 (0.7)	6 (2.3)	2 (0.8)
Tardive dyskinesia	0 (0.0)	1 (0.7)	1 (0.4)	1 (0.4)
Dystonic event[a]	5 (1.9)	2 (1.5)	11 (4.2)	6 (2.3)
Dystonia	NR	NR	3 (1.1)	0 (0.0)
Muscle rigidity	3 (1.1)	1 (0.7)	1 (0.4)	2 (0.8)
Muscle spasms	1 (0.4)	1 (0.7)	6 (2.3)	4 (1.5)
Trismus	1 (0.4)	0 (0.0)	NR	NR
Nuchal rigidity	NR	NR	1 (0.4)	0 (0.0)
Parkinsonism event[a]	22 (8.2)	4 (3.0)	15 (5.7)	11 (4.1)
Bradykinesia	NR	NR	1 (0.4)	0 (0.0)
Hypokinesia	NR	NR	0 (0.0)	1 (0.4)
Cogwheel rigidity	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Extrapyramidal disorder	2 (0.7)	0 (0.0)	5 (1.9)	2 (0.8)
Hypertonia	1 (0.4)	1 (0.7)	NR	NR
Parkinsonian gait	0 (0.0)	1 (0.7)	NR	NR
Parkinsonism	2 (0.7)	0 (0.0)	2 (0.8)	0 (0.0)
Tremor	16 (5.9)	2 (1.5)	8 (3.0)	9 (3.4)

	Study 246		Study 247	
	ARIP IM (N = 269), n (%)	PBO (N = 134), n (%)	ARIP IM (N = 265), n (%)	ARIP Oral (N = 266), n (%)
Residual event[a]	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)
Muscle twitching	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)

AE = adverse event; ARIP = aripiprazole; EPS = extrapyramidal symptoms; IM = intramuscular; n = Number of events; N = number of evaluated; NR = not reported; PBO = placebo.
[a] Patients with multiple adverse event terms within the same category were counted only once toward the total.
Source: Study 246, p. 337; Study 247, p. 328–329.

TABLE 33: ADJUSTED MEAN CHANGE FROM BASELINE IN SAS, AIMS, AND BARS SCORES

	Study 246				Study 247			
	ARIP IM		PBO		ARIP IM		ARIP Oral	
	n	LSM Change (SE)[a]	n	LSM Change (SE)[a]	n	LSM Change (SE)[a]	n	LSM Change (SE)[a]
SAS								
Baseline Value[b]	269	10.60 (1.66)	134	10.57 (1.36)	265	10.86	266	11.03
LSM Change (SE)[a]	267	–0.02 (0.06)	132	–0.06 (0.09)	262	–0.04 (0.08)	260	−0.07 (0.08)
P Value		*P* = 0.69				*P* = 0.81		
AIM								
Baseline Value[b]	269	0.27 (1.13)	134	0.16 (0.75)	265	0.35	266	0.43
LSM Change (SE)[a]	267	–0.02 (0.03)	132	–0.02 (0.05)	262	–0.01 (0.05)	260	−0.08 (0.05)
P Value		*P* = 0.96				*P* = 0.32		
BARS								
Baseline Value[b]	269	0.09 (0.36)	134	0.13 (0.52)	265	0.15	266	0.12
LSM Change (SE)[a]	267	0.02 (0.02)	132	–0.02 (0.03)	262	0.07 (0.03)	260	−0.01 (0.03)
P Value		*P* = 0.3029				*P* = 0.047		

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; ARIP = aripiprazole; BARS = Barnes Akathisia Rating Scale; IM = intramuscular; LSM = least squares means; n = number of events; N = number evaluated; PBO = placebo; SAS = Simpson–Angus Scale; SE = standard error.
[a] LSMs and *P* values are derived from analysis of covariate model with treatment as a term and baseline as a covariate. Week 52 for Study 246; week 38 for Study 247.
[b] For baseline, n and means (SD) are provided for the actual value.
Note: Patients with baseline or at least one post-baseline are included.
Source: Study 246, p. 340–342; Study 247, p. 331–333.

TABLE 34: INCIDENCE OF POTENTIALLY CLINICALLY RELEVANT WEIGHT GAIN OR LOSS

Source	Study 246				Study 247			
	ARIP IM (N = 269)		PBO (N = 134)		ARIP IM (N = 265)		ARIP Oral (N = 266)	
	Ne	n (%)	Ne	n (%)[b]	Ne	n (%)	Ne	n (%)
Weight Gain ≥ 7%								
Last Visit	267	17 (6.4)	134	7 (5.2)	264	25 (9.5)	266	31 (11.7)
End of Trial[a]	25	5 (20.0)	4	0 (0.0)	193	20 (10.4)	171	27 (15.8)
Weight Loss ≥ 7%								
Last Visit	267	17 (6.4)	134	9 (6.7)	264	27 (10.2)	266	12 (4.5)
End of Trial[a]	25	2 (8.0)	4	1 (25.0)	193	19 (9.8)	171	8 (4.7)

ARIP = aripiprazole; IM = intramuscular; n = number of patients meeting the criteria for potential clinical relevance; Ne = total number of patients with a post-baseline weight result at the visit; PBO = placebo.
Note: A potentially clinically relevant weight gain or loss is defined as a weight gain or loss of 7% or more over baseline.
[a] End of trial indicated at week 52 for Study 246 or week 38 for Study 247.
Source: Study 246, p. 344; Study 247, p. 336.

TABLE 35: MEAN CHANGE FROM BASELINE IN PROLACTIN VALUES AT THE LAST VISIT

Source	Study 246		Study 247	
	ARIP IM	PBO	ARIP IM	ARIP Oral
n[a]	**254**	**124**	**252**	**243**
Baseline Mean[b]	5.84	5.58	5.94	5.70
Mean Change (SD) From Baseline at Last Visit	−0.38 (3.03); $P < 0.0001$	1.67 (6.02)	–0.33(3.07) $P = 0.003$	0.79 (5.30)

ARIP = aripiprazole; IM = intramuscular; PBO = placebo; SD = standard deviation.
[a] n = total number of patients with at least one observation of the given parameter.
[b] Baseline is defined as value at the end of the IM Depot Stabilization Phase for Study 246 and the end of the oral stabilization phase in Study 247.
[c] *P* values are derived from analysis of covariate model with treatment as term and baseline as covariate.
Source: Study 246, p. 357–358; Study 247, p. 347.

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- Positive and Negative Syndrome Scale (PANSS)
- Clinical Global Impressions — Severity of illness (CGI–S), Severity of Suicidality (CGI–SS), or Improvement (CGI–I)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)
- Simpson–Angus Scale (SAS)
- Personal and Social Performance (PSP)

To give a brief description of the following scales:

- Columbia Classification Algorithm of Suicide Assessment (C–CASA)
- Columbia–Suicide Severity Rating Scale (C–SSRS)
- Tower of London (TOL) test
- University of Maryland: Letter–Number Span Test
- Drug Attitude Inventory Score (DAI–10 and DAI–30)
- Investigator's Assessment Questionnaire (IAQ)
- Medication Adherence Questionnaire (MAQ) or Medical Adherence Rating Scale (MARS).

Findings

The scales used for main and secondary outcome measures, such as PANSS, CGI, BARS, AIMS, and SAS, are briefly summarized in Table 36.

TABLE 36: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Evidence of Validity	MCID	References
PANSS	30-item rating scale (1 to 7 scale): Positive symptoms, negative symptoms, and general psychopathology.	Yes	Unclear; depends on baseline severity	36-42
CGI	3-item scale: severity of illness (-S), global improvement (-I), and efficacy index (-E). CGI–S and –I are rated from 1 (normal or very much improved) to 7 (extremely ill or very much worse) and are considered separately.	No	1 point	27,28,43
CGI–SS	Derivative of the CGI scale that is specific for severity of suicidality. Rated from 1 (not at all suicidal) to 5 (attempted suicide).	No	Unknown	26
BARS	4-item scale: observation, awareness, distress, and global clinical assessment.	Yes	Unknown	44-46
AIMS	12-item scale: 7 on abnormal movements, 3 on global assessment, and 2 items specific to dentition.	Yes	Unknown	47-52
SAS	10-item scale: one measuring gait, six measuring rigidity, and three measuring glabella tap, tremor, and salivation.	Yes	0.3 to 0.65	53,54

Instrument	Type	Evidence of Validity	MCID	References
PSP	4-item scale: socially useful activities, including work, personal, and social relationships, self-care, and disturbing and aggressive behaviours.	Yes	10 points	[55-57]

AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CGI = Clinical Global Impression; CGI–SS = CGI Severity of Suicidality; MCID = minimal clinically important difference; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance; SAS = Simpson–Angus Scale.

Psychotic Disorder Scales

Positive and Negative Syndrome Scale

The PANSS was developed as a 30-item rating scale, which adapted 18 items from the Brief Psychiatric Rating Scale (BPRS) and 12 items from the Psychopathology Rating Schedule.[37] The PANSS requires a 30- to 40-minute patient interview to gather information with which to assess the patient with regard to the presence and severity of psychopathology in the previous week. The PANSS instrument provides a complete definition of each item as well as detailed anchoring criteria for each of seven rating points: 1 = absent; 2 = minimal; 3 = mild; 4 = moderate; 5 = moderate–severe; 6 = severe; and 7 = extreme. In the 30-item scale, seven items are related to positive symptoms, seven items to negative symptoms, and 16 items to general psychopathology (as shown below). The General Psychopathology Scale is considered an adjunct to the positive–negative assessment, since it provides a separate but parallel measure of schizophrenia severity that can serve as a point of reference for interpreting the positive and negative scores.[37] Finally, a composite scale may be derived by subtracting the negative from the positive score. This scale expresses the direction and magnitude of difference between positive and negative syndromes. This score may reflect the degree of predominance of one syndrome over the other based on the valence (positive or negative).

TABLE 37: THIRTY ITEMS OF THE POSITIVE AND NEGATIVE SYNDROME SCALE[38]

Positive Scale	General Psychopathology Scale
P1. Delusions	G1. Somatic concern
P2. Conceptual disorganization	G2. Anxiety
P3. Hallucinatory behaviour	G3. Guilt feelings
P4. Excitement	G4. Tension
P5. Grandiosity	G5. Mannerisms & posturing
P6. Suspiciousness	G6. Depression
P7. Hostility	G7. Motor retardation
	G8. Uncooperativeness
Negative Scale	G9. Unusual thought content
N1. Blunted affect	G10. Disorientation
N2. Emotional withdrawal	G11. Poor attention
N3. Poor rapport	G12. Lack of judgment & insight
N4. Passive/apathetic social withdrawal	G13. Disturbance of volition
N5. Difficulty in abstract thinking	G14. Poor impulse control
N6. Lack of spontaneity & flow of conversation	G15. Preoccupation
N7. Stereotyped thinking	G16. Active social avoidance

In clinical trials, changes from baseline in the PANSS total score, as well those for the positive and negative subscales, are typically used as study end points. The PANSS total is scored by summing ratings

across items: the potential ranges are 7 to 49 for the Positive and Negative Scales and 16 to 112 for the General Psychopathology Scale. Thus, the range of possible scores is 30 to 210. The General Psychopathology Scale is usually not rated individually, but it is captured in the total score. The range of scores for the composite scale is from –42 to 42, which may be used to characterize whether positive or negative symptoms predominate, and is not a part of the PANSS total score.

Kay et al. reported on psychometric testing of the PANSS in 101 in-patients with schizophrenia.[37] Scores on all subscales were reported to exhibit a normal distribution, suggesting suitability for parametric statistical analysis. Further, the range of scores was lower than the potential, suggesting a lack of ceiling effect. Internal consistency was demonstrated for the positive (alpha = 0.73), negative (alpha = 0.83), and general psychopathology (alpha = 0.79) subscales. Test–retest reliability was assessed three to six months later on a cohort of 15 patients who remained hospitalized; Pearson correlation coefficients were 0.80, 0.68, and 0.60 for the positive, negative, and general psychopathology subscales respectively.[37] Peralta and Cuesta reported on the inter-rater reliability of the PANSS from a sample of 100 consecutively admitted patients with schizophrenia.[41] Positive and negative scales showed good inter-rater reliability: interclass correlation coefficients (ICC) of 0.72 and 0.80, respectively. Inter-rater reliability was moderate for the General Psychopathology Scale: ICC = 0.56.

More recently, a number of investigators have conducted principal components analysis to expand the identification of discrete dimensions of schizophrenia beyond the focus on positive and negative symptoms. A number of similar five-factor models, including most or all of the original PANSS items, have been proposed and tested for reliability and validity.[40,58-61] One such model was proposed by Marder et al., and categorizes all original PANSS items into five dimensions: positive symptoms (eight items), negative symptoms (seven items), disorganized thought (seven items), uncontrolled hostility/excitement (four items), and anxiety/depression (four items).[40]

It is unclear what degree of improvement in the PANSS total or subscale scores is clinically important. However, in a comparison of PANSS to the CGI scale, it was suggested that an absolute reduction of 15 in the total PANSS score corresponds to “minimally improved” on the CGI–I score, and a reduction of the CGI–SS by one severity step.[39] In comparison, a reduction of 33 in the total PANSS score corresponds to “much improved” on the CGI–I score. However, the above estimates were sensitive to baseline severity of illness to the extent that participants with a lower baseline required smaller reductions in the PANSS to produce a particular improvement in the CGI. For this reason it has been suggested that change in PANSS score has limited usefulness as a primary outcome, due to variability in baseline symptom intensity.[36,42] Rather, a set of standardized remission criteria, which may be suitable for use in clinical practice and clinical trials, has been proposed. Specifically, a score of ≤ 3 on eight PANSS items (P1, P2, P3, N1, N4, N6, G5, and G9) for a period of at least six months is considered to represent remission of disease.[36,42]

Mental Health Status and Functioning

Clinical Global Impressions

The CGI scale is a three-item scale used to assess the overall severity and response to treatment of mental disorders.[27] It is not specific to schizophrenia, although efforts to adapt the scale specifically to this disorder have been undertaken.[28] The more usual CGI scale items include severity of illness (CGI–S) at the time of the assessment on a 7-point scale (1=normal; 7=extremely ill), global improvement (CGI–I) relative to baseline on a 7-point scale (1=very much improved; 7=very much worse), and an efficacy index that incorporates the clinician’s assessment of therapeutic effect in relation to adverse effects in a 4-point x 4-point grid rating scale (where 0 = marked improvement and no adverse events; 4 =

unchanged or worse; and adverse events outweigh therapeutic events).[27] The difficulty of combining the concepts of efficacy and adverse events has led to criticism of this last item.[28] However, there is no total score for the CGI; rather, scores on the individual items are considered separately.

The CGI–SS scale is a derivative of CGI that has been adapted to assess global severity of suicidality.[26] It is a 5-point scale (where 1 = not at all suicidal; 2 = mildly suicidal; 3 = moderately suicidal; 4 = severely suicidal; and 5 = attempted suicide).[26]

As the CGI is quick to administer, it is suited to clinical settings; however, there is little information regarding its reliability or validity. Rabinowitz et al. sought to validate the CGI–S via a comparison of PANSS and CGI–S scores from seven trials of risperidone in schizophrenia.[43] CGI–S scores from the pooled trials corresponded to the following mean PANSS scores: 1 (normal) = PANSS 55.5; 2 (borderline ill) = PANSS 67.0; 3 (mildly ill) = PANSS 79.6; 4 (moderately ill) = PANSS 92.4; and 5 (markedly ill) = PANSS 99.7. Predefined measures of clinical improvement were a 20% reduction in the PANSS score and a 1-point decrease on the CGI–S. The sensitivities and specificities for the CGI–S to detect this level of improvement in the seven trials ranged from 64.5% to 89.6% and 65.7% to 82.8%, respectively. From this assessment, it appears that the CGI–S and PANSS are correlated and exhibit substantial agreement in detecting change.

Adverse Events: Extrapyramidal Symptoms

Barnes Akathisia Rating Scale

BARS is the most commonly used scale to measure antipsychotic-induced akathisia in clinical trials.[45] The BARS is a four-item scale that scores patients' akathisia based on: (i) brief observation by the clinician (ranked 0 to 3); (ii) patient report of awareness of restlessness (ranked 0 to 3); (iii) patient report of distress related to restlessness (ranked zero to three), which produces (iv) a global clinical assessment of akathisia.[44] The global clinical assessment contains five well-defined severity categories, which are considered clinically relevant: 0 = absent; 1 = questionable; 2 = mild; 3 = moderate; 4 = marked; and 5 = severe.[45] Inter-rater reliability for all four items, based on duplicate rating of 42 chronic in-patients and measured by Cohen's kappa, were observation (0.74), awareness (0.83), distress (0.90), and global clinical assessment (0.96).[44] The BARS has been reported to correlate only weakly with motor activity measured by actometry, potentially due to the fact that actometry measures only actual movement, while the BARS also measures the patient experience of awareness and distress.[46]

Abnormal Involuntary Movement Scale

The AIMS is a 12-item scale for assessing dyskinesias, to be completed by clinician or researcher. The first seven items pertain to abnormal movements in three specific anatomical sites: facial and oral movements (four items); extremity movements (two items); and trunk movements (1 item).[47] The remaining items are global assessments (three items, including global severity, incapacitation, and patient awareness), and two items specific to dentition. Except for items related to dentition, items are scored on a 5-point scale: none, normal (one), minimal (two), mild (three), moderate (four), or severe (five). Inter-rater reliability in a sample of 38 outpatients with a history of dyskinesia was reported to be high; Pearson correlation coefficient = 0.87 for all items except those related to dentition.[48] However, inter-rater reliability is reported to be higher among experienced raters.[52] The validity of the AIMS has been established via comparisons to other similar instruments: the Extrapyramidal Symptom Rating Scale (ESRS) and the Schedule for the Assessment of Drug-Induced Movement Disorders (SADIMoD).[49,50] Gharabawi et al. examined associations between individually related and overall severity scores from the AIMS and ESRS via logistic regression.[49] R^2 values ranged from 0.30 (trunk movements) to 0.67 (lips and perioral area); the R^2 value was 0.56 for global severity. Loonen examined associations between: (i)

total AIMS scores; (ii) total items excluding global and dental items; and (iii) four facial and oral movement items.[50] Spearman's correlation coefficients between the active global dyskinesia subscale of the SADIMoD and the above AIMS scores were 0.76, 0.82, and 0.83, respectively. It is unclear what would constitute a meaningful change in the AIMS. However, the presence of tardive dyskinesia is accepted based on a rating of mild in two or more anatomical areas, or moderate or greater symptoms in one of more anatomical areas.[49,51]

Simpson–Angus Scale

The SAS was developed in the 1960s to identify neuroleptic-induced Parkinsonism. The scale contains 10 items: one measuring gait, six measuring rigidity, and three measuring glabella tap, tremor, and salivation.[53] Each item is scored on a 5-point scale from 0 (complete absence) to 4 (extreme), and a total score is obtained by adding all item scores and dividing by 10 (the total number of items). Scores of up to 0.3 were considered to be within the normal range. However, recently it has been suggested that the upper limit of normal be raised to 0.65.[53] Inter-rater reliability of the SAS between two physicians in a trial of haloperidol containing 14 participants was determined (correlation coefficient of 0.87).[54] In this same trial, SAS scores were significantly higher for participants treated with haloperidol compared with placebo, supporting the discriminant validity of the SAS.

Personal and Social Performance

A relatively recent development to assess social functioning in schizophrenia,[56] the PSP assesses the existence and level of difficulties in function over the previous month in four main areas: (a) socially useful activities including work; (b) personal and social relationships; (c) self-care; and (d) disturbing and aggressive behaviours. A single score from 0 to 100 is assigned by the clinician, with a higher score indicating higher functioning. Explicit criteria for scoring based on observed or reported functioning within each of the four areas above are used to assign patients to a percentile rank. The level of functioning in other areas is used to adjust the rating inside the decimal level; e.g., between 61 and 70. The reliability and validity of the PSP has been tested in patients in both the acute and stable phases of schizophrenia.[55,57] Reported intra-class correlation coefficients were > 0.70 in stable patients and > 0.80 for acute patients, and in both instances the PSP was able to discriminate between different levels of the CGI–S scale and was sensitive to changes in the PANSS score. Based on comparisons to the CGI–S, it has been suggested that a 10-point increase in the PSP is clinically meaningful for patients in both the acute and stable phases of schizophrenia.[55,57]

A brief description of other scales used in the included trials

Columbia Classification Algorithm of Suicide Assessment

The C–CASA is a standardized suicidal rating system that provides data for the suicidal risk analysis of antidepressants.[62]

Columbia–Suicide Severity Rating Scale

The C–SSRS is a standard method to quantify the severity of suicidal ideation and behaviour.[63]

Tower of London

The TOL is a measure of patient planning ability, based on a puzzle game similar to Tower of Hanoi.[64] Total move score is the total number of moves to complete the game, but total score would also depend on the number of puzzle pieces provided to the participant.

University of Maryland: Letter–Number Span Test

This is a test requiring patients to mentally reorder an orally presented list containing letters and numbers and repeat them back.[65] The total number of correct answers is used as the score. This test is part of the MATRICS Consensus Cognitive Battery of tests. It is also called working memory Letter–Number Span Test.

Drug Attitude Inventory Score
The aim of the DAI–10 and DAI–30 questionnaires is to gain some understanding of what people think about medications and what experiences people have of them.[33]

Investigator's Assessment Questionnaire
The IAQ is a clinical tool for the relative assessment of response to antipsychotics in patients with schizophrenia and schizoaffective disorder.[66] The IAQ has 10 items that cover common symptoms of schizophrenia or side effects. Scores are obtained for each item and there is also a composite score. The items are Positive Symptoms, Negative Symptoms, Other Efficacy Symptoms, Somnolence, Weight Gain, Prolactin Elevation, Akathisia, Other Extrapyramidal Symptoms (EPS), Other Safety or Tolerability Issues, Cognition, Energy, and Mood.

Medication Adherence Questionnaire or Medical Adherence Rating Scale
The MAQ or MARS is a structured, four-item, self-reported adherence measure.[34] A version has been adapted for use with psychoses.[35]

Conclusion

A majority of the scales used in the present submission for main outcomes measures are accepted and validated, except for the CGI, which has not been truly validated. The minimal clinically important difference for these scales nevertheless remains unclear, except for the CGI, SAS, and PSP.

APPENDIX 6: SUMMARY OF OTHER STUDIES

An extension study (Study 248)[9] was carried out after the completion of pivotal studies 246 and 247. Study 248 was a 52-week, open-label, multi-centre, single-arm trial. Its primary objective was to evaluate the safety and tolerability of 300 mg and 400 mg aripiprazole intramuscular (IM) depot administered every four weeks to participants with schizophrenia. The secondary objectives were to evaluate the efficacy of aripiprazole and its impact on social functioning.

Study Characteristics

Study characteristics are summarized in Table 38. [redacted]. Inclusion criteria for the enrolment of new patients were similar to those used in studies 246 and 247.

The primary efficacy end point was the percentage of stable participants at baseline (i.e., at the beginning of the maintenance phase) who remained stable at the last visit. Criteria to define stability were the same as in studies 246 and 247. The key secondary efficacy end point was the proportion of participants meeting the impending relapse criteria (criteria were the same as in studies 246 and 247) at any time during the maintenance phase.

TABLE 38: CHARACTERISTICS OF STUDY 248

Study	Population	Intervention	Comparator	Outcomes
Study 248: a 52-week, open-label, multi-centre, single-arm trial	[redacted]	Aripiprazole intramuscular depot 300 mg or 400 mg[b] every 4 weeks	None	Efficacy: proportion of stable patients at last visit; proportion of patients meeting impending relapse Scales: [redacted]

[redacted]

Study Design

Study 248 was conducted in four phases: a screening phase, a conversion phase, an oral stabilization phase, and a maintenance phase. Its design has been summarized in Table 39. A 26-week follow-up was also conducted by the investigators of Study 248 after the maintenance phase.

TABLE 39: STUDY DESIGN

Phase	Duration	Description
1. Screening phase	Up to 42 days	New patients and late patients (more than 30 days after withdrawal or completion) coming from studies 246 and 247 were screened for inclusion or exclusion. Criteria were similar to criteria for entering studies 246 and 247. Patients directly entering (less than 30 days) from studies 246 and 247 were not screened again.
2. Conversion phase	4 to 6 weeks	New participants taking other antipsychotics (except clozapine which was an exclusion criterion) were cross-titrated from these antipsychotics to a starting dose of oral aripiprazole 10 mg or 15 mg/day.
3. Stabilization phase	Up to 16 weeks	Participants were stabilized on oral aripiprazole 10 mg to 30 mg daily. Patients coming from studies 246 and 247 were put back on oral aripiprazole for stabilization.
4. Maintenance phase	52 weeks	Participants received monthly aripiprazole intramuscular depot (300 mg or 400 mg, depending on tolerability). Participants also received oral aripiprazole (10 mg to 20 mg daily) for the first 2 weeks to maintain therapeutic plasma concentration.

Efficacy

In addition to the aforementioned primary and key secondary efficacy end points, some other secondary efficacy end points were assessed. [redacted] Efficacy end points are summarized in Table 40.

[redacted]

TABLE 40: SUMMARY OF EFFICACY END POINTS OF STUDY 248

End Points	n/N	%
Among patients stable at baseline: • Remained stable at their last visit[a]	[redacted]	[redacted]
Proportion of participants who met impending relapse criteria at any time during the maintenance phase	[redacted]	[redacted]
Among participants who remained in the trial for at least 6 months:[b] • Proportion who achieved remission during maintenance phase	[redacted]	[redacted]
Among participants who were stable at baseline and completed the week 28 visit of the maintenance phase: • Proportion who remained stable at week 28	[redacted]	[redacted]

	N	Mean	SD
PANSS Total Score Baseline Week 52 Change from baseline	[redacted]	[redacted]	[redacted]
	N	**Mean**	**SD**
PANSS Positive Subscale Score Baseline Week 52 Change from baseline	[redacted]	[redacted]	[redacted]
PANSS Negative Subscale Score Baseline Week 52 Change from baseline	[redacted]	[redacted]	[redacted]
CGI–S Baseline Week 52 Change from baseline	[redacted]	[redacted]	[redacted]
CGI–I Baseline Week 52 Change from baseline	[redacted]	[redacted]	[redacted]

CGI–I = Clinical Global Impressions — Improvement; CGI–S = Clinical Global Impressions — Severity; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.

[a] Last visit was defined as the last visit with available data whether the participant completed the 52 weeks or was an early termination.

[b] The time of 6 months is calculated from the day of enrolment, not the beginning of the maintenance phase.

Note: Baseline is measured at the beginning of the maintenance phase.

[redacted]

[redacted]

Safety

[redacted].

[redacted] Table 41. [redacted]

TABLE 41: SUMMARY OF ADVERSE EVENTS DURING MAINTENANCE PHASE OF STUDY 248

Adverse Events	Occurrence	
	n/N	%
Serious TEAEs (> 1% occurrence)		
All	[redacted]	[redacted]
Schizophrenia	[redacted]	[redacted]
Psychotic disorder	[redacted]	[redacted]
TEAEs (> 5% occurrence)		
Headache	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
TEAEs related to:		
Weight	[redacted]	[redacted]
Prolactin	[redacted]	[redacted]
TEAEs resulting in discontinuation of drug		
All	[redacted]	[redacted]
Schizophrenia	[redacted]	[redacted]
Psychotic disorder	[redacted]	[redacted]
Deaths		
All causes (but not related to drug)	[redacted]	[redacted]
Suicidal events		
All	[redacted]	[redacted]
Suicidal ideation	[redacted]	[redacted]
Suicide attempt	[redacted]	[redacted]
Completed suicide	[redacted]	[redacted]

TEAE = treatment-emergent adverse event.

Critical Appraisal

[redacted]

Conclusions

[redacted]

APPENDIX 7: SUMMARY OF MANUFACTURER-SUBMITTED MIXED TREATMENT COMPARISON

Since the time that this section was written and confidential information was redacted or deleted as requested by the manufacturer, the results of the manufacturer-conducted mixed treatment comparison have been published: Majer IM et al., 2015.[67]

The manufacturer conducted a mixed treatment comparison (MTC)[68] based on a systematic review to evaluate the relative efficacy of aripiprazole long-acting injection (Abilify Maintena) (300 mg and 400 mg vial) once daily compared with first- and second-generation long-acting injectable (LAI) antipsychotics and relevant oral antipsychotics. This brief provides a summary and critical appraisal of the methods and main findings of the MTC.

Summary of network meta-analysis

Since none of the included pivotal randomized controlled trials (RCTs) for this submission were designed to compare aripiprazole administered intramuscularly (IM) with relevant active antipsychotics IM, an MTC was performed by the manufacturer to estimate the comparative efficacy of aripiprazole IM, paliperidone IM (i.e., paliperidone palmitate), risperidone IM, olanzapine pamoate, haloperidol IM, aripiprazole oral, and olanzapine oral on the following outcomes: relapse and the discontinuation of maintenance therapy due to adverse events (AEs). The AEs included the number of patients experiencing EPS and weight gain.

Methods

Eligibility Criteria

The MTC was based on a systematic review. The main inclusion criteria for the systematic review were RCTs in adult patients (≥ 18 years old) with schizophrenia who were stabilized and not treatment-resistant. Interventions and comparators included aripiprazole IM, olanzapine pamoate, paliperidone IM, risperidone IM, and haloperidol IM. The sample size was at least 10 patients; trial duration had to be at least 24 weeks in order to be included. Stable disease was generally defined by a PANSS score of approximately 60 (range: 60 to 80) and outpatient status. Schizoaffective disorder was not considered in this review. The outcomes of interest were relapse, discontinuation of the maintenance therapy, EPS, or weight gain.

Mixed Treatment Comparison at 26 Weeks

[redacted]

[redacted]

Results

Study and Patient Characteristics

[redacted] (Figure 11). [redacted] [19,71] [72] [19,71] [19] [71] [73] [74] [redacted] (See Table 42.)

In the MTC, a quality assessment of all selected RCTs was performed, evaluating the types of bias (i.e., selection bias, performance bias, detection bias, attrition bias, and reporting bias) in accordance with Centre for Reviews and Dissemination and Cochrane guidelines.[75] A complete overview of the performed quality assessment is presented in Table 43. Few details were provided on the method of randomization or allocation concealment. Baseline demographic and disease characteristics were reported in all studies. In all six publications, providers and participants were reported to be blind to treatment. Outcomes for all participating patients were reported, and the last observation carried forward (LOCF) approach was used to account for missing data. Imputed data (mostly for PANSS scores) may have affected the outcomes of interest indirectly since, in several cases, the definition of relapse depended on the actual PANSS score. Nonetheless, it is not expected that such attrition bias affected the results of the studies. There were no selective reporting issues with regard to the primary outcomes in the publications of the included RCTs. Overall, the RCTs were of comparable quality. Treatment arms were reportedly balanced at baseline. All RCTs included an intention-to-treat (ITT) analysis. It was generally unclear whether there were unexpected imbalances in dropouts between groups (Table 43).

Results of the Meta-Analysis

Risk of relapse at 26 weeks

The efficacy outcomes and estimated hazard ratios for each active treatment relative to placebo are presented in Table 44, Table 45, and Table 46. Also see Figure 12: Estimated 26-Week Probabilities and 95% Credible Intervals for the Four Outcomes.

[redacted]

Risk of Discontinuation at 26 Weeks

[redacted] (Table 45, Table 46). [redacted] (See Table 46.)

Risk of Weight Gain (≥ 7%) at 26 Weeks

[redacted] Table 46. [redacted] The 95% CrIs were large, indicating substantial uncertainty around the point estimates.

Six sensitivity analyses excluding specific RCTs were performed for all above outcomes of interest. Overall, the differences between the estimates in the base case analysis and the six alternative models were relatively small. All scenarios lead to the same conclusions in terms of the risks of relapse and

discontinuation due to AEs. Thus, it was concluded by the author that the results of the MTC were robust.

Critical Appraisal of Network Meta-Analysis

The quality of the manufacturer-submitted network meta-analysis (NMA) was assessed according to recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[76] Details and commentary for each of the relevant items identified by ISPOR are provided in Table 47.

Strengths

The MTC appears to satisfy many of the ISPOR criteria. It was based on a systematic review to identify all relevant studies. The validity of all individual studies was assessed using CRD and Cochran guidelines.[72] Patient characteristics in the individual studies were well reported and key characteristics appeared to be similar across studies. To account for differences in study duration (range: 24 weeks to 52 weeks), all of the efficacy parameters in the MTC were assessed at 26 weeks. The analysis was conducted using an appropriate and well-reported methodology (i.e., Bayesian analysis models created with WinBUGS 1.4.1). The outcome measures assessed in the MTC were appropriate and consistent with the key efficacy assessments included in the CADTH Common Drug Review (CDR). Six sensitivity analyses excluding specific RCTs were performed. The DIC was used to compare model fit between the fixed- and random-effects models.

Limitations

A potential limitation was heterogeneity in terms of the population, intervention, and duration of the follow-up in the review. For example, 7.6% of patients included in one study[73] had schizoaffective disorder, despite schizoaffective disorder being one of the exclusion criteria in the systematic review. As well, the criteria for patients being considered stable were variable from study to study, and not all patients included in one study[72] were stabilized. Various dosages were used in the original included RCTs. Most of the dosages of study medications were consistent with recommendations in the Canadian product monographs, except for olanzapine IM, which is not marketed in Canada.

Secondly, in the MTC, the efficacy of different doses (olanzapine IM, haloperidol IM) was assumed to be equal; therefore, they were considered as a single treatment category; the efficacy of the sub-therapeutic dose was considered equal to that of placebo. The CADTH clinical expert involved in this review indicated that dose equivalence between different drugs used in the MTC cannot be made.

Third, the trial duration was 24 weeks, while the MTC analysis lasted 26 weeks. However, various sensitivity analysis results excluding specific RCTs have shown a similar to base-case analysis; therefore, a significant impact of the heterogeneity on the overall evidence is unlikely. This was confirmed in the validated analyses[77] conducted by Red Outcomes, in which, when testing the competing risk model against a univariate model to explore the potential bias incurred by outcome heterogeneity in the competing risk model, results were comparable. Although the above assumptions were endorsed by European regulatory authorities for both aripiprazole IM and olanzapine IM, and further supported by clinical expert opinion, the actual impact of the assumption on the analysis was unknown. Assumption of sub-therapeutic dose equivalency to placebo is also a potential limitation. Since the list of excluded studies was not provided in the MTC, whether all eligible studies (e.g., placebo-controlled trials on risperidone IM) were included in the MTC is uncertain.

Fourth, due to the lack of any direct head-to-head trial among different IM antipsychotics, a comparison of direct and indirect estimates of effect is not estimable; this is important information to assess inconsistency.

Finally, substantial uncertainty surrounded the estimates. This can be explained by several factors: the multinomial nature of the mutually exclusive outcomes contributed to the high uncertainty, since, in general, fewer events are observed for an end point if more end points are defined; although the random-effects model had a better fit on the data than did the fixed-effects model, it entailed larger uncertainty around the point estimates, and by construction of the MTC, the uncertainty around point estimates was larger for treatments for which only indirect evidence was available (i.e., risperidone IM).

Summary

In the absence of adequate head-to-head trial data for aripiprazole IM with other IM antipsychotics, the manufacturer conducted a Bayesian MTC analysis based on a systematic review of RCTs to compare aripiprazole IM with paliperidone IM, risperidone IM, olanzapine IM and haloperidol IM. In terms of relapse and discontinuation from treatment, the MTC indicated that aripiprazole IM was similarly efficacious compared with other IM antipsychotics. [redacted] Although generally well conducted, because of several key limitations of the MTC, the clinical similarity of aripiprazole long-acting injectable (LAI) with paliperidone LAI and risperidone LAI is uncertain. The MTC suffered from a weakly linked network; from combining all different doses of individual comparators together; from assuming sub-therapeutic doses were equivalent to placebo; and from the unexplained exclusion of trials that might have strengthened the network and/or validated the results (e.g., placebo-controlled risperidone LAI trials). Also, the assumption of equivalence of doses of treatments within the MTC may not be reasonable. Finally, the comparative effectiveness of LAI AAPs in the specific population of patients at risk of nonadherence, or who have inadequate control on oral AAPs or long-acting typical antipsychotics (i.e., the manufacturer's requested listing), has not been established.

FIGURE 11: EVIDENCE NETWORK FOR EFFICACY (PANEL A) AND FOR SAFETY (PANEL B)

Figure 11 contained confidential information and was removed at the request of the manufacturer.

Source: CADTH Common Drug Review submission,[22] Majer et al.[68]

TABLE 42: DESCRIPTION OF INCLUDED STUDIES ASSESSING LONG-ACTING INJECTABLE ANTIPSYCHOTICS

Study	Patient Characteristics	Inclusion Criteria	Exclusion Criteria	Medication
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study	Patient Characteristics	Inclusion Criteria	Exclusion Criteria	Medication
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AP = antipsychotic; BPRS = Brief Psychiatric Rating Scale (unusual thought content, conceptual disorganization, hallucinations, suspiciousness); CGI–I = Clinical Global Impressions–Improvement of Illness; CGI–S = Clinical Global Impressions–Severity of Illness; CGI–SS = Clinical Global Impressions–Severity of Suicidality; DSM = Diagnostic and Statistical Manual of Mental Disorders; ECG = electrocardiogram; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale.
Source: CADTH Common Drug Review submission,[22] Majer et al.[68]

TABLE 43: QUALITY ASSESSMENT OF THE INCLUDED RANDOMIZED CONTROLLED TRIALS

Trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Was randomization carried out appropriately?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Was the concealment of treatment allocation adequate?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Were the groups similar at the outset of the study in terms of prognostic factors?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Were the care providers, participants, and outcome assessors blind to treatment allocation?	[redacted]	[redacted][a]	[redacted][a]	[redacted][a]	[redacted][a]	[redacted][a]
Were there any unexpected imbalances in dropouts between groups?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Did the analysis include ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ITT = intention-to-treat.

[a] [redacted]

Source: CADTH Common Drug Review submission,[22] Majer et al.[68]

TABLE 44: SUMMARY OF (EFFICACY) DATA REPORTED IN THE RCTS INCLUDED IN THE SYSTEMATIC REVIEW

Study	Intervention /Comparators	Total No. of Patients	Time Horizon (Weeks)	No. of Patients with Relapses	No. of Patients WDAE	No. of Patients W/D Due to Other Reasons	No. of Completers
[redacted]							
[redacted]							
	[redacted][a]						
[redacted]							
[redacted]	[redacted][b]						
	[redacted][a]						
[redacted]	[redacted][c]						
	[redacted][a]						
[redacted]							

RCT = randomized controlled trial; W/D = withdrawal; WDAE = withdrawal due to adverse events.

[a] [redacted]

[b] [redacted]

[c] [redacted]

Source: CADTH Common Drug Review submission,[22] Majer et al.[68]

TABLE 45: RESULTS OF MTC ANALYSIS — EFFICACY OUTCOMES (RANDOM-EFFECTS MODEL)

	HR (95% CI)	6-Month Probability, % (95% CI)
Relapse		
[redacted]		
Discontinuation due to AEs		
[redacted]		

	HR (95% CI)	6-Month Probability, % (95% CI)
[redacted]	[redacted]	[redacted]
Discontinuation due to other than relapse and AEs		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Continuing treatment		
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

CI = confidence interval; DIC = deviance information criterion; HR = hazard ratio; MTC = mixed treatment comparison; NA = not applicable.
Note: DIC for efficacy outcomes: [redacted].
Source: CADTH Common Drug Review submission,[22] Majer et al.[68]

FIGURE 12: ESTIMATED 26-WEEK PROBABILITIES AND 95% CREDIBLE INTERVALS FOR THE FOUR OUTCOMES

Figure 12 contained confidential information and was removed at the request of the manufacturer.

ARIP = aripiprazole IM; HALO = haloperidol IM; IM = intramuscular; OLAN = olanzapine IM; PALI = paliperidone IM; PLB = placebo (in injectable form); RISP = risperidone IM.
Source: CADTH Common Drug Review submission,[22] Majer et al.[68]

TABLE 46: RESULTS OF THE MIXED TREATMENT COMPARISON ANALYSIS: SIGNIFICANT (> 7%) WEIGHT GAIN AS ADVERSE EVENT (FIXED-EFFECTS MODEL)

Treatment	Weight Gain (> 7%)		EPS	
	Odds Ratio	Probability %, (95% CI)	Odds Ratio	Probability %, (95% CI)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	Weight Gain (> 7%)		EPS	
	Odds Ratio	Probability %, (95% CI)	Odds Ratio	Probability %, (95% CI)
[redacted]				
[redacted]				
[redacted]				
[redacted]				

AE = adverse event; CI = confidence interval; DIC = deviance information criterion; NR = not reported.
Note: DIC for safety outcomes: [redacted].
Source: CADTH Common Drug Review submission,[22] Majer et al.[68]

TABLE 47: APPRAISAL OF NETWORK META-ANALYSIS USING ISPOR CRITERIA

ISPOR Checklist Item		Details and Comments
1.	Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting an NMA and the study objectives were clearly stated.
2.	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• The eligibility criteria for individual RCTs were clearly stated. • All treatment administration was double blind. Information sources and search strategy were well reported. • Methods for selection process and data extraction were clearly reported. • The list of exclusion studies was not provided. • The validity of individual studies was assessed using CRD and Cochrane guidelines.[75]
3.	Are the outcome measures described?	• Outcomes assessed in the NMA were clearly stated. • Justification of the outcome measures was provided as follows: "*The main goal of treatment during the stable phase are to ensure that symptom remission or control is sustained, that the patient is maintaining or improving their level of functioning and quality of life, that monitoring for adverse treatment effects continues, and to prevent relapse.*"[78]
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• A description of the statistical model was provided. • The report states that the DIC was used to compare the fixed-effects models with random-effects models. • Due to lack of head-to-head trials, the report did not include a comparison of direct and indirect estimates of effect.
5.	Are sensitivity analyses presented?	• Sensitivity analyses were performed by excluding some specific RCTs, without between-trial correlations, or with true placebo s included only.
6.	Do the results include a	• A table with study and patient characteristics was provided; the

ISPOR Checklist Item		Details and Comments
	summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	characteristics appear to be similar across the individual studies. • A figure showing the network of studies was provided. • Trial duration of all included studies ranged from 24 to 52 weeks. Two studies were terminated early.
7.	Does the study describe an assessment of model fit?	• Both fixed- and random-effects models were considered, with model selection based on the DIC model fit measure.
8.	Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported for each outcome measure, including point estimates and 95% credible intervals as a measure of uncertainty.
9.	Sensitivity/scenario analyses	• Results of the sensitivity analyses were presented in the report.

CRD = Centre for Research and Dissemination; DIC = deviance information criterion; NMA = network meta-analysis; RCT = randomized controlled trial.

REFERENCES

1. Kasper S, Lerman MN, McQuade RD, Saha A, Carson WH, Ali M, et al. Efficacy and safety of aripiprazole vs. haloperidol for long-term maintenance treatment following acute relapse of schizophrenia. Int J Neuropsychopharmacol. 2003 Dec;6(4):325-37.
2. Health Canada. Schizophrenia. In: A report on mental illnesses in Canada [Internet]. Ottawa: Health Canada; 2002 [cited 2014 Jul 25]. Chapter 3. Available from: http://www.phac-aspc.gc.ca/publicat/miic-mmac/chap_3-eng.php
3. Goeree R, Farahati F, Burke N, Blackhouse G, O'Reilly D, Pyne J, et al. The economic burden of schizophrenia in Canada in 2004. Curr Med Res Opin. 2005;21(12):2017-28.
4. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4th ed., text revision. Washington: American Psychiatric Association; 2000.
5. National Institute for Health and Care Excellence. Schizophrenia: core interventions in the treatment and management of schizophrenia in adults in primary and secondary care [Internet]. London: NICE; 2009. [cited 2014 Jul 25]. (NICE clinical guideline 82). Available from: http://www.nice.org.uk/guidance/CG82
6. Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry. 2004 Feb;161(2 Suppl):1-56.
7. Clinical Study Report: 31-07-246. A 52-week, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of an intramuscular depot formulation of aripiprazole (OPC-14597) as maintenance treatment in patients with schizophrenia "ASPIRE US" (Aripiprazole Intramuscular Depot Program in Schizophrenia) [**CONFIDENTIAL** internal manufacturer's report]. Rockville (MD): Otsuka Pharmaceutical Development & Commercialization; 2011 Jul 22; amended 2012 Aug 9.
8. Clinical Study Report: 31-07-247. A 38-week, multicenter, randomized, double-blind, active-controlled study to evaluate the efficacy, safety, and tolerability of an intramuscular depot formulation of aripiprazole (OPC-14597) as maintenance treatment in patients with schizophrenia "ASPIRE EU" (Aripiprazole Intramuscular Depot Program in Schizophrenia) [**CONFIDENTIAL** manufacturer's report]. Rockville (MD): Otsuka Pharmaceutical Development & Commercialization; 2012 Oct 19.
9. Clinical Study Report: 31-08-248. A 52-week, multicenter, open-label trial to evaluate the effectiveness of aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia "ASPIRE OPEN-LABEL" (Aripiprazole Intramuscular Depot Program in Schizophrenia) [**CONFIDENTIAL** internal manufacturer's report]. Rockville (MD): Otsuka Pharmaceutical Development & Commercialization; 2014 May 7.
10. Pharmacoeconomic evaluation. In: CDR submission: [Pr]Abilify Maintena™ aripiprazole prolonged release suspension for injection 300 mg and 400 mg vial. Company: Otsuka Pharmaceutical Co., Ltd. [**CONFIDENTIAL** manufacturer's submission]. Tokyo: Otsuka Pharmaceutical Co., Ltd; 2013 Dec 19.
11. O'Carroll R. Cognitive impairment in schizophrenia. Adv Psychiatr Treat. 2000;6:161-8.
12. Marder SR, McQuade RD, Stock E, Kaplita S, Marcus R, Safferman AZ, et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. Schizophr Res. 2003 Jun 1;61(2-3):123-36.

13. Lehman AF, Kreyenbuhl J, Buchanan RW, Dickerson FB, Dixon LB, Goldberg R, et al. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2003. Schizophr Bull. 2004;30(2):193-217.
14. Jibson MD. Overview of antipsychotic medications. 2007. In: UpToDate [database]. Version 15.2. Waltham (MA): UpToDate; c2005 - . Subscription required.
15. [Pr]Abilify Maintena™ (aripiprazole) prolonged release suspension for injection 300 mg and 400 mg vial [product monograph]. Tokyo: Otsuka Pharmaceutical Co., Ltd.; 2014 Feb 6.
16. e-CPS [Internet]. Ottawa: Canadian Pharmacists Association. Risperdal® Consta® (risperidone); 2013 [cited 2014 Oct 3]. Available from: http://www.e-therapeutics.ca Subscription required.
17. e-CPS [Internet]. Ottawa: Canadian Pharmacists Association. Invega Sustenna® (paliperidone palmitate); 2014 [cited 2014 Oct 3]. Available from: http://www.e-therapeutics.ca Subscription required.
18. Abilify (aripiprazole) tablets: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg [product monograph]. Montreal: Bristol-Myers Squibb Canada; 2013 May 27.
19. Kane JM, Sanchez R, Perry PP, Jin N, Johnson BR, Forbes RA, et al. Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2012 May;73(5):617-24.
20. Fleischhacker WW, Sanchez R, Johnson B, Jin N, Forbes RA, McQuade R, et al. Long-term safety and tolerability of aripiprazole once-monthly in maintenance treatment of patients with schizophrenia. Int Clin Psychopharmacol. 2013 Jul;28(4):171-6.
21. Fleishhacker WW, Sanchez R, Perry PP, Jin N, Peters-Strickland T, Johnson BR, et al. Aripiprazole once-monthly for treatment of schizophrenia: a double-blind, randomised, non-inferiority study. Br J Psychiatry [Internet]. 2014 Jun 12 [cited 2014 Aug 7];205:135-44. Available from: http://bjp.rcpsych.org/content/205/2/135.full.pdf+html
22. CDR submission: [Pr]Abilify Maintena™ aripiprazole prolonged release suspension for injection 300 mg and 400 mg vial. Company: Otsuka Pharmaceutical Co., Ltd. [**CONFIDENTIAL** manufacturer's submission]. Tokyo: Otsuka Pharmaceutical Co., Ltd.; 2013 Dec 19.
23. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s). In: Aripiprazole extended release suspension for injection (Abilify Maintena). Company: Otsuka Pharmaceutical. Application no.: NDA 202971. Approval date: 28/02/2013 [Internet]. Rockville (MD): FDA; 2013 [cited 2014 Jun 19]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/202971Orig1s000MedR.pdf
24. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s). In: Aripiprazole extended release suspension for injection (Abilify Maintena). Company: Otsuka Pharmaceutical. Application no.: NDA 202971. Approval date: 28/02/2013 [Internet]. Rockville (MD): FDA; 2013 [cited 2014 Jun 19]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/202971Orig1s000StatR.pdf
25. Health Canada reviewer's report: Abilify Maintena (aripiprazole prolonged release suspsension for injection) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2014 Feb 7.
26. Lindenmayer JP, Czobor P, Alphs L, Nathan AM, Anand R, Islam Z, et al. The InterSePT scale for suicidal thinking reliability and validity. Schizophr Res. 2003 Sep 1;63(1-2):161-70.

27. Guy W. ECDEU assessment manual for psychopharmacology [Internet]. Revised edition. Rockville (MD): U.S. Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976. 603 p. Section 028 CGI Clinical Global Impressions; p. 217-222. [cited 2014 Aug 27]. (DHEW publication no. (ADM) 76-338). Available from: https://archive.org/stream/ecdeuassessmentm1933guyw#page/218/mode/2up

28. Haro JM, Kamath SA, Ochoa S, Novick D, Rele K, Fargas A, et al. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. Acta Psychiatr Scand Suppl. 2003;(416):16-23.

29. Carson WH. Clinical Study Report: CN138-047. A multicenter, randomized, double-blind, placebo-controlled, 26 week study of a fixed dose of aripiprazole in the treatment if stabilized patients with chronic schizophrenia. New York: Bristol-Myers Squibb Company; 2001.

30. Bassler D, Briel M, Montori VM, Lane M, Glasziou P, Zhou Q, et al. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. JAMA. 2010 Mar 24;303(12):1180-7.

31. Committee for Medicinal Products for Human Use (CHMP). Points to consider on switching between superiority and non-inferiority [Internet]. London: European Medicines Agency (EMA), Evaluation of Medicines for Human Use; 2000 Jul 27. 10 p. Report No.: CPMP/EWP/482/99. [cited 2014 Oct 1]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003658.pdf

32. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Guidance for industry: non-inferiority clinical trials. In. Rockville (MD): FDA; 2010 Mar. Draft guidance.

33. Hogan TP, Awad AG, Eastwood R. A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. Psychol Med. 1983 Feb;13(1):177-83.

34. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986 Jan;24(1):67-74.

35. Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. Schizophr Res. 2000 May 5;42(3):241-7.

36. Andreasen NC, Carpenter WT, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. Am J Psychiatry. 2005 Mar;162(3):441-9.

37. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261-76.

38. Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the Positive and Negative Syndrome Scale for schizophrenics. Psychiatry Res. 1988 Jan;23(1):99-110.

39. Leucht S, Kane JM, Etschel E, Kissling W, Hamann J, Engel RR. Linking the PANSS, BPRS, and CGI: clinical implications. Neuropsychopharmacology [Internet]. 2006 Oct [cited 2014 Aug 19];31(10):2318-25. Available from: http://www.nature.com/npp/journal/v31/n10/pdf/1301147a.pdf

40. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry. 1997 Dec;58(12):538-46.

41. Peralta V, Cuesta MJ. Psychometric properties of the Positive and Negative Syndrome Scale (PANSS) in schizophrenia. Psychiatry Res. 1994 Jul;53(1):31-40.
42. van Os J, Burns T, Cavallaro R, Leucht S, Peuskens J, Helldin L, et al. Standardized remission criteria in schizophrenia. Acta Psychiatr Scand. 2006 Feb;113(2):91-5.
43. Rabinowitz J, Mehnert A, Eerdekens M. To what extent do the PANSS and CGI-S overlap? J Clin Psychopharmacol. 2006 Jun;26(3):303-7.
44. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989 May;154:672-6.
45. Barnes TR. The Barnes Akathisia Rating Scale -- revisited. J Psychopharmacol. 2003 Dec;17(4):365-70.
46. Janno S, Holi MM, Tuisku K, Wahlbeck K. Actometry and Barnes Akathisia Rating Scale in neuroleptic-induced akathisia. Eur Neuropsychopharmacol. 2005 Jan;15(1):39-41.
47. Abnormal Involuntary Movement Scale (AIMS). Psychopharmacol Bull. 1988;24(4):781-3.
48. Chien CP, Jung K, Ross-Townsend A, Stearns B. The measurement of persistent dyskinesia by piezoelectric recording and clinical rating scales. Psychopharmacol Bull. 1977 Jul;13(3):34-6.
49. Gharabawi GM, Bossie CA, Lasser RA, Turkoz I, Rodriguez S, Chouinard G. Abnormal Involuntary Movement Scale (AIMS) and Extrapyramidal Symptom Rating Scale (ESRS): cross-scale comparison in assessing tardive dyskinesia. Schizophr Res. 2005 Sep 15;77(2-3):119-28.
50. Loonen AJ, Doorschot CH, van Hemert DA, Oostelbos MC, Sijben AE. The Schedule for the Assessment of Drug-Induced Movement Disorders (SADIMoD): test-retest reliability and concurrent validity. Int J Neuropsychopharmacol. 2000 Dec;3(4):285-96.
51. Rey JM, Hunt GE, Johnson GF. Assessment of tardive dyskinesia in psychiatric outpatients using a standardized rating scale. Aust N Z J Psychiatry. 1981 Mar;15(1):33-7.
52. Taksh U. A critical review of rating scales in the assessment of movement disorders in schizophrenia. Curr Drug Targets. 2006 Sep;7(9):1225-9.
53. Janno S, Holi MM, Tuisku K, Wahlbeck K. Validity of Simpson-Angus Scale (SAS) in a naturalistic schizophrenia population. BMC Neurol. 2005 Mar 17;5(1):5.
54. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl. 1970;212:11-9.
55. Gagnon D. Reliability, validity and sensitivity to change of the personal and social performance scale in patients with stable schizophrenia [abstract]. Int J Neuropsychopharmacol. 2006;9 Suppl 1:S288.
56. Morosini PL, Magliano L, Brambilla L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. Acta Psychiatr Scand. 2000 Apr;101(4):323-9.
57. Patrick D. Reliability, validity and sensitivity to change of the personal and social performance scale in patients with acute schizophrenia [abstract]. Int J Neuropsychopharmacol. 2006;9 Suppl 1:S287-S288.
58. Bell MD, Lysaker PH, Milstein RM, Beam-Goulet JL. Concurrent validity of the cognitive component of schizophrenia: relationship of PANSS scores to neuropsychological assessments. Psychiatry Res. 1994 Oct;54(1):51-8.
59. Bell MD, Lysaker PH, Beam-Goulet JL, Milstein RM, Lindenmayer JP. Five-component model of schizophrenia: assessing the factorial invariance of the Positive and Negative Syndrome Scale. Psychiatry Res. 1994 Jun;52(3):295-303.

60. Lançon C, Auquier P, Nayt G, Reine G. Stability of the five-factor structure of the Positive and Negative Syndrome Scale (PANSS). Schizophr Res. 2000 May 5;42(3):231-9.

61. Lindenmayer JP, Bernstein-Hyman R, Grochowski S. A new five factor model of schizophrenia. Psychiatr Q. 1994;65(4):299-322.

62. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007 Jul;164(7):1035-43.

63. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011 Dec;168(12):1266-77.

64. Shallice T. Specific impairments of planning. Philos Trans R Soc Lond B Biol Sci. 1982 Jun 25;298(1089):199-209.

65. Gold JM, Carpenter C, Randolph C, Goldberg TE, Weinberger DR. Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. Arch Gen Psychiatry. 1997 Feb;54(2):159-65.

66. Tandon R, Devellis RF, Han J, Li H, Frangou S, Dursun S, et al. Validation of the Investigator's Assessment Questionnaire, a new clinical tool for relative assessment of response to antipsychotics in patients with schizophrenia and schizoaffective disorder. Psychiatry Res. 2005 Sep 15;136(2-3):211-21.

67. Majer IM, Gaughran F, Sapin C, Beillat M, Treur M. Efficacy, tolerability, and safety of aripiprazole once-monthly versus other long-acting injectable antipsychotic therapies in the maintenance treatment of schizophrenia: a mixed treatment comparison of double-blind randomized clinical trials. J Mark Access Health Policy. 2015;3.

68. Majer I, Hennequin M, Tempest M, Treur M, Pharmerit BV. Aripiprazole once-monthly in relapse prevention in patients with schizophrenia: systematic literature review and mixed treatment comparison. In: CDR submission: [Pr]Abilify Maintena™ aripiprazole prolonged release suspension for injection 300 mg and 400 mg vial. Company: Otsuka Pharmaceutical Co., Ltd. [**CONFIDENTIAL** manufacturer's submission]. Tokyo: Otsuka Pharmaceutical Co., Ltd.; 2013 Dec.

69. Ades AE, Mavranezouli I, Dias S, Welton NJ, Whittington C, Kendall T. Network meta-analysis with competing risk outcomes. Value Health. 2010 Dec;13(8):976-83.

70. Ades AE, Sculpher M, Sutton A, Abrams K, Cooper N, Welton N, et al. Bayesian methods for evidence synthesis in cost-effectiveness analysis. PharmacoEconomics. 2006;24(1):1-19.

71. Hough D, Gopal S, Vijapurkar U, Lim P, Morozova M, Eerdekens M. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. Schizophr Res. 2010 Feb;116(2-3):107-17.

72. Fleischhacker WW, Gopal S, Lane R, Gassmann-Mayer C, Lim P, Hough D, et al. A randomized trial of paliperidone palmitate and risperidone long-acting injectable in schizophrenia. Int J Neuropsychopharmacol. 2012 Feb;15(1):107-18.

73. Kane JM, Davis JM, Schooler N, Marder S, Casey D, Brauzer B, et al. A multidose study of haloperidol decanoate in the maintenance treatment of schizophrenia. Am J Psychiatry. 2002 Apr;159(4):554-60.

74. Kane JM, Detke HC, Naber D, Sethuraman G, Lin DY, Bergstrom RF, et al. Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. Am J Psychiatry. 2010 Feb;167(2):181-9.

75. Systematic reviews: CRD's guidance for undertaking reviews in health care. York, UK: Centre for Reviews and Dissemination, University of York; 2009.

76. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health. 2011 Jun;14(4):417-28.

77. Redwood Outcomes. Validation of indirect comparisons of aripiprazole and other long-acting injectables for the maintenance therapy of schizophrenia. In: CDR submission: [Pr]Abilify Maintena™ aripiprazole prolonged release suspension for injection 300 mg and 400 mg vial. Company: Otsuka Pharmaceutical Co., Ltd. [**CONFIDENTIAL** manufacturer's submission]. Project no. LO001613. Tokyo: Otsuka Pharmaceutical Co., Ltd.; 2013 Dec 19.

78. Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. World J Biol Psychiatry. 2013 Feb;14(1):2-44.