CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207533Orig1s000

SUMMARY REVIEW

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date	(electronic stamp)
From	Mitchell V. Mathis, MD
Subject	Division Director Summary Review
NDA/BLA #	207533, O-1
Applicant Name	Alkermes, Inc.
Date of Submission	8/22/2014
PDUFA Goal Date	8/22/2015
Proprietary Name / Established (USAN) Name	Aristada/ (aripiprazole lauroxil) ER IM
Dosage Forms / Strength	IM Injectable 441 mg, 662 mg and 882 mg
Proposed Indication(s)	Treatment of Schizophrenia
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Lucas Kempf, MD
Statistical Review	Jinglin Zhong, Ph.D. Peiling Yang, Ph.D. H.M. James Hung, Ph.D.
Pharmacology Toxicology Review Supervisory	Amy Avila, Ph.D. Aisar Atrakchi, Ph.D.
CMC Review/OBP Review	Sherita McLamore-Hines, Ph.D. Wendy Wilson-Lee, Ph.D.
Office of Process and Facilities (OPF)	Norman Schmuff, Ph.D.
Microbiology Review	Vinayak Pawar, Ph.D.
Clinical Pharmacology Review, Genomics Review, and Pharmacometrics	Praveen Balimane, Ph.D. Xiaofeng Wang, Ph.D. Kevin Krudys, Ph.D. Jeffrey Kraft, Ph.D. Christian Grimstein, Ph.D. Ping Zhao, Ph.D. Hao Zhu, Ph.D. Elsbeth Chikhale, Ph.D.
OPDP	Jessica Fox, PharmD
OSI	Jen Sellers, MD

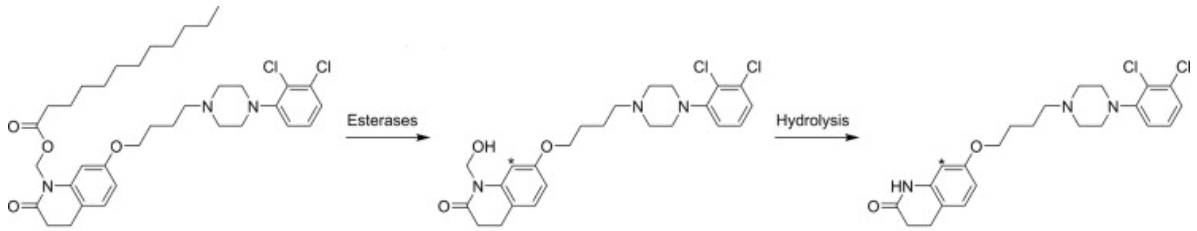
	Susan D. Thompson, M.D. Kassa Ayalew, M.D.
OSE/DMEPA	Loretta Holmes, PharmD Danielle Harris, PharmD
Other	
Pediatrics and Maternal Health	Leyla Sahin, M.D. Tamara Johnson, M.D. Lynne Yao, M.D.
CDRH	Ryan McGowan

OND=Office of New Drugs
OSI=Office of Scientific Investigation
OPDP=Office of Prescription Drug Promotion
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
CDRH=Center for Devices and Radiologic Health
CMC=Chemistry, Manufacturing, and Controls

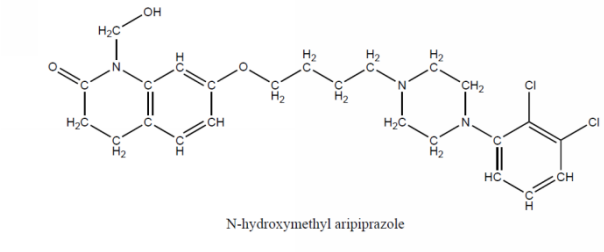
Background and Summary

Aripiprazole lauroxil (N-lauroyloxymethyl aripiprazole) is a prodrug of N-hydroxymethyl aripiprazole, which in turn is a prodrug of and is subsequently metabolized to aripiprazole. There are structural differences between aripiprazole lauroxil and aripiprazole. Aripiprazole is the active moiety in a number of other drug products that the Agency has approved for the treatment of schizophrenia.[1] Aripiprazole lauroxil is an ester of N-hydroxymethyl aripiprazole, not aripiprazole. N-hydroxymethyl aripiprazole is a new active moiety.

Biosynthesis of Aripiprazole from Aripiprazole Lauroxil



N-hydroxymethyl aripiprazole (new active moiety)



[1] These include Abilify (aripiprazole) Tablets (NDA 21436), Abilify (aripiprazole) Oral Solution (NDA 021713), Abilify (aripiprazole) Orally Disintegrating Tablets (NDA 021729), Abilify (aripiprazole) solution for intramuscular injection (NDA 021866), and Abilify Maintena (aripiprazole) (NDA 202971).

The proposed aripiprazole lauroxil product is formulated as an extended-release suspension in pre-filled syringes to be administered IM into the deltoid (441 mg) or gluteal (441 mg, 662 mg, or 882 mg) muscles for the treatment of schizophrenia. Because aripiprazole lauroxil contains an active moiety (N-hydroxymethyl aripiprazole) that has not been previously approved in any NDA, it is a New Chemical Entity (NCE). This application was submitted as a 505(b)(2) NDA relying on the Agency's previous findings of safety and efficacy for Abilify (aripiprazole) Tablets (NDA 21436).

The efficacy of aripiprazole lauroxil extended release IM injection was evaluated in a Phase 3 safety and efficacy study (ALK9072-003) that demonstrated efficacy of two doses (441 mg and 882 mg, both given monthly) in patients with schizophrenia. The Agency's previous finding of safety and efficacy from oral aripiprazole tablets was considered as evidence, along with pharmacokinetic evidence from the applicant's studies that demonstrate similar serum concentrations for oral aripiprazole given daily at approved doses and aripiprazole lauroxil given monthly at the studied doses. Therefore, a single trial with aripiprazole lauroxil and the evidence from the Agency's previous finding with the aripiprazole oral tablet formulation, along with the pharmacokinetic data generated by the applicant provide the substantial evidence of efficacy required to recommend approval of this formulation. In addition to the Phase 3 clinical trial, the sponsor submitted single and multiple dose Phase 1 PK studies.

From the applicant's submission, an adequate pharmacokinetic link between aripiprazole lauroxil ER IM and Abilify (aripiprazole) Tablets has been established and the doses proposed by the applicant are acceptable and sufficient to support once-monthly or once-every-six-week dosing provided the initiation period includes oral aripiprazole for the first three weeks of treatment.

I have reviewed the data and received input from the review teams and I agree that the applicant has demonstrated that aripiprazole lauroxil has been shown to be effective in the treatment of schizophrenia. The drug has many of the same safety signals as other drugs in the class, particularly its listed drug Abilify Tablets (oral aripiprazole tablets), and will be labeled to provide clinicians with the information they need to safely use the product.

Clinical Summary and Statistics

Efficacy

Dr. Lucas Kempf conducted the clinical review and Dr. Jinglin Zhong conducted the statistical review.

Drs. Kempf and Zhong have reviewed the development program for schizophrenia and have agreed that substantial evidence of effectiveness has been presented to support the approval of aripiprazole lauroxil for the treatment of schizophrenia, and I agree with them.

The applicant submitted one positive Phase 3, multiple-dose, multi-national, randomized, double-blind, placebo-controlled study in patients experiencing an acute exacerbation of the symptoms of schizophrenia. In this study, aripiprazole lauroxil's efficacy was demonstrated by mean reduction in the Positive and Negative Syndrome Scale (PANSS) total score at Day 85 using an analysis of covariance (ANCOVA) model with last observation carried forward (LOCF) imputation for missing data. The Clinician Global Impression – Improvement (CG-I) score at Day 85 was the secondary efficacy endpoint.

Study ALK9072-003) Design

Adult patients with acutely exacerbated schizophrenia were admitted to an inpatient study unit and discontinued from all antipsychotic drugs they were taking. For patients never exposed to aripiprazole, a test dose of oral aripiprazole 5 mg was administered orally for two days prior to randomization to ensure tolerability prior to injecting the extended-release study drug.

Patients tolerant of aripiprazole (historically or tolerant to the oral test doses) were randomized on Day 1 in a 1:1:1 ratio to one of three treatment groups:

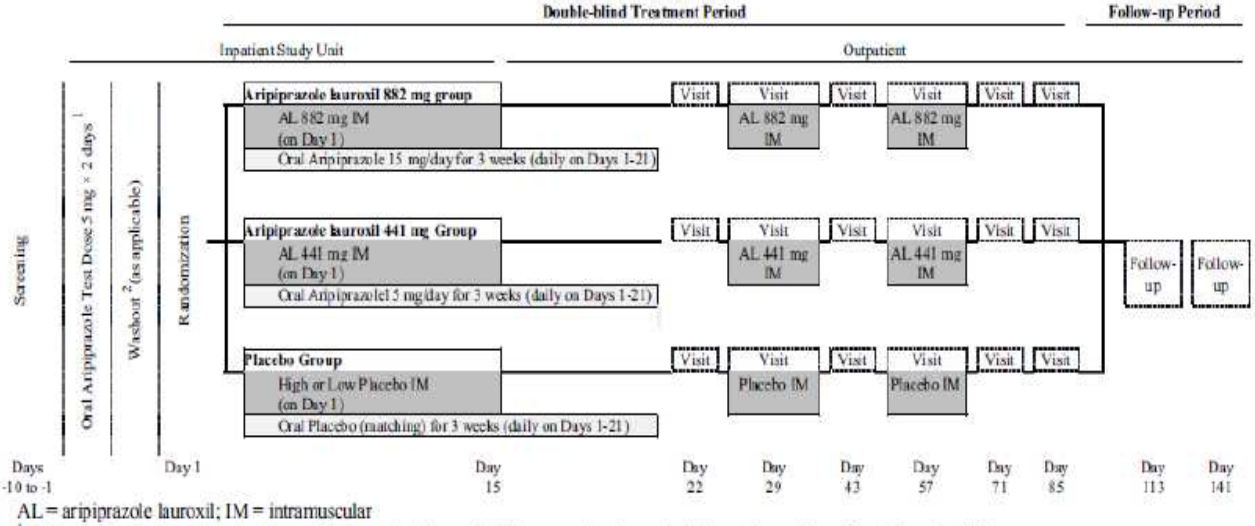
- Aripiprazole lauroxil 882 mg (with oral aripiprazole for the first 3 weeks of study)
- Aripiprazole lauroxil 441 mg (with oral aripiprazole for the first 3 weeks of study)
- Injectable placebo (with oral placebo for the first three weeks of study)

The first dose of study drug was administered on Day 1, the second dose on Day 29, and the third dose on Day 57. The study design is presented graphically below.

Phase 3 Study ALK9097-003

Protocol Number	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
ALK9072-003	Phase 3, double-blind, placebo-controlled, conducted at 107 centers in US, Asia, and Europe	12 weeks double blind treatment	8 weeks	Placebo 208 441 mg 207 882 mg 208	Adults 18 – 70 with acute exacerbation of schizophrenia

Study Design ALK9097-003



AL = aripiprazole lauroxil; IM = intramuscular

[1] Subjects who had previously taken and tolerated aripiprazole did not receive the oral aripiprazole test dose (5 mg) for tolerability

[2] Washout included washout of prohibited medications including antipsychotics

Source: Statistical Review

Results

Dropouts

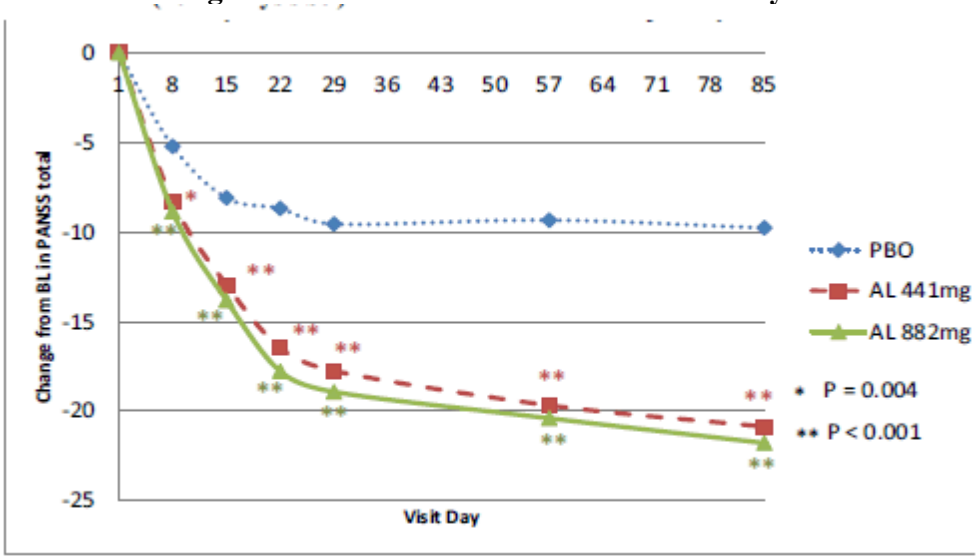
A higher proportion of patients completed the study to endpoint in the aripiprazole lauroxil treatment arms (63% for 441 mg, 65% for 882 mg), compared to placebo (46%). The most common reasons for discontinuation were withdrawal by patient (14%), lack of efficacy (10%), and adverse event (9%). There were more discontinuations due to lack of efficacy in the placebo group (18%) than in the aripiprazole lauroxil groups (4% in the 441 mg group and 8% in the 882 mg group), and more discontinuations due to

adverse events in the placebo group (17%) than in the aripiprazole lauroxil groups (7% in the 441 mg group and 3% in the 882 mg group). The statistical team conducted several analyses to assess the impact of dropouts on the primary efficacy endpoint, including imputing data from the worst observed change at Day 85 and plotting cumulative distribution functions for change in PANSS total score based upon different imputation methods, and the results were largely unchanged. See the statistical review for details.

Primary Endpoint

The primary efficacy endpoint was change in the PANSS total score from baseline to day 85 using ANCOVA as the model and LOCF as the imputation method. CGI-I was the secondary endpoint. The primary efficacy results are presented graphically below.

Change from Baseline in PANSS Total Score by Visit



Abbreviations: AL=aripiprazole lauroxil; ANCOVA=analysis of covariance; PBO=placebo; PANSS=Positive and Negative Syndrome Scale; LOCF=last observation carried forward.

Source: Statistical Review

LOCF was the pre-specified method for imputing missing data. During the protocol review, FDA raised concerns that LOCF was not the most sensible imputation method to use when the dropout rate was expected to be high (dropout rate was about 42% in this trial), so we asked MMRM for (Mixed-Effect Model Repeated Measure) as a sensitivity analysis. The results were positive for both methods and are presented below.

Change from Baseline at Day 85 in PANSS Total Score ANCOVA with LOCF

Visit Statistics	Placebo (N=194)	Aripiprazole Lauroxil 441 mg (N=193)	Aripiprazole Lauroxil 882 mg (N=202)
Baseline: Mean (SD)	93.5 (10.72)	92.7 (10.11)	92.1 (10.82)
Change from Baseline at Day 85			
n	192	193	201
LS Mean (SE)	-9.83 (1.414)	-20.48 (1.412)	-21.77 (1.375)
LS Mean Difference against Placebo (SE)	–	-10.65 (1.861)	-11.94 (1.844)
95% CI		-14.30, -6.99	-15.56, -8.32
p-value against placebo		<0.001	<0.001

Abbreviations: CI=confidence interval; LS=least squares; PANSS=positive and negative syndrome scale; SD=standard deviation; SE=standard error.

Note: For the ANCOVA model using the LOCF approach, the dependent variable is change from baseline in the PANSS total score at Day 85, with study region and treatment group as fixed effects and the baseline PANSS total score as a covariate.

Change from Baseline at Day 85 in PANSS Total Score with MMRM

Visit Statistics	Placebo (N=196)	Aripiprazole Lauroxil 441 mg (N=196)	Aripiprazole Lauroxil 882 mg (N=204)
Baseline: Mean (SD)	93.9 (11.28)	92.6 (10.20)	92.0 (10.77)
Change from Baseline at Day 85			
n	96	133	137
LS Mean (SE)	-10.57 (1.60)	-22.33 (1.48)	-22.92 (1.43)
LS mean Difference against placebo (SE)		-11.76 (2.14)	-12.35 (2.12)
95% CI		-15.97, -7.56	-16.51, -8.19
p-value against placebo		<0.001	<0.001

Abbreviations: CI=confidence interval; LS=least squares; PANSS=Positive and Negative Syndrome Scale; SD=standard deviation; SE=standard error.

Note: Mixed model for repeated measures (MMRM) is based on the observed case without imputation of missing data. The MMRM model uses the change from baseline in the PANSS total score at each post-baseline visit as the dependent variable, and includes study region, treatment group, visit, and treatment group-by-visit interaction as factors and baseline PANSS total score as a covariate. An unstructured covariance structure will be applied for MMRM. The Kenward-Roger approximation is used to adjust the denominator degree of freedom.

Reviewer Comment: This placebo-controlled, parallel-group design is a typical design for IM injection treatment studies in schizophrenia, but the twenty-one day treatment with oral drug/placebo complicates interpretation of the efficacy results. It could reasonably be asked if the placebo group should have also received active oral drug for the first three weeks of treatment to provide a more fair comparison of the injectable drug to injectable placebo. Several analyses were performed to examine this design and to evaluate the findings with and without the influence of oral aripiprazole and the reviewer's conclusions are that efficacy has been demonstrated in this study.

The statistical team repeated the primary analysis using PANSS data from Day 22 and Day 29 as the baseline. The results of these analyses are presented below.

Change from Baseline in PANSS Total Score using ANCOVA LOCF with Day 22 as Baseline

	Total (n = 455)		
	Placebo (n=136)	441 mg (n =154)	882 mg (n = 165)
Day 22: Mean (SD)	79.9 (17.3)	74.6 (15.6)	73.3 (15.7)
Day 85: Mean (SD)	79.7 (20.2)	69.7 (18.6)	69.2 (19.0)
Change from Day 22 to Day 85: Mean (SD)	-0.2 (14.7)	-4.8 (11.3)	-4.2 (13.9)
LSmean change from Day 22 to Day 85 Mean(95% CI)	-0.6 (-2.9, 1.6)	-5.9 (-8.1, -3.7)	-5.3 (-7.4, -3.2)
Diff from placebo: LSMean (95% CI) pvalue		-5.3 (-8.3, -2.3) 0.0005	-4.6 (-7.6, -1.7) 0.002

Change from Baseline in PANSS total Score using ANCOVA LOCF with Day 29 as Baseline

	Total (n=412)		
	Placebo (n=115)	441 mg (n=144)	882 mg (n=153)
Day 29: Mean (SD)	76.5 (17.2)	72.6 (16.9)	71.5 (16.8)
Day 85: Mean (SD)	76.8 (19.1)	68.8 (18.6)	68.2 (18.9)
Change from Day 29 to Day 85: Mean (SD)	0.2 (13.8)	-3.9 (11.6)	-3.2 (12.1)
LSmean change from Day 29 to Day 85 Mean(95% CI)	-0.01 (-2.3, 2.3)	-4.5 (-6.6, -2.4)	-4.0 (-6.0, -2.0)
Diff from placebo: LSMean (95% CI) pvalue		-4.5 (-7.4, -1.6) 0.0026	-4.0 (-6.9, -1.1) 0.0073

Source: Statistical Review

Reviewer Comment: When Day 22 or Day 29 are used as baseline, the results remain statistically significant compared to Day 85 for each active treatment group compared to placebo.

Secondary Endpoint

The secondary efficacy endpoint was CGI-I at day 85. CGI-I for both aripiprazole lauroxil groups was statistically significantly lower than that for placebo.

CGI-I Score at Day 85, LOCF

CGI-I Score	Placebo (N=196)	Aripiprazole Lauroxil 441 mg (N=196)	Aripiprazole Lauroxil 882 mg (N=204)
1: Very much improved n(%)	15 (7.7)	27 (13.8)	25 (12.3)
2: Much improved n(%)	33 (16.8)	68 (34.7)	81 (39.7)
3: Minimally improved n(%)	43 (21.9)	45 (23.0)	52 (25.5)
4: No change n(%)	42 (21.4)	32 (16.3)	24 (11.8)
5: Minimally worse n(%)	37 (18.9)	11 (5.6)	16 (7.8)
6: Much worse n(%)	23 (11.7)	12 (6.1)	5 (2.5)
7: Very much worse n(%)	3 (1.5)	1 (0.5)	1 (0.5)
P-value against placebo[1]	-	< 0.001	< 0.001
Adjusted p-value[2]		< 0.001	< 0.001

Abbreviations: CGI-I=Clinical Global Impression-Improvement; LOCF=last observation carried forward; PANSS=positive and negative syndrome scale. Source: Table 14.2.3.1

[1] p-values are based on non-parametric Wilcoxon rank sum test

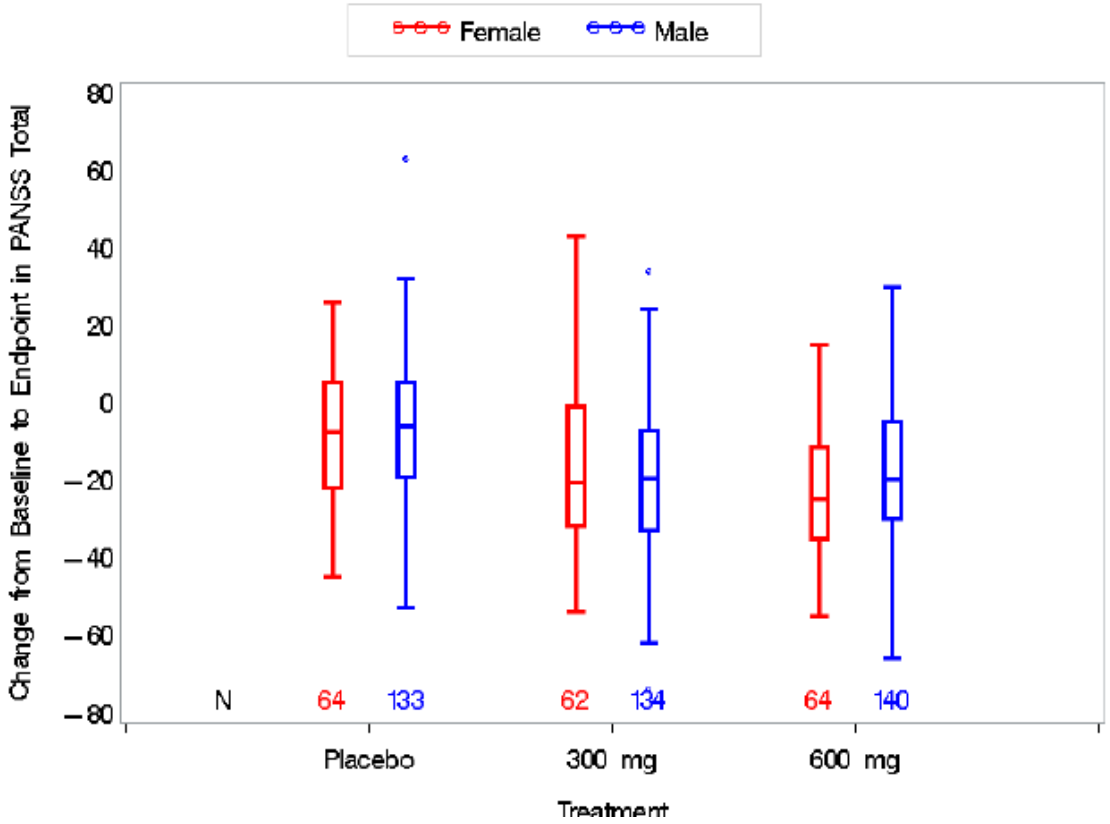
[2] Adjusted p-values using Simes-Hommel approach

Source: Statistical Review

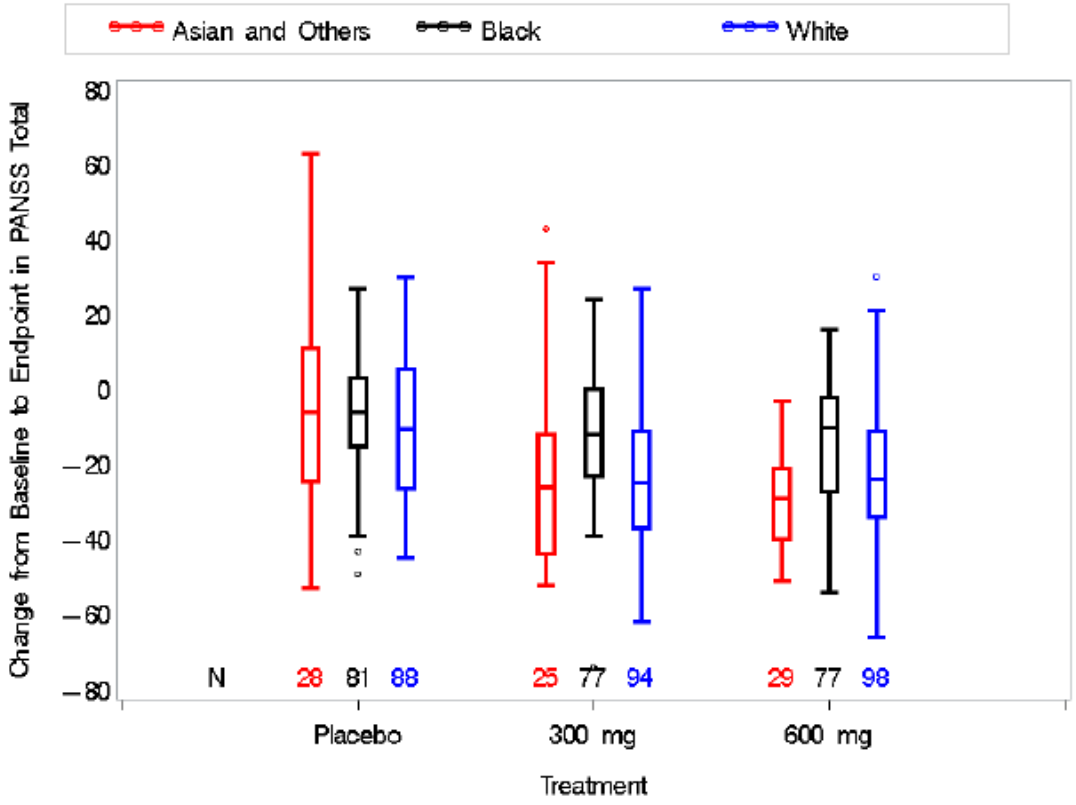
Subgroup Analyses

Several exploratory subgroup analyses were performed by the statistical reviewer and the conclusions were that the treatment effect was smaller in back patients than overall, and that patients in North America had a smaller effect than other regions. Graphical representations of these analyses are presented below.

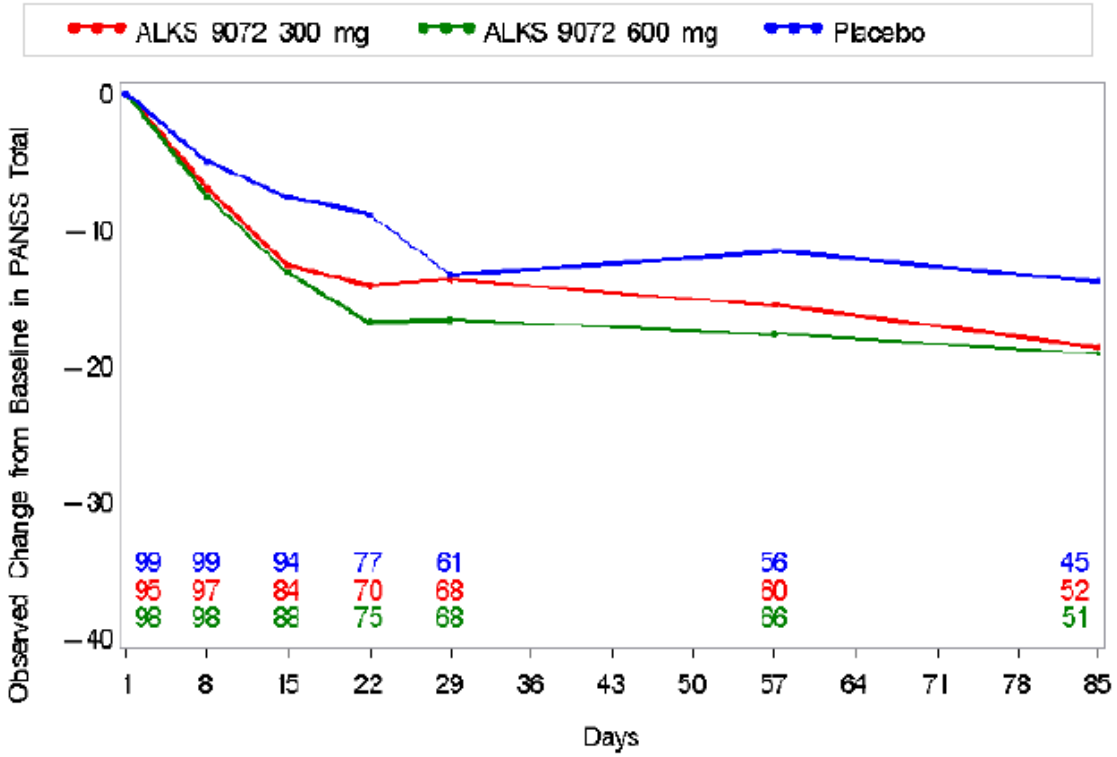
Change from Baseline in PANSS total score by Gender



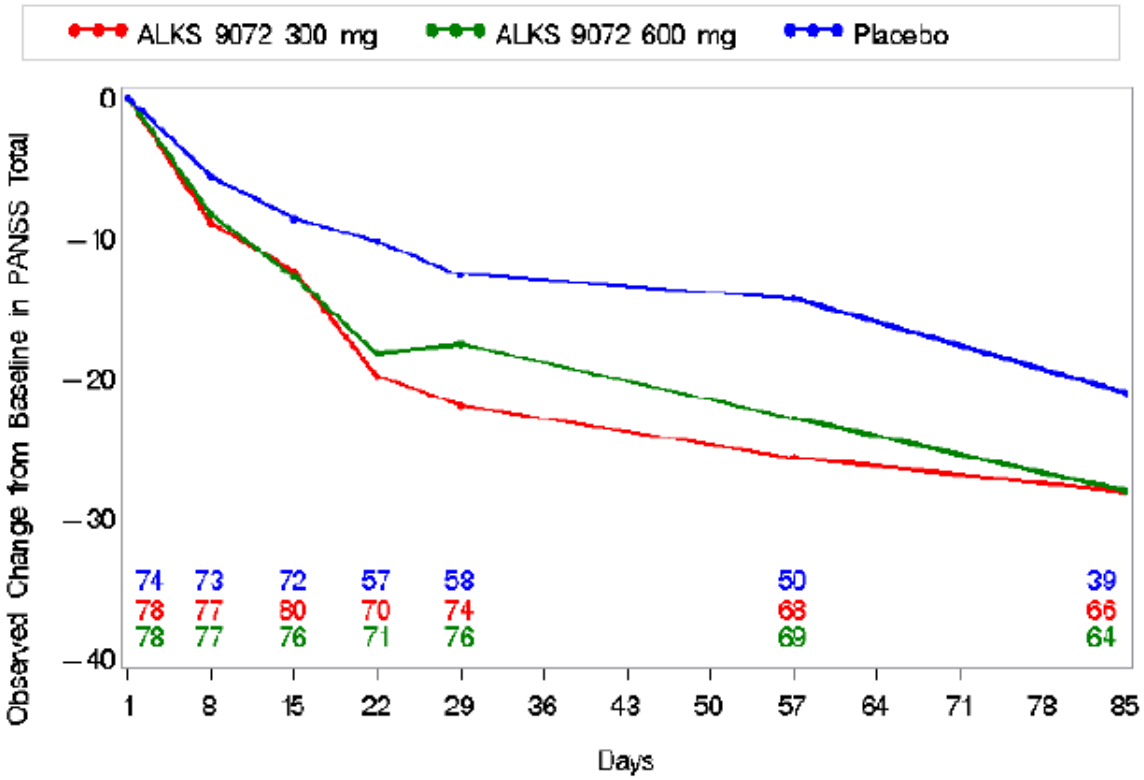
Change from Baseline in PANSS Total Score by Race



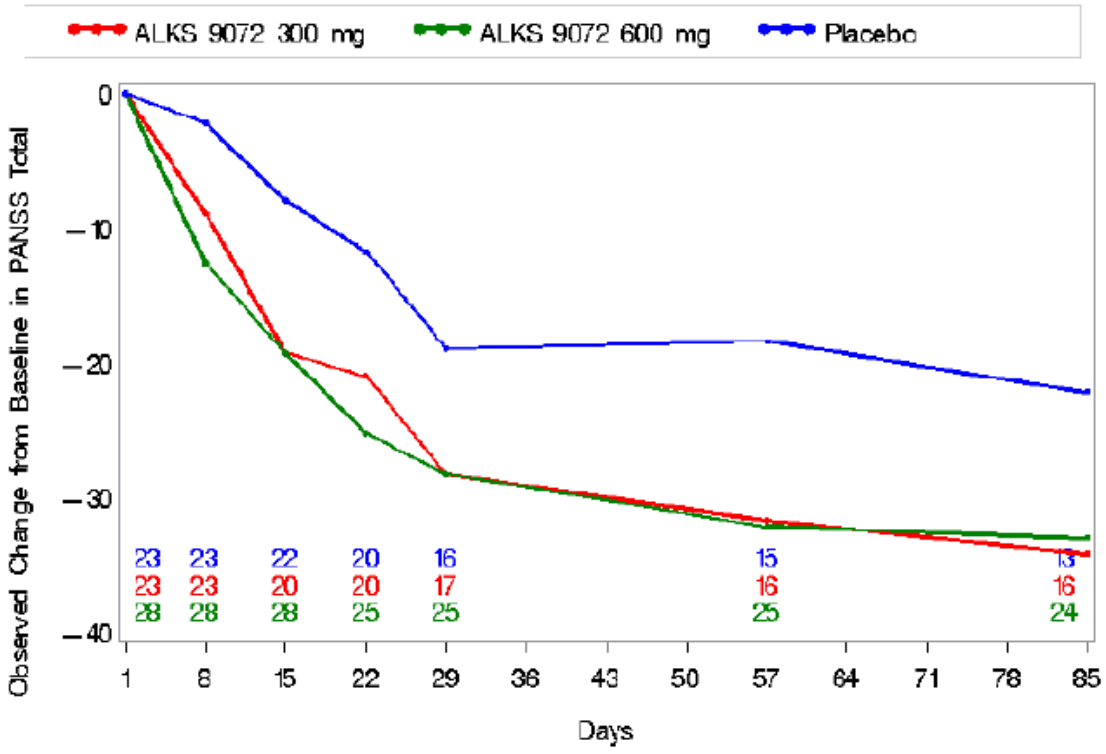
Change from Baseline PANSS Total Score—North America



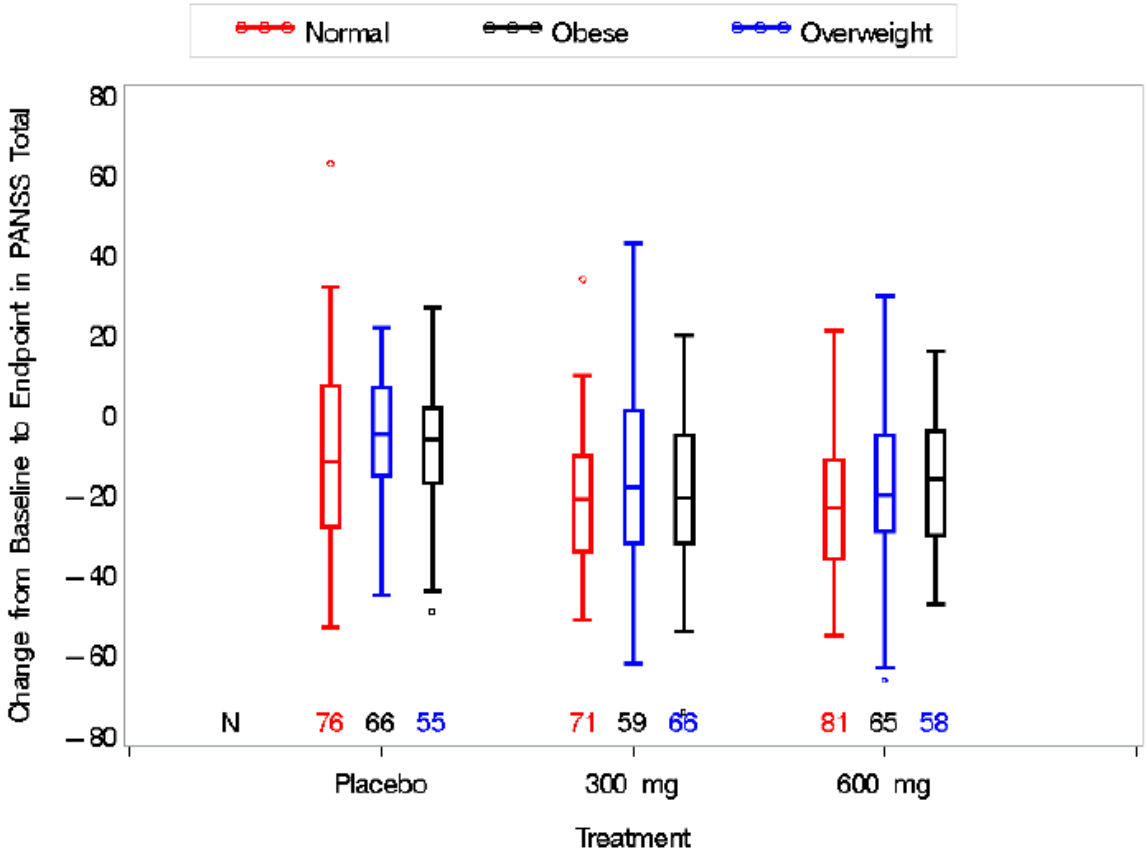
Change from Baseline in PANSS Total Score—Europe



Change from Baseline in PANSS Total Score—Asia



Change from Baseline in PANSS Total Score by Body Mass Index (BMI)



Efficacy Conclusions
The clinical and statistical teams agree that the primary and secondary endpoints of the study were met. The change from baseline from Day 22 or Day 29 to Day 85 was statistically significantly better for each active treatment group (aripiprazole lauroxil 441 mg and 882 mg) than for placebo. CGI-I scores at Day 85 were statistically significantly better for each active treatment group than for placebo. No significant subgroup differences were identified.

Reviewer Comment: The results of this single study support the effectiveness of the product, together with additional pharmacokinetic data that provides an adequate bridge to the Agency's efficacy findings for Abilify Tablets (oral aripiprazole tablets); and provide safety information for the new drug.

Safety
There were no new safety findings for this new active moiety compared to what is known about oral aripiprazole, except for injection site reactions.

Exposure
As of the safety database cutoff date of 30 April 2014, 880 subjects had received at least one injection of aripiprazole lauroxil. Of these, 662 received at least 3 injections, 276 received at least 6 injections, and 66 received at least 12 injections.
Deaths

Two fatal events were reported—homicide by gunshot by a patient on placebo, and suicide in a patient assigned to aripiprazole lauroxil after discontinuing from the study for worsening schizophrenia. These deaths have been interpreted as related more to disease than to drug, and I agree.

Nonfatal Serious Adverse Events (SAEs)
There were 12 patients with SAEs in the controlled trial, and 10 patients with SAEs from the long-term extension trial, most related to the known pharmacology of antipsychotics or to the disease characteristics of schizophrenia. Convulsion occurred in one patient in the 882 mg drug group, but was thought to not be related to study drug by the investigator. This same patient subsequently discontinued the study secondary to a diagnosis of squamous cell carcinoma.

Relevant Negative Findings
There were no hypersensitivity or allergic reactions, no reports of neuroleptic malignant syndrome, deep vein thrombosis, or pulmonary embolism. There were no post-injection CNS changes consistent with post-injection delirium/sedation syndrome (PDSS).

Injection Site Reactions
Overall the injections were well tolerated with the 882 mg group reporting the most injection site pain.

Common Adverse Events
The most significant treatment-emergent adverse event occurring in greater than 5% of patients on drug and at least twice the rate of patients on placebo was akathisia (11% in both aripiprazole lauroxil groups and 4% in the placebo group). Injection site pain was greater in the 822 mg group.

Treatment Emergent Adverse Events

System Organ Class Preferred Term	Placebo (N=207) n (%)	Aripiprazole Lauroxil 441 mg (N=207) n (%)	Aripiprazole Lauroxil 882 mg (N=208) n (%)
Any treatment emergent adverse event	**129 (62.3)**	**122 (58.9)**	**119 (57.2)**
Gastrointestinal disorders			
Toothache	1 (0.5)	5 (2.4)	8 (3.8)
Nausea	4 (1.9)	6 (2.9)	7 (3.4)
Constipation	8 (3.9)	6 (2.9)	5 (2.4)
Diarrhoea	7 (3.4)	5 (2.4)	5 (2.4)
Dyspepsia	4 (1.9)	6 (2.9)	4 (1.9)
Dry mouth	5 (2.4)	2 (1.0)	0
General disorders and administration site conditions			
Injection site pain	4 (1.9)	7 (3.4)	10 (4.8)
Investigations			
Weight increased	1 (0.5)	6 (2.9)	5 (2.4)
Blood creatine phosphokinase increased	1 (0.5)	9 (4.3)	3 (1.4)
Weight decreased	5 (2.4)	1 (0.5)	2 (1.0)
Musculoskeletal and connective tissue disorders			
Neck pain	3 (1.4)	2 (1.0)	5 (2.4)
Nervous system disorders			
Akathisia	9 (4.3)	24 (11.6)	24 (11.5)
Headache	17 (8.2)	17 (8.2)	18 (8.7)
Sedation	3 (1.4)	4 (1.9)	5 (2.4)
Dizziness	6 (2.9)	2 (1.0)	2 (1.0)

Laboratory Findings
No clinically meaningful changes in renal, hepatic, or hematologic parameters were found.

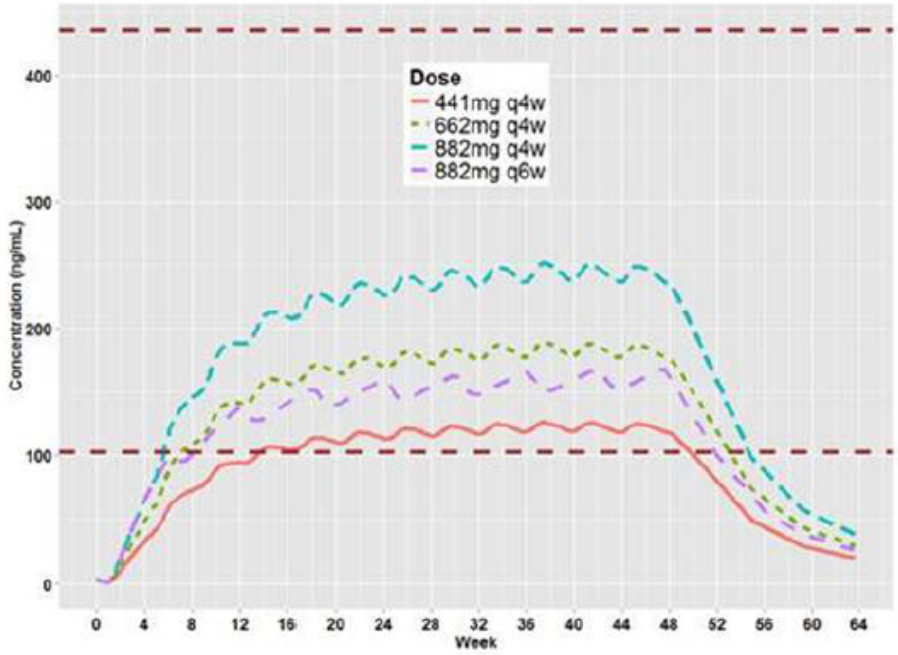
Vital Signs
There were no clinically meaningful changes in vital signs observed in the study.

Office of Clinical Pharmacology (OCP)
Dr. Balimane was the primary reviewer for this application. His findings are summarized below.

- An adequate link between aripiprazole lauroxil IM injection and oral aripiprazole has been established from the applicant's data.
- Aripiprazole lauroxil IM injection is efficacious in treating patients with schizophrenia.
- The pharmacokinetic profile of aripiprazole lauroxil IM injection is sufficient to support a once monthly or once every 6-week dosing regimen (for the 882 mg dose). Oral aripiprazole should be given for the first three weeks along with the first injection of aripiprazole lauroxil to provide appropriate exposure early in treatment.
- There is no evidence from the trials of dose dumping.
- Drug and CYP interactions have been characterized and can be labeled.
- Missed doses have been simulated and the procedure for handling missed doses has been outlined in labeling.

OCP also confirmed that the relative bioavailability of aripiprazole following IM aripiprazole lauroxil injection was 58% compared to oral aripiprazole, which was derived from population PK modeling by simultaneously fitting oral aripiprazole tablet and IM aripiprazole lauroxil data, all obtained from the applicant's data. Aripiprazole lauroxil IM injection leads to a sustained PK profile for aripiprazole exposure that is within the same concentration range as oral aripiprazole but with a much longer half-life than the oral formulation, which was the objective of this development program.

Figure 1: Shows the simulated mean aripiprazole Concentration Time Profiles following 441 mg, 662 mg, and 882 mg Monthly and 882 mg every 6 weeks doses up to Steady State. The Lower Dash Line Represents the Mean Steady State Cmin following 10 mg Daily Oral Doses of Abilify Tablets and the Upper Dash Line Represents the Mean Steady State Cmax following 30 mg Daily Oral Doses of AbilifyTablets.



Overall, the Office of Clinical Pharmacology has recommended approval and I agree with them.

OCP Genomics

Drs. Kraft and Grimstein reviewed the application. They confirmed that the classification of patients as extensive (EM), intermediate (IM), or poor (PM) metabolizers based on haplotype of genotype alleles to be acceptable. These classifications were used to assess impact of metabolizer status on aripiprazole exposures and to inform labeling.

Chemistry Manufacturing and Controls (CMC)

Drs. McLamore-Hines and Wilson-Lee have recommended approval. Adequate information was provided for a satisfactory evaluation of the quality of both the drug substance and the drug product. The expiry was supported to 27 months. (b) (4) but the amounts from the maximum 882 mg dose are negligible and levels of

(b) (4) from the batches on long term stability indicate that (b) (4) is not present in any batch at an appreciable level.

Office of Process and Facilities (OPF)
Dr. Norman Schmuff confirmed the NCE status of aripiprazole lauroxil as it pertains to the Federal Food, Drug, and Cosmetic Act and FDA regulations. While aripiprazole lauroxil is an ester, it is not an ester of aripiprazole, but an ester of N-hydroxymethyl aripiprazole, an active moiety not previously approved by FDA (see structures above).[2]

Microbiology
Dr. Pawar reviewed this application and recommended approval without postmarketing commitments.

Office of Scientific Investigation—Facilities Inspections
OSI inspected three US sites and found no action was indicated and no deviation from regulations. They deemed the data reliable and acceptable from these sites.

CDRH
This drug product is dispensed in a pre-filled syringe and so is a combination drug-device product. CDRH conducted a device design review and concluded that the application could be approved with one negotiated agreement of performing ongoing stability analyses to assess the mechanical reliability of the fully assembled device through the expiry date of the drug product. The applicant agreed to include this information in the annual reports to the NDA and CDRH found this acceptable.

Pediatric and Maternal Health
The Division of Pediatric and Maternal Health (DPMH) reviewed the Pregnancy and Nursing Mothers subsections of labeling. From limited available published data, it is estimated that less than 10% of the maternal weight adjusted dose of aripiprazole is present in the breast milk, but the data are not sufficient to evaluate safety, therefore DPMH recommends that this information not be included in labeling. DPMH was present at labeling meetings and their edits have been included in the final negotiated label.

Office of Prescription Drug Promotion (OPDP)
OPDP reviewed the medication guide and the prescribing information and had several recommendations which were included in the final negotiated label.

Division of Medication Error Prevention and Analysis (DMEPA)
DMEPA reviewed the container labels, carton labeling, and Instructions for Use and found them acceptable from an medication error perspective.

Nonclinical Pharmacology/Toxicology

[2] I note that some disciplinary reviews included background information on aripiprazole lauroxil and incorrectly referred to the active moiety as ariprazole and also included various inaccurate statements regarding the related chemistry. These incorrect characterizations were not essential to their reviews. Further, the primary review for the active moiety (or NCE) determination is set forth in Dr. Schmuff's memo and I agree with it.

Drs. Avila and Atrakchi conducted the nonclinical review. They concluded that aripiprazole lauroxil was adequately assessed in the nonclinical studies and that there were no findings that would prevent approval of the drug. Standard nonclinical studies were adequately conducted to support chronic use of aripiprazole lauroxil.

Labeling
The team constructed labeling based upon the data from this application using other drugs in the class as models. Comments/suggestions/edits from the team were considered and sent to the applicant multiple times for concurrence. The Office of Prescription Drug Promotion also reviewed the label and the changes that they suggested were incorporated. The applicant has accepted the labeling changes and a final version will be attached to the letter.

Advisory Committee
Not applicable.

Postmarketing Requirements/Commitments
None identified.

Conclusions
Sufficient information has been submitted to conclude that aripiprazole lauroxil is safe and effective for the treatment of patients with schizophrenia. I recommend that this application be approved.

The labeling has been negotiated to current Division standards.

There are no post-marketing commitments or requirements.

The applicant has agreed to the negotiated label.

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

/s/

MITCHELL V Mathis
10/02/2015