

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-436/S-018

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name	Aripiprazole
Trade Name	Abilify®
Therapeutic Class	atypical antipsychotic
Applicant	Otsuka Pharmaceutical Developmental & Commercialization, Inc
Priority Designation	P
Formulation	2, 5, 10, 15, 20, 30 mg oral tablet
Dosing Regimen	2-20 mg/day; 5 mg/day starting dose
Indication	Adjunctive treatment with antidepressant therapy of Major Depressive Disorder
Intended Population	Major Depressive Disorder

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EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

An approvable action is recommended, from a clinical perspective.

From a clinical perspective:

- The two pivotal Phase 3 trials are positive for efficacy and
- Aripiprazole (Arip) is adequately safe for adjunctive treatment of Major Depressive disorder (for adjunctive treatment in patients receiving concomitant antidepressant medications).

Specific issues are raised in Section 9 of this review that can be adequately addressed in labeling (Section 9.4 of this review provides key labeling recommendations). Postmarketing risk management activities are also recommended (as outlined below and discussed in Section 9.3 of this review).

Input from other disciplines is also recommended (OCPB, Biometrics and DSI).

Before considering a final approval action on this NDA it is recommended that issues and labeling are adequately resolved (as recommended in Section 9 of this review and as recommended by other review disciplines).

1.1.1 Risk Management Activity

In addition to postmarketing monitoring and reporting as required by the regulations, it is recommended that the sponsor's postmarketing surveillance program include monitoring for potential antidepressant (ADT)-Arip interaction effects on safety (e.g. for identifying and revealing events that are unexpected with respect to severity or with the nature or type of the event).

The following discusses the rationale for recommendations on risk management activity regarding a potential ADT-Arip interaction effect on safety.

Phase 3 Major Depressive disorder (MDD) trials were not designed to allow for direct comparisons between antidepressant (ADT)-Arip treatment to each monotherapy condition (and ideally to a placebo-placebo condition). Consequently, the trials were not specifically designed for a systematic examination of potential ADT-Arip interaction effects on safety. However, the placebo controlled pivotal trials included an ADT monotherapy which allowed for comparisons between placebo-ADT and ADT-Arip groups, although ADT was given under OL conditions and not DB conditions. Given these study design limitations the primary focus of the safety

review was to determine if the safety profile (the nature of adverse events or clinical parameter changes) in ADT-Arip treated subjects was unexpected (based on known AEs associated with either ADTs or Arip treatment alone). The studies did not reveal an unexpected safety profile. Also the safety results were reviewed to determine if the extent of any of the observed adverse effects was unexpectedly serious or clinically remarkable (based on known serious events associated with either drug alone). No serious and unexpected safety signal was revealed by the adjunctive Phase 3 MDD trials and the safety profile of adverse effects observed with adjunctive treatment was similar to that expected for either drug alone. Additionally, there is extensive postmarketing experience with approved antipsychotic drugs that includes Arip, since off-label combination treatment is common in the psychiatric clinical setting.

The placebo controlled trials were designed to allow for a comparison between ADT-Arip and ADT-placebo groups on each safety parameter, but the interpretation of the results are limited given the study design, as previously discussed (the trials did not employ a DB design for both drugs and did not include at least a DB placebo-Arip monotherapy group). The results on the treatment group differences (between ADT-placebo and Arip-ADT groups) on the incidence of adverse (AEs) in these trials were suggestive of a possible ADT-Arip interaction effect on some AEs that are known to be associated with each drug alone. Some of these AEs also showed a numerically greater treatment group difference on the incidence of the given AE for a particular ADT subgroup or subgroup(s) compared to another ADT subgroup that was either in a different drug class or had potential effects on PK (although the sponsor reports no meaningful ADT-Arip interaction effects on PK). Potential ADT-Arip interactions effects on exaggerating adverse events that are known to be associated with both drugs (e.g. weight gain, sedative effects, among others) would not be surprising. Section 9.2 of this review discusses safety observations in short-term and in the ongoing longterm adjunctive MDD trials. The limitations with interpreting these safety results are also discussed. Section 9.3.1 of this review discusses postmarketing surveillance activities.

1.1.2 Required Phase 4 Commitments

Phase 4 commitments are not recommended, since issues raised in Section 9.2 can be adequately addressed in labeling. Additionally, postmarketing surveillance activities are recommended (as outlined below and in Section 9.3 of this review).

1.1.3 Other Phase 4 Requests

Section 9.2 discusses issues relevant to potential pseudospecific effects on efficacy measures in the pivotal trials. For reasons discussed in Section 9.2 of this review, consider the following Phase 4 requests:

- A Phase 4 request for conducting efficacy MDD trial(s) that exclude(s) patients with Generalized Anxiety disorders (GAD) and that also possibly exclude(s) patients using substances of abuse. A monotherapy MDD trial (that does not restrict entry criteria to partial responders) would be more feasible for excluding GAD patients and for excluding active substance users (in order to achieve a sufficient sample size that may not be achieved by restricting the trial to only including partial responders). Such a

study would allow for examining the potential influence of other factors on efficacy and in identifying potential predictors of response.

- A Phase 4 request for conducting ADT-Arip adjunctive MDD trial(s) that include(s) placebo controlled double-blind (DB) monotherapy groups in order to allow for direct comparisons between a DB placebo-ADT control group and DB Arip-placebo group on safety variables (ideally the study would also include a placebo-placebo group). The specifics on the study design of such a study would need further consideration and discussions with the sponsor. Refer to Section 9.2 regarding a potential ADT-Arip interaction effect on safety and the limitations with interpreting these safety results.
- Since the MDD trials did not examine the safety of simultaneously initiating ADT with Arip treatment, consider a Phase 4 request for trials designed to examine the safety of concurrent initiation of both drugs. The initiation of both drugs simultaneously, could arise in the clinical setting, since it is not uncommon for treatment resistant patients or partial responders to discontinue to treatment or for patients to present at a later date acutely depressed (and sometimes suicidal) after ADT treatment was terminated. Consequently, initiating adjunctive treatment (both drugs, simultaneously) would be a clinical consideration and relevant to common clinical practices.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

Abilify® (aripiprazole) is an atypical neuroleptic drug approved for schizophrenia and other indications.

The proposed indication of oral Abilify® is for the treatment of MDD as an adjunctive therapy with ADT.

Two pivotal Phase 3 trials were conducted (CN138139 and CN138163 also referred to as C-139 and C-163, respectively). These studies were placebo controlled, randomized, double-blind (DB), multi-center studies (that included US study sites). Generally healthy adult patients with MDD were included in these trials. Subjects had to have an inadequate response to at least one, but no more than 3 treatment courses with an approved antidepressant drug (ADT). Each study had 3 phases, as follows:

- Phase A (Screening Phase): 7-28 days of screening.
- Phase B (8-week Prospective Treatment Phase; 1611 subjects entered Phase B in the studies, combined): subjects received single-blind (SB) placebo treatment coadministered with 1 out of 5 specified ADTs (escitalopram, sertraline, venlafaxine extended-release, fluoxetine or paroxetine controlled-release).
- Phase C (6-week DB Treatment Phase): 741 subjects (in the 2 studies, combined) were identified as showing an inadequate response to ADT during the Prospective Treatment Phase (using prespecified criteria). These subjects were randomized to either:
 - DB placebo or

- Aripiprazole (Arip) treatment
DB treatment was administered over 6-weeks using a flexible dose design. The daily dose range of Arip treatment was either:
 - 2 to 15 mg daily in subjects receiving an ADT that is also a potent CYP2D6 inhibitor (fluoxetine or paroxetine) or,
 - 2 to 20 mg daily in subjects receiving any of the other ADTs employed in the trial.

The primary efficacy data was collected from a total of 367 aripiprazole subjects and 356 placebo treated subjects (in the two trials combined).

The safety results primarily came from the following clinical trial databases:

- The 2 pivotal short-term Phase 3 MDD efficacy trials C-139 and C-169 (371 aripiprazole and 366 placebo treated subjects provided safety data),
- All-Arip treated safety dataset (N=1055) that included all Arip treated subjects in all completed trials and all ongoing open-label Arip trials involving different patient populations (all Phase 2-4 trials). The results were generally provided by diagnostic group categories that included an MDD group. The MDD group included subjects from:
 - The 2 pivotal short-term Phase 3 MDD trials (C-139 and C-163).
 - One ongoing longterm (52 week) open-label (OL) MDD study C-164 (Arip and concomitant ADT treatment) with 930 subjects (includes subjects completing the 2 short-term Phase 3 MDD trials and additional subjects who were retrospectively identified as partial responders to past ADT treatment, as defined in the protocol).
- 2 Small Phase I Arip-ADT interaction studies (C-462 and C-463) in which pharmacokinetic drug-drug interaction effects were examined.

1.2.2 Efficacy

Each pivotal Phase 3 study (C-139 and C-163) was positive for efficacy on the primary efficacy variable (the Montgomery-Asberg Depression Rating Scale). The Arip group of each trial showed a significantly ($p < 0.01$) greater mean change (for improvement from the end of Phase B to the end of Phase C) on the primary efficacy variable compared to the placebo group (using the last-observed-carried-forward approach).

The Sheehan Disability scale (SDS) was a key secondary endpoint that showed trends for greater improvement ($p < 0.06$) or showed significantly greater improvement ($p < 0.025$) in Arip subjects compared to placebo subjects in Study C-139 and Study C-163, respectively.

1.2.3 Safety

Safety results failed to reveal any new and clinically remarkable safety profile or signal that is not already described in approved labeling, except that some of the results were suggestive of an exaggerated effect of combining Arip with ongoing ADT treatment. The incidence of some adverse events (including some events leading to discontinuation of treatment) suggested a greater incidence (or an exaggerated effect) in patients receiving combined ADT-Arip treatment for some of the AEs that are known to be associated with either drug alone. However, the

interpretation of these results is limited since placebo controlled monotherapy groups were not included in the MDD trials, as previously discussed.

Section 7.1 of this review provides a synopsis of key observations on safety in the short term and long term MDD trials that impact on recommendations provided in Section 9 of this review. Section 9.2 also outlines key safety observations relevant to recommendations on postmarketing activities (Section 9.3 of this review) and to recommendations on labeling (Section 9.4 of this review).

1.2.4 Dosing Regimen and Administration

The trials showed efficacy for adjunctive Arip treatment by using a flexible dose design. Subjects ADTs known to be potent CYP2D6 inhibitors (paroxetine or fluoxetine) were to receive a flexible daily-dose-range of 5-15 mg. Subjects receiving other ADTs employed in the trials were to receive a flexibly daily dose range of 5-20 mg. The starting daily dose-level in the pivotal trials was 5 mg. The daily dose-level could be increased in increments of no greater than 5 mg that had to occur at no less than a 1 week interval from the previous dose increase. The final mean dose that Arip subjects received (at treatment endpoint) in each of the 2 pivotal studies was 10.7 and 11.4 mg daily, respectively.

Since a flexible dose design was employed, these efficacy trials did not examine the dose-response curve or determine dose-dependent effects on efficacy.

Section 9 of this review discusses key issues relevant to dosing that can be adequately addressed in labeling.

1.2.5 Drug-Drug Interactions

Potential ADT-Arip interaction effects on safety were previously described.

2 Phase I studies were conducted to examine Arip-ADT interactions on pharmacokinetic properties (PK) in healthy adults (19-44 years old). Study CN138462 (C-462) examined venlafaxine-XR-Arip interaction effects and Study CN138463 (C-463) examined escitalopram-Arip interactions effects. No clinically relevant effects on PK were observed in these trials, according to the sponsor. From a clinical perspective these trials failed to reveal any clinically remarkable safety signal (noting that the trials were not specifically designed for this purpose).

The 2 pivotal Phase 3 MDD trials (Studies -139 and -163) included some blood sampling for population PK analyses. No clinically relevant effects on PK were observed according to the sponsor. Subjects receiving ADTs of potent CYP 2D6 inhibitors (paroxetine or fluoxetine) received no greater than 15 mg of aripiprazole daily in these trials, while all other subjects could receive up to 20 mg daily.

OCPB input is recommended regarding the results on PK and on potential PK-pharmacodynamic interactions.

1.2.6 Special Populations

Results of Subgroup Analyses

A significant gender by treatment group interaction effect was observed in Study C-139 that revealed a greater mean improvement on the primary efficacy variable in females than in males. Trends for a similar gender by treatment group interaction effect observed in Study C-163.

Additional subgroup analyses revealed no significant subgroup by treatment group interaction effects on the primary efficacy variable. These analyses were conducted to examine the potential influence of possible predictors of response such as age, the ADT given during the study, and ethnicity or race, among other potential factors. However, the sample size of some of subgroups examined was generally insufficient to make conclusions on the basis of these results.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The sponsor is seeking approval of Abilify as an adjunctive treatment with concomitant antidepressant drugs (ADTs) in adult patients with Major Depressive disorder (MDD). The sponsor conducted 2 pivotal Phase III trials (CN138139, CN138163 also referred in this review as Study C-139 and C-163). Safety results from completed and ongoing trials were also provided, as discussed later in this review.

Abilify (aripiprazole) is an atypical neuroleptic that is approved for Schizophrenia and other psychiatric indications (e.g. Bipolar I-mixed/mania) as described in approved labeling.

2.2 Currently Available Treatment for Indications

There is no other drug in this drug class approved for treatment of MDD ((b) (4) (b) (4) as an adjunctive therapy).

See the previous section regarding other approved drugs in this drug class.

2.3 Availability of Proposed Active Ingredient in the United States

Abilify® has been on the market for a number of years. The original NDA21436 submission for the oral tablet formulation was approved in November 2002.

2.4 Important Issues With Pharmacologically Related Products

Refer to labeling of approved drugs in this drug class that describe important issues relevant to safety. Other safety related sections of this review also discuss safety related issues or potential issues, when applicable. The final section of this review summarizes any new and clinically remarkable safety findings.

2.5 Presubmission Regulatory Activity

The MDD indication for adjunctive-treatment of Arip with ADT was developed under IND 76132. The sponsor refers to the following meetings or correspondence regarding feedback they received from the Division regarding aspects of their development program:

- February 2004 development program meeting
- December 14, 2006 Pre-supplemental NDA (sNDA) correspondence from the Division providing feedback on their proposed plans for the sNDA. The sponsor also

refers to feedback in this letter regarding a request for pediatric waiver. See Section 8.4 of this review for issues relevant to pediatric clinical issues.

Refer to the meeting minutes and correspondence in DFS for any issues previously discussed with the sponsor. The focus of this review is on the actual data submitted under sNDA21436 for assessing adequate efficacy and safety for the proposed efficacy claim. See section 4 of this review for the review strategy of the sNDA21436.

2.6 Other Relevant Background Information

The sponsor provides a listing of approved applications for foreign marketing of Arip and discusses their foreign marketing experience in Section 6 of Module 2.7.4 of the submission.

Abilify® had not been previously submitted for approval for an (b) (4) indication.

Abilify® is approved for the indications of schizophrenia and/or bipolar mania in approximately 40 countries (the sponsor lists the countries in Table 6.1.A in Section 6 of Module 2.7.4). Arip was first approved for schizophrenia in Mexico on July 17, 2002 and later in the USA on November 15, 2002.

The sponsor notes that Arip has not been withdrawn for the market (in any country).

The sponsor also lists a number of marketing applications that are under review in other countries (as of 12/31/06).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Reviews from disciplines assigned to this NDA remains pending at the time of this writing. An 8/17/07 mid-review-cycle meeting was held. Each reviewer that attended the meeting had no major issues at that time (Biometrics, OCPB, and CMC).

3.1 CMC (and Product Microbiology, if Applicable)

The undersigned reviewer is not aware of any major issues from CMC (Dr. Thomas Oliver and Dr. Nallaperum Chidambaram) at the time of this writing.

3.2 Animal Pharmacology/Toxicology

Since Abilify™ is already approved, the undersigned reviewer is not aware of any new preclinical data.

3.3 Biometrics

Biometric reviewer Dr. Jialu Zhang's review remains pending. The undersigned reviewer is not aware of any major issues from Biometric at the time of this writing.

The undersigned reviewer informed the Biometric team of findings showing gender by treatment group interaction effects (as discussed in Section 6 of this review). Final conclusions from the Biometric team remains pending at the time of this writing.

3.4 OCPB

The undersigned reviewer is not aware of any major issues from OCPB (reviewer Dr. Andre Jackson is assigned to the NDA).

3.5 DSI

DSI reviewer Dr. Dianne Tesch is assigned to this NDA and DSI inspections are underway at the time of this writing.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

In accordance with the Clinical Review MAPP this section outlines datasources:

- The primary dataset is the data from clinical trials (see tables in Section 4.2 of the trials).
 - Efficacy Data: 2 Pivotal Completed MDD Phase III Trials intended to support the proposed indication (C-139 and C-163)
 - Safety Data:
 - From the 2 above MDD trials, pooled
 - Safety data from other Phase 1-4 trials. Refer to Section 4.3 for review strategy of results that were selected for the purposes of this review and for sections of the submission that were reviewed. Section 4.2 below shows tables for all studies providing the source of safety datasets used for results provided in Module 2.7.4 of the submission.
- Secondary datasources are:
 - Postmarketing results
 - Literature review
 - Any additional datasources are specified in appropriate sections of this review

Results from the above datasources are summarized in appropriate sections of this review.

4.2 Tables of Clinical Studies

Therefore, the table below only outlines trials in each dataset, in a condensed manner (40 trials total. Module 2.7.4 (Introduction and Appendices IA and IB) provides more details.

Efficacy Studies*	
MDD Phase 3 Study C-139	8-week treatment phase: OL ATD +SB PBO treatment 6-week DB phase of partial responders: Arip (188 ITT Ss) or PBO (172 ITT Ss) given with ADT treatment
MDD Phase 3 Study C-163	Methods are virtually identical to those of the above Study -139 (similar sample size)
Total completers:	Placebo: 322 subjects Arip: 322 subjects
Total of ITT Safety Subjects:	Placebo: 366 subjects Arip: 371 subjects
Total of ITT Efficacy Subjects:	Placebo: 356 subjects Arip: 366 subjects

* Arip=aripiprazole ADT=concomitant antidepressant treatment, MDD=Major Depressive disorder, OL=open-label DB=double-blind SB=single blind PBO=placebo

Studies for Each Integrated Safety Datasets from Phase 2/3/4 MDD and Other Psychiatric Patients*	
“All Aripiprazole Dataset:” Completed Trials:	
Pivotal Completed MDD Studies C-139 and -163	See above
Ongoing OL MDD Longterm Study C-164	OL Arip (2-20 mg) with ADT study (primarily of selective serotonin reuptake inhibitors and venlafaxine) with 930 subjects (included subjects who were not randomized to DB treatment in Studies -163 and -139).
Total of ITT Safety Arip Subjects:	1055 Total Subjects (153 subjects exposed to up to 360 days of treatment based on results shown in Table 1.2.2.1A of Module 2.7.4)
53 Completed DB and OL Trials of Other Psychiatric Patients involving different study designs (different dose-levels, duration of treatment and other key study design differences)	30 Schizophrenia Trials 2 Schizoaffective Trials 13 Bipolar Trials 7 AD with psychosis Trials 1 Early AD Trial
Ongoing OL Trials of Other Psychiatric Patients	OL Trials or OL Extension trials to several of the completed trials on other psychiatric populations (e.g. Schizophrenia, BP, AD and others)
3 Special Studies of Other Psychiatric Patients	1 oral/IM Schizophrenia trial 1 Trial of Parkinson’s Disease Patients with Psychosis 1 Study on Patients with Alcoholism
Total of ITT Safety Arip Subjects:	12925 Total Subjects (based on Table 1 of Module 2.7.4 which also enumerates subjects by diagnostic categories)

“Blinded Studies Dataset” of Blinded Ongoing Studies:	
Phase III Efficacy MDD Study C-165	Study design is similar to that of the 2 Pivotal Efficacy MDD Studies C-139 and -163 (see previous table)
4 Bipolar Studies	Involving different study designs (including different dose-levels and treatment duration)
2 Schizophrenia Studies	Involving different study designs

* ADT=concomitant antidepressant treatment, Arip=aripiprazole MDD=Major Depressive disorder, OL=open-label DB=double-blind SB=single blind AD=Alzheimer's disease, PBO=placebo

Other Studies of Additional Pooled or Unpooled Safety Datasets*	
<u>2 Phase I Studies C138462 & CN138463 (referred to as Studies C-462 and C-463)</u>	Arip treatment studies on steady state PK properties of venlafaxine (C-462) or escitalopram (C-463) treatment given over 14 days.
Sample Sizes (based on Table 5.3.1 of Module 2.7.4)	Study -462: 38 enrolled and 27 completed subjects Study -463: 25 enrolled and 17 completed subjects
<u>2 Completed Studies (31-02-A01 & OBRI 0002) in Patients with Schizophrenia that were conducted in Asian Countries (Taiwan and China)</u>	Results are summarized in Section 5.9 on Special Populations and in Appendix 5.9 of Module 2.7.4
Sample Sizes (Appendix 5.9 in Module 2.7.4 provides more details)	120 Arip subjects in China and 49 Arip subjects in Taiwan

*Arip=aripiprazole PK=pharmacokinetic properties

4.3 Review Strategy

The following table lists the datasources that were reviewed, as described in more detail in subsections that follow.

TABLE 4.3.1: ITEMS THE REVIEWED	
Submission Date	Items Reviewed
5/16/07	Clinical Study Reports (selected sections): Studies C...139 and C...163 Module 2.7.3: Section 3.3 Module 2.7.4: in-text and selected appendices/attachments and narratives (narrative were provided in Appendix 2.2B) Proposed Labeling (side-by-side version) Financial Disclosure Certification Literature Search Item 8 (litserach.pdf) Selected Case Report Forms
9/5/07 and 9/6/07	Responses to inquiries (refer to 8/30/07 Telecon document under the NDA).

The following bolded subsections outline specific in-text sections of the submission that were reviewed for each objective as specified. The review strategy includes the purpose, the selection of datasets and materials for review, the selection of specific results that were reviewed. Subsections below discuss each of these aspects of the review strategy.

The review strategy described below was discussed with Team Leader, Dr. Mitch Mathis who did not have any feedback to provide or comments to add to this review strategy.

Efficacy Review:

- Methods and efficacy-related sections of the Clinical Study Reports (CSRs) for the 2 Completed Phase 3 Efficacy Trials C...139 and C...163 were reviewed. The purpose of this efficacy review was to determine if studies were adequately designed and if efficacy was adequately demonstrated, as proposed.
- The in-text Section 3.3 of Module 2.7.3 was reviewed for efficacy results analyzed by population subgroups (gender, age and race and any other subgroups analyses as specified in appropriate sections of this review).
- Some tables and results that were reviewed were obtained from other sources (e.g. in other sections of the submission or in appendices or attachments) as specified in applicable sections of this review.

Safety Review: Refer to Section 4.2 of this review for the datasets from which the sponsor provided safety results.

The purpose of the review of safety results of this NDA (as found in Module 2.7.4, unless otherwise specified in this review) was to find any potentially new and remarkable safety signal in MDD patients that would impact on recommendations provided in Section 9 of this review (relevant to the overall action on this NDA and relevant to labeling for the proposed indication).

The primary focus of the safety review was on safety results obtained from MDD trials as found in in-text sections of Module 2.7.4. Other safety results (involving other diagnostic groups or Phase I trial results) were not reviewed for a number of reasons such as the following.

Subsections that follow outline each aspect of the review strategy. The final subsection below is a discussion of the overall rationale for the strategy selected for the safety review of this NDA.

Review Strategy of Integrated and Unpooled Safety Datasets (in Module 2.7.4).

The following discusses the review strategy for results from integrated safety datasets:

- Integrated Pivotal MDD Trial Dataset referred by the sponsor as the “Placebo-controlled Studies in MDD dataset.” This dataset:
 - Is referred to as the 2-Phase 3 MDD Trial dataset in Section 7 of this review
 - Consisted of data from the 2 pivotal, short-term, completed Phase 3 MDD trials, C...163 and C...139

Materials reviewed consisted of:

- All in-text sections of Module 2.7.4 that correspond to safety sections 7.1.1 to 7.1.9 of this review were reviewed (unless otherwise specified later in these safety sections). This includes safety results on deaths, SAEs, ADOs, AEs, and clinical parameter results and selected narratives.
- As specified in corresponding subsections of Section 7 additional results found in other sections of the NDA (e.g. in attachments or appendices or elsewhere) were selected for reasons provided in the given subsection where applicable.

- Integrated “All Aripiprazole Dataset.”

The focus of the review of this dataset was on results from MDD trials and not on results from trials involving other patient populations. This dataset consisted of data from:

- All Arip treated subjects in all completed trials and of all ongoing OL trials, combined (without regard to study design, treatment regimen or other key differences among the trials).
- The sponsor provided results were provided by diagnostic groups and for subjects combined (MDD, schizophrenia, Bipolar I-mania, Bipolar I-depression, and dementia). The dataset also includes psychotic patients with Parkinson’s disease, and patients with alcoholism.

The MDD diagnostic group included the subjects from:

- Short-term Studies: The 2 pivotal MDD Phase III short-term trials involving adjunctive ADT treatment (-163 and -139)
- Longterm Ongoing OL Study: The 1 ongoing OL longterm MDD Phase III trial that was also an ADT adjunctive study (-164). This longterm study is an ongoing study involving OL treatment for up to 1 year in duration. This trial included subjects that were not randomized to DB treatment in the short term trials C-139 and -163.

The results from the All-Arip MDD Treated dataset (and not the results from other diagnostic groups) were the main focus of the review in Section 7. Materials reviewed were:

- Corresponding in-text sections of Module 2.7.4 for the MDD diagnostic group that summarized results on deaths, the incidence of SAEs and ADOs (and selected narratives) unless otherwise specified in Section 7 of this review (in corresponding sections under Section 7).
- Some additional safety results from clinical safety parameters were found in Module 2.7.4 and were generally summarized in corresponding subsections of Section 7 of this review.

- Safety Results from Individual Studies

- 2 Phase I trials: Studies C-463 and -464 were conducted to examine ADT-Arip interaction effects on PK for selected ADTs. The focus of the review of safety information found in Module 2.7.4 was on deaths, SAEs and ADOs (as found in in-text sections, unless otherwise specified in this review).

- Blinded Safety Results

- Only deaths and SAEs of MDD patients as described in Module 2.7.4 were reviewed (primarily the corresponding in-text sections of Module 2.7.4 were reviewed unless otherwise specified). An in-text section on ADOs could not be

found in Module 2.7.4. However, a line listing was found (as described in Section 7.1.3.2 of this review).

Refer to Section 4.2 of this review listing all trials that generated safety results that includes results from trials that did not involve MDD patients and were therefore, were generally not reviewed, unless otherwise specified in corresponding subsections of Section 7 of this review.

Overall Rationale for the Above Review Strategy

The focus of this review is on results from MDD trials, since the sponsor is seeking an (b) (4) indication. Placebo controlled trial results provide the most interpretable and meaningful results in contrast to OL trial results and blinded trial results. The results from placebo controlled trials are most meaningful given the trial design employed. These trials involved randomized, DB design, among other features) and the manner in which results were presented that involved treatment group comparisons on each dependent variable that was examined (the results on deaths, SAEs, ADOs, AEs and clinical parameter results). Therefore, the main focus of the review is on the placebo controlled trial MDD dataset. OL trial results are more difficult to interpret but offer some safety results involving longer term treatment. Therefore, the primary focus of review of OL results that involved MDD patients was on a review of the deaths, SAEs and ADOs, although Section 7 of this review also summarizes some additional safety results from these trials, as found in Module 2.7.4. Note that the safety data from the OL longterm safety trial in MDD patients was integrated with data from placebo controlled MDD trial data, since the OL longterm study (Study -164) was ongoing (such that a CSR was not provided and unpooled results were not provided in Module 2.7.4). Therefore, the safety results of the OL longterm MDD trial was provided as integrated results as part of the All-Arip Treated MDD dataset. Blinded results are most difficult to interpret (as study drug assignment is blinded), such that this review only summarizes results of any reported deaths, SAEs and ADOs (ADOs were found in a line listing, rather than summarized in in-text sections of Module 2.7.4 and as specified later).

It is difficult to extrapolate results from other trials or integrated safety datasets involving other patient or non-patient populations. Therefore, for the purposes of this review, safety results from other datasets or trials involving non-MDD populations were generally not reviewed (unless otherwise specified in corresponding subsections of Section 7 of this review).

The following paragraphs discuss some key limitations with the pooled MDD (All-Arip Treated) dataset and with other safety datasets that were generally not subject to review or were not the focus of the review (as previously discussed above).

- The Integrated Datasets (All-Arip Treated MDD, All-Arip dataset of other diagnostic groups, and the Blinded dataset): the sponsor integrated safety results from trials involving different study designs and treatment regimens within each patient population for the All-Arip Treated and Blinded integrated safety datasets. The trials differed in

trial design, treatment regimens and in treatment duration and in other respects (e.g. some trials are ongoing and others are completed). Another key problem is that these pooled safety datasets involved different patient populations even for some of the diagnostic categories of the All-Arip dataset (e.g. it appears that schizophrenia and schizoaffective trials were pooled, trials involving patients with alcoholism or Parkinson's appeared to be pooled with other trials involving other diagnostic categories). Given these limitations with these safety datasets the results are difficult to interpret and are also difficult to extrapolate to the MDD population for the proposed treatment regimen.

- All-Arip Treated MDD Dataset: While there are results for an MDD diagnostic subgroup as previously discussed, these results are in part redundant with the pooled placebo controlled MDD trial dataset (C...139 and C...163) since these 2 studies are also pooled with the All-Arip treated dataset MDD diagnostic subgroup in which only one other trial is pooled with this subgroup. The third trial is of the ongoing OL MDD long-term study C...164.
- "Asian" Trial safety data involved a schizophrenia population.
- The Phase I trial dataset is of results conducted in healthy adults who were generally young adults and did not include placebo controlled groups, since these trials were studies to examine Arip-ADT (venlafaxine or escitalopram) interaction studies that generally used lower dose-levels of ADT than are used in the MDD population. Consequently, it is difficult to interpret the safety results from these trials and extrapolate results to the MDD population. However, the results of deaths, SAEs and ADOs from these Phase 1 trials was reviewed since they involved ADT combined with Arip treatment and examined potential drug-drug interaction effects on PK.

Review of Information for Other Sections of this Review and for Secondary Safety

Datasources: the information reviewed for other sections of this review (e.g. Financial Disclosures, Data Quality and Integrity, secondary safety datasources as listed in Section 4.1 of this review and other sections) are specified in each corresponding section of this review.

Additional Comments on the Review Strategy

Limitations with information reviewed in the NDA are also described in corresponding sections of this review that also impact on the review strategy. Therefore, additional comments on review strategy and rationale are provided in the applicable sections in this review.

4.4 Data Quality and Integrity

Reviewer Conclusion: *Overall the data quality and integrity is adequate for the purposes of this review based on the following reviews:*

- DSI inspections as previously summarized in Section 3.4.

- Efficacy datasets (reviewed by the statistical reviewer) did not reveal any major issues regarding quality and integrity of the efficacy data to the knowledge of the undersigned reviewer (refer to section 3.4 of this review).
- An audit conducted by the undersigned reviewer of comparing adverse event (AE) data found in CRFs to SAEs described in narratives of 3 arbitrarily selected patients, as described in more detail below.
- Also refer to Section 7.2.8 of this review.

Methods of the CRF and Narrative Audit

CRF to Narrative comparisons for each arbitrarily selected subject revealed no inconsistencies as follows (SAE terms were compared for each subject but other items selected for comparisons were arbitrarily selected items for each subject):

- Subject CN138096-48-178: Compared SAE terms and timing relative to DB treatment, age, and gender and the information matched.
- Subject CN138139-19-509: Compared SAE terms, the action taken and the timing of the SAE relative to DB treatment, age, gender, an OL ADT and the information matched.
- Subject CN138163-36-5862: Compared SAE terms and timing relative to DB treatment and AE terms and this information matched.

4.5 Compliance with Good Clinical Practices

DSI has not conveyed any key concerns to the undersigned reviewer at the time of this writing.

Studies C...139 and C...163 (and the ongoing Study C...164) were conducted in accordance to the Declaration of Helsinki and Good Clinical Practice (GCP) and the International Conference on Harmonization (ICH) guidelines.

4.6 Financial Disclosures

Item 19 of the submission provided the source of information described in this section of the review. 2 Certification forms of “Financial Interests and...Investigators” (Form FDA 3435) were signed by Dr. Jack Grebb, Vice President, GCR Neurosciences of Bristol Myers Squibb Co. with Item 1 checked off and Dr. William Carson, Vice President of Global Development of Otsuka America Pharmaceutical, Inc. with Items 2 and 3 checked off, respectively. A listing of investigators followed in which only 3 investigators had not responded to the sponsor’s inquiries using methods for contacting these investigators, as outlined in the Item 19 of the submission and for reasons specified in their investigator listings for outstanding statements not yet received. The studies specified for which investigators were contacted were Studies C..139, C...163, -462 and -463 (the 2 pivotal Phase III MDD trials and the 2 Phase I Arip-antidepressant drug interaction studies (Arip and venlafaxine or escitalopram interactions were examined in each study, respectively). All investigators that the sponsor listed were specified as having no

disclosable information, except for the 3 investigators with outstanding information. These 3 investigators were subinvestigators and were summarized in the following tables (copied from the submission).

Table B: CN138139: Outstanding Financial Interests Statements

Investigator Subinvestigator	Protocol & Site No.	Participated as Principal Investigator (Yes/No)	Number of Patients Randomized at the Site	Were Patients Enrolled by the Individual	Comments/Status
(b) (4)					

Table B: CN138163: Outstanding Financial Interests Statements

Investigator Subinvestigator	Protocol & Site No.	Participated as Principal Investigator (Yes/No)	Number of Patients Randomized at the Site	Were Patients Enrolled by the Individual	Comments/Status
(b) (4)					

Reviewer Comments

DSI was informed of the above investigator with (b) (4) subjects who had an outstanding financial interest statement (DSI input remains pending at the time of this writing). Unless DSI identifies issues relevant to this site, the financial information provided does not reveal any major issues relevant to the integrity of the pivotal trials. Moreover, studies employed a double-blind placebo controlled design in order to minimize potential bias.

5 CLINICAL PHARMACOLOGY

The OCPB review is pending at the time of this writing. Therefore, this section of the clinical review presents the sponsor results and conclusions with some reviewer comments but input from the OCPB Team is recommended.

5.1 Pharmacokinetics

The sponsor conducted 2 Phase I trials to examine potential drug-drug interactions between Pal and venlafaxine XR (Study C...462) or escitalopram (Study C...463) on steady state pharmacokinetics (PK) of the ADT, respectively. The sponsor also conducted population PK analyses in the 2 pivotal MDD trials (C-139 and C-163). The synopses-studies.pdf document was reviewed for the below methods and results of the two Phase 1 Studies C-463 and Studies -462. Note that OCPB input remains pending such that results below are only provided, according to that described by the sponsor.

Study C-463

Study C...463 was an OL trial involving treatment as follows (18-45 year old, generally healthy subjects were included):

- Escitalopram (Lexapro®) 10 mg daily on Days -7 to 14.
- Arip 10 mg daily on Days 1 to 14.

Blood sample collection for PK analysis occurred over a 24 hour period on the following days:

- Days -1 and 14 for PK analysis of escitalopram (SCT)
- Days 14 and 15 for PK analyses of Arip and dehydro-Arip

The CSR in the submission provides more details on the methods of this study.

The following tables were provided as a summary of the study results on PK (in the synopses-studies.pdf file of the submission).

The following table shows Day 14 PK results.

Pharmacokinetic Parameter	Treatment	
	Escitalopram (N=17)	Escitalopram + Aripiprazole (N=17)
C_{max} (ng/mL)		
Geom. Mean	19.17	19.95
(CV%)(between subject)	(25.96)	(26.89)
AUC(TAU) (ng·h/mL)		
Geom. Mean	308.16	330.89
(CV%)(between subject)	(30.23)	(29.58)
T_{max} (h)		
Median	3.0	3.0
Min, Max	(1.0, 8.0)	(1.0, 6.0)

Results of Statistical Analysis on Escitalopram Pharmacokinetic Parameters				
Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means	
	Treatment	Geometric Mean	Point Estimate	90% Confidence Limits
C_{max} (ng/mL)	escitalopram	19.173	1.04	(0.99, 1.09)
	escitalopram + aripiprazole	19.946		
AUC(TAU) (ng•h/mL)	escitalopram	308.16	1.07	(1.04, 1.11)
	escitalopram + aripiprazole	330.89		

The sponsor concludes that a small increase in Arip exposure was observed at steady-state during SCT treatment (a 7% increase in AUC of SCT was observed). The sponsor concludes that this small increase is not a meaningful increase, such that they predict that no drug-drug interaction effects on PK with Arip and concomitant SCT treatment. Consequently, the sponsor indicates that no dose adjustment is needed when these 2 drugs are coadministered.

Study C-462

Study C-462 was an OL trial involving treatment as follows (18-45 year old, generally healthy subjects were included):

- Venlafaxine (Effexor® XR) 75 mg daily on Days -4 to 14.
- Arip dose titration from Days 1 through 14 as follows: 10 mg daily for 3 days, 15 mg daily for 4 days and 20 mg daily for 7 days

Blood sample collection for PK analysis occurred over a 24 hour period on the following days:

- Days -1 and 14 for PK analysis of venlafaxine (Ven) and O-desmethylVen
- Days 14 and 15 for PK analyses of Arip and dehydro-Arip

The CSR in the submission provides more details on the methods of this study.

The following results were provided as a summary of the study results on PK. The first table shows Day 14 results.

Summary Statistics for Venlafaxine Pharmacokinetic Parameters			
Pharmacokinetic Parameter	Treatment		
	Venlafaxine XR 75 mg (N=27)	Venlafaxine XR 75 mg + Aripiprazole (N=27)	
C_{max} (ng/mL)			
Geom. Mean	48.82	56.06	
(CV%)	(55)	(57)	
AUC(TAU) (ng•h/mL)			
Geom. Mean	657.05	777.27	
(CV%)	(77)	(70)	
T_{max} (h)			
Median	6.0	6.0	
Min, Max	(5.0, 8.0)	(4.0, 10.0)	

Results of Statistical Analyses for Venlafaxine Pharmacokinetic Parameters

Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means	
	Treatment	Geometric Mean	Point Estimate	90% Confidence Limits
C _{max} (ng/mL)	venlafaxine	48.82	1.148	(1.083, 1.217)
	venlafaxine + aripiprazole	56.06		
AUC(TAU) (ng•h/mL)	venlafaxine	657.05	1.183	(1.130, 1.238)
	venlafaxine + aripiprazole	777.27		

The sponsor concludes that a small increase in Ven exposure (14.8% increase in C_{max} and an 18.3% increase in AUC) that occurred during the up-titration in the daily dose of Arip. However, the sponsor concludes that this small increase is not meaningful to warrant the need for dose adjustment of Ven. The sponsor also concludes that Arip or dehydro-Arip exposure was not affected by coadministration with Ven. Consequently, the sponsor indicates that no dose adjustment is needed when these 2 drugs are coadministered.

Reviewer Comments. *It is not clear to the undersigned reviewer if the above findings from these 2 trials are sufficient to rule out potential drug-drug interaction effects that may impact on efficacy results of the sponsor’s pivotal efficacy trials. The sponsor only examined PK at a single daily dose-level of Arip and SCT in the SCT trial and did not examine the maximal recommended dose-levels for either drug or for Ven. OCPB input is recommended regarding the adequacy of the methods and of the trials for the purposes of this NDA and also on the interpretation of the results (with respect to potential Arip-ADT interactions on PK and on PK-pharmacodynamic properties on efficacy and safety).*

Population PK Results from the Two Pivotal MDD Trails

Blood samples for PK analyses were also collected from subjects in the 2 pivotal placebo-controlled, short-term MDD trials (C...163 and C...139) at study visits on Weeks 4,6, and 8 during Phase B of the study and at Weeks 12, 13 and 14 during Phase C of the study. Phase B of the study involved 8-weeks of OL ADT treatment (escitalopram, fluoxetine, paroxetine, paroxetine CR venlafaxine XR or sertraline). Subjects failing to meet responder criteria during Phase B were then randomized to placebo or Arip treatment to be given over 6-weeks during the DB Phase C of the study. Arip treated patients assigned to paroxetine, paroxetine CR, or fluoxetine received 2-15 mg of Arip daily while all other Arip treated subjects received 2-20 mg of Arip using a flexible dose design. For more details on the study design refer to Sections 6 and Appendix 10.1 of this review. The statistical methods for PK analyses are provided in detail in the CSR for this study in the submission.

The sponsor concludes that the PK results of Studies C...139 and C...163 show no evidence for substantial drug-drug interactions that would warrant dose adjustments of the ADTs examined when treatment is combined with Arip treatment. The sponsor notes that sample sizes of subjects receiving fluoxetine and paroxetine CR were not adequate for yielding a “robust” assessment of PK for these drugs and their metabolites. However, the sponsor concludes that the

data obtained “are consistent” with their overall conclusion that a dose adjustment of ADT is not needed when combining treatment with Arip.

Reviewer Comments. *The undersigned reviewer notes the following potential limitations with the sponsor’s results:*

- *Sample sizes were small for at least some ADT subgroups and for PK analyses of some ADT metabolites (as shown in the above table) in which some Arip subgroups had only approximately 13 to 25 subjects (in Study C..139). The sponsor also notes small sample sizes for some ADT groups in Study C...163.*
- *The MDD trials did not include an examination of PK results based on genotype for extensive or poor metabolizers (e.g. for 2D6CYP metabolism for ADTs metabolized via 2D6 or for paroxetine treated subjects since paroxetine is a 2D6 inhibitor). It is not clear to the undersigned reviewer if further examination based on genotyping is needed.*
- *The MDD trials did not appear to examine PK of Arip which may be needed at least for some drugs.*

OPCB review is underway at the time of this writing and OCPB input is recommended.

5.2 Pharmacodynamics

Results on PK-pharmacodynamic (PK-PD) interactions could not be found in the sum-clin-pharm.pdf document of the submission. Phase 1 trials involved a generally healthy population involving treatment regimens (e.g. dose-levels, titration phases) that are not generally comparable to treatment regimens employed in the psychiatric patient population. Therefore it is difficult to extrapolate potential PK-PD interaction effects from these trials. An examination of potential PK-PD interaction effects in the two pivotal MDD trials could also not be found in the sum-clin-pharm.pdf document or in Module 2.7.4. These 2 trials conducted population PK analyses. OCPB review is pending at this time.

5.3 Exposure-Response Relationships

MDD Phase III studies employed a flexible dose design. Therefore, the dose by response relationships (related to efficacy or safety) were not systematically examined. See Section 7.2.1 for results and comments on adequacy of exposure.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor is seeking a claim of Arip as “adjunctive treatment to antidepressant therapy” in the treatment of MDD. The 2 Phase I studies (in Section 5.1 of this review) did

6.1.1 Methods

Two multicenter studies were conducted to establish safety and efficacy of adjunctive Arip treatment in adult MDD patients. The study design of each of these studies is summarized in Section 6.1.3 of this review.

6.1.2 General Discussion of Endpoints

The Agency informed the sponsor that the MADRS and SDS would be considered as acceptable primary and key secondary variables (the undersigned reviewer attempted to search DFS for meeting minutes and found 2/25/94 meeting minutes of a 2/18/04 meeting regarding the design of an acceptable pivotal study). Other aspects of the study design were also discussed, including key features of defining the study population. The statistical methods for these variables (summarized in the next subsection) are consistent with methods generally employed for MDD trials. The statistical reviewer did not identify any major issues regarding these methods during the midcycle review team meeting held on 8/16/07.

6.1.3 Study Design

Two pivotal Phase 3 trials (CN138139 and CN138163 also referred to as C-139 and C-163, respectively) served as the basis of the proposed indication (367 aripiprazole subjects and 356 placebo treated subjects). The studies were placebo controlled, randomized, double-blind (DB), multi-center studies (involving US study sites) conducted on generally healthy adult patients with MDD who retrospectively showed an inadequate response to 1 to no more than 3 antidepressant treatment (ADT) courses (of an approved antidepressant drug) during their current depressive episode (using prespecified criteria using a treatment response questionnaire).

Eligible subjects underwent the following 2 study phases:

- 8-week Prospective Treatment Phase: subjects received single-blind (SB) placebo treatment coadministered with 1 out of 5 specified ADTs (escitalopram, sertraline, venlafaxine extended-release, fluoxetine or paroxetine controlled-release).
- 6-week DB Treatment Phase: subjects that were identified as showing an inadequate response during the Prospective Treatment Phase (using prespecified criteria) were randomized to DB placebo or aripiprazole treatment that was administered over 6-weeks. Using a flexible dose design the daily dose range of aripiprazole treatment was either:

- 2 to 15 mg daily in subjects receiving ADT of a potent CYP2D6 inhibitor (fluoxetine or paroxetine)
- 2 to 20 mg daily in subjects receiving other ADTs.

Refer to Appendix 10.1 of this review for details on the study design of these studies, as well as an outline of the disposition of subjects in this study.

Reviewer comments. *The sponsor used a questionnaire for retrospectively rating treatment response that was based on the patient's recall of response and their treatment regimen. The adequacy of these methods is not clear to the undersigned reviewer (e.g. using retrospective recall of past treatment and the acceptability of the questionnaire as an adequate tool for the purposes of this trial). Refer to 2/25/4 meeting minutes in DFS under the IND in which potential concerns were discussed and recommendations. The undersigned reviewer finds that the study methods are adequate for the purposes of this review (specific for this priority NDA and given the proposed claim of adjunctive treatment for MDD), along with the following reasons:*

- *An inadequate historical response had to occur during the current depressive episode (as preferred by the Division, as described in the 2/25/07 minutes),*
- *Subjects underwent a prospective observational phase that used an acceptable rating scale (the HAM-D) and adequate cut-off criteria for eligibility, and*
- *Baseline characteristics of the study sample regarding their current depressive episode and other aspects of their MDD, as well as baseline efficacy results were indicative of ongoing symptomatology (based on in-text section 5 of the CSRs).*

6.1.4 Efficacy Findings

Primary and Key Secondary Efficacy Results

The following tables are copied from the clinover.pdf section of the submission and outline efficacy results on the primary and key secondary efficacy variables.

TABLE 4.2.1. CLINICAL SUMMARY

FIGURE 2.2. CLINICAL SUMMARY

Table 4.2.1: Mean Change from End of Phase B (Week 8) to End of Phase C (Week 14, LOCF) in MADRS Total Score (CN138139, CN138163)

Protocol/ Treatment	N	MADRS Total Score ^a			
		Mean End of Phase B	Mean Change at End of Phase C	Treatment Difference (95% CI) Versus Placebo	P-Value ^b
CN138139					
Placebo	172	25.65	-5.77	--	--
Aripiprazole	181	25.88	-8.78	-3.01 (-4.66, -1.37)	< 0.001
CN138163					
Placebo	184	26.55 ^c	-5.65	--	--
Aripiprazole	185	24.59 ^c	-8.49	-2.84 (-4.53, -1.15)	0.001

^a MADRS Total Score is from 0 to 60. A negative change score signifies improvement.

^b ANOVA model, with double-blind treatment and study center as main effects, is used for end of Phase B comparisons. ANCOVA model, with double-blind treatment and study center as main effects, and end of Phase B assessment as covariate, is used for mean change from end of Phase B comparisons. Means, treatment differences between aripiprazole and placebo, 95% CIs for the differences and the p-values for treatment comparisons are based on ANOVA/ANCOVA model.

^c Treatment difference between placebo and aripiprazole statistically significant at end of Phase B, p < 0.001.

The following summarizes results on the key secondary variable (copied from the clinover.pdf section of the submission).

Table 4.2.2A: Mean Change from End of Phase B (Week 8) to End of Phase C (Week 14, LOCF) in SDS Mean Score (CN138139, CN138163)

Protocol/ Treatment		SDS Mean Score ^a				P-Value ^b
		N	Mean End of Phase B	Mean Change at End of Phase C	Treatment Difference (95% CI) Versus Placebo	
CN138139						
Placebo	164	5.35	-0.65	--	--	
Aripiprazole	167	5.69	-1.11	-0.46 (-0.93, 0.01)	0.055	
CN138163						
Placebo	168	5.35	-0.73	--	--	
Aripiprazole	180	5.06	-1.31	-0.57 (-1.02, -0.13)	0.012	

^a The SDS Mean Score is the average of 3 item scores, each ranging from 0 through 10. A negative change score signifies improvement.

^b ANOVA model, with double-blind treatment and study center as main effects, is used for end of Phase B comparisons. ANCOVA model, with double-blind treatment and study center as main effects, and end of Phase B assessment as covariate, is used for mean change from end of Phase B comparisons. Means, treatment differences between aripiprazole and placebo, 95% CIs for the differences and the p-values for treatment comparisons are based on ANOVA/ANCOVA model.

Tables 10.3.5-7 in Appendix 10.3 shows secondary efficacy results (that were not of key secondary parameters).

Magnitude of Treatment Effect

Reviewer Comments. *The magnitude of treatment group the effect on the primary efficacy variable in each study is previously shown in this review and is generally comparable to those observed in MDD trials of approved ADTs. Furthermore, the sponsor shows at least trends for positive effects of Arip over placebo adjunctive treatment on most secondary efficacy variables. Secondary variables examined in trials included the SDS (as a key secondary variables), self ratings of depressive symptoms, clinician ratings of overall improvement or severity, the incidence of responders based on cut-off criteria on efficacy scores, among others. Consequently, the magnitude of effect is considered clinically relevant and adequate to consider the trials positive for supporting an efficacy claim.*

Refer to the last section of this review regarding any key issues relevant to efficacy with respect to proposed labeling.

Duration of the Treatment Effect

The pivotal trials were short-term 6-week trials. A maintenance treatment or a longterm placebo controlled trial that was designed for examining longterm efficacy was not conducted (based on a review of the information found in Module 2.7.4 and of the sponsor's tabular listing of clinical trials (clinstat\other\studylist.pdf)).

Predictors of Response based on Pooled Data Analyses

The Clinical Summary of Efficacy, Module 2.7.3 summarizes results of subgroup analyses on each of the following independent variables (using data from both studies, pooled):

- Gender
- Age-groups of > and ≤50 year olds
- "Race"
- Ethnicity
- End of Phase B MADRS Total Score for each of the following subgroup categories:
 - ≤ and > 26 score points
 - < and ≥ 25% improvement categories
- Number of Previous ADTs during the current phase: 1 ADT (N=237), 2 ADTs (N=95) and at least 3 ADTs (N=23)
- Duration of Current Episode of > 19.2 and ≤ 19.2 month categories (19.2 months was the median duration of the current episode among the subjects)
- Concomitant ADT treatment categories: Escitalopram (N=99), fluoxetine (N=52), Paroxetine (N=27), Sertraline (N=74), Venlafaxine (N=104)
- All SSRI Category (N=252): all subjects except for venlafaxine subjects.

All subgroup analyses yielded no statistical treatment group by subgroup interactions effects except for gender which showed a statistical interaction effect ($p < 0.005$) in which females showed a greater treatment group effect in favor of Arip than was observed in males. Although, males showed numerical trends for efficacy when comparing mean values in the Arip group to those of the placebo group (mean change from end of Phase B to end of Phase C on the MADRS total score of -6.93 and -6.29, respectively).

Results of Gender Subgroup Analyses for Each Study

An analyses of data from each study revealed that treatment group by gender interactions were statistically significant in Study C...139 but not for Study C...163. The latter study only showed numerical trends for greater treatment group differences (in favor of Arip treatment) in females compared to treatment group differences in males. The former study, Study C...139 showed a mean change that was unexpectedly slightly greater in the placebo group compared to the Arip group among males. The sponsor indicates that the male placebo group of this study showed an "increase" in improvement over the last 2 weeks of the study that may account for treatment group by gender interaction effects observed in this study and may also account for treatment group by gender interaction effects observed with the pooled dataset (of data from both studies pooled).

Appendix 10.3 of this review provides summary tables (Tables 10.3.1-3) and figures (Figures 10.3.3-4) of the efficacy results by gender of the pooled and unpooled datasets (tables and figures were copied from Module 2.7.3 of the NDA).

Reviewer Comments. *Although there appears to be an unexpected increase in improvement in male placebo subjects in Study C...139 (that is also observed with the OC dataset) this observation along alone does not appear to fully account for gender by treatment group interaction effects, as follows. Upon visual examination of the sponsor's figures, the results suggest a reproduceable numerically greater treatment group effect in Arip treated females compared to males in each independent study in that (as shown in Figures 10.3.3-4 in Appendix 10.3 of this review). Furthermore, the placebo groups generally showed similar group mean values between males and females in each study (except for the last 2 weeks in Study C...139). Upon examination of results found in the CSRs, the undersigned reviewer notes a larger within group variance and test-retest variability in males compared to females (based on numerical comparisons). Note that the sample size of males is also smaller than that of females (as is typical for the MDD population).*

The sponsor's overall conclusion (in the last paragraph of page 55 of Module 2.7.3) is that "females responded better to adjunctive Arip treatment than males in both studies." The undersigned reviewer agrees with this conclusion with one key caveat as follows. The results do not take into account potential gender-related confounding variables that could possibly account for this observation (e.g. consider differences in BMI, potential differences in drop out rates over time, in the severity of MDD at baseline, demographic features, clinical presentation of MDD or comorbidity such as chronic pain or use of substances, among other potential clinical differences, among other potential contributing factors). An examination of results for these potential gender differences and on their potential effect on efficacy results could not be found in the submission.

Sample sizes for interpreting results of "race" and "ethnicity" were insufficient to yield interpretable results since only one subgroup for each independent variable had at least 100 subjects (other subgroups had 30 or less subjects in a given subgroup). The sample sizes of some of the subgroups for other independent variable were also insufficient as follows: the ≥ 3 ADTs subgroup (for the number of previously-used-ADTs during the current episode variable) and the paroxetine ADT subgroup (among the adjunctive DB treatment subgroups). All other subgroups for each independent variable were generally at least 100 subjects.

It is important to note that each ADT group including the venlafaxine group generally showed a similar magnitude of the treatment group effect (between Arip and placebo groups) except that the numerically largest treatment group effect was in the paroxetine group but the sample size in this latter ADT group was insufficient to yield interpretable results (N=27 in this ADT group). These results are shown in Table 10.3.1 in Appendix 10.3 of this review (as provided by the sponsor).

Refer to the last section of this review for recommendations based on the above results.

6.1.5 Clinical Microbiology

This topic is not applicable since this NDA is an efficacy supplemental NDA of an already approved formulation.

6.1.6 Efficacy Conclusions

Reviewer Conclusions: *The two pivotal trials are considered by the undersigned reviewer as positive trials for efficacy. Any major issues or potential issues are discussed in Section 9 of this review.*

The following comments are based on the undersigned reviewer's understanding of the Clinical Review MAPP. Some key results that are relevant to adequately establishing efficacy are to be provided in Appendices 10.1 and 10.3 (e.g. results on disposition, demographic features are provided in Appendix 10.1, tables and figures on efficacy results can be provided in Appendix 10.3). The current in-text efficacy section of this review (Section 6) only provides some highlights on the study design and on specific efficacy results (as specified in the MAPP) from pivotal trials. A discussion of specific aspects of the pivotal trials is to be provided in Section 6 as specified in the MAPP (e.g. a discussion of the endpoints and conclusions are to be provided and appear in Sections 6.1.2 and 6.1.6, respectively). Therefore, refer to Appendices 10.1 and 10.3 for additional key information relevant to efficacy.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and a Synopsis of Key Findings

The undersigned review includes a synopsis of key safety findings in this section which follows the subsection on methods below.

Methods

Refer to Section 4.1 for the primary and secondary datasources, Sections 4.2 for a table summarizing the clinical trials, and Section 4.3 for a description of safety datasets and the review strategy. For the convenience of the reader the following outlines the clinical trial safety datasets from which safety results were reviewed for the purposes of this NDA and from which safety results are summarized in Section 7 (and as discussed in Section 4.3 of this review):

- Integrated Safety Datasets:
 - 2-Phase III MDD Trial Dataset (2 pivotal short-term ADT-Adjunctive MDD Studies -163 AND -139): see Section 6 and Appendix 10.1 for the study design and other details of these studies.
 - All-Arip Treated MDD Dataset: includes Arip treated subjects from all other completed or ongoing OL trials with results provided in Module 2.7.4 by diagnostic categories (MDD, Bipolar categories, schizophrenia and others). However, the focus of the review is on the MDD group, given the proposed indication. Refer to Section 4 of this review for more details on this dataset.

- Blinded Studies Dataset: of Phase II-IV trials that remain blinded and involve a various diagnostic groups. The focus of review is on deaths, SAEs and ADOs of MDD patients in this dataset.
- Safety Results from Individual Studies
 - 2 Phase I trials: Any deaths, SAEs or ADOs described in Module 2.7.4 were reviewed and summarized in this review. The study design of the 2 Phase I Trials described in Module 2.7.4 are outlined below. Section 5.1 of this review also summarizes these trials and the PK results, but does not describe the study design with respect to safety, as outlined below.

Study C...463 was an OL trial involving treatment as follows (25 enrolled healthy subjects):

- Escitalopram (Lexapro®) 10 mg daily on Days -7 to 14.
- Arip 10 mg daily on Days 1 to 14.

Study C...462 was an OL trial involving treatment as follows (38 enrolled healthy subjects):

- Venlafaxine (Effexor® XR) 75 mg daily on Days -4 to 14.
- Arip dose titration from Days 1 through 14 as follows: 10 mg daily for 3 days, 15 mg daily for 4 days and 20 mg daily for 7 days

Both studies involved tolerability testing of vital signs (and orthostatic vital sign assessments) prior to initiating Arip treatment. These assessments were also conducted prior to each dose increase of Arip in Study C...462. It is also important to note that subjects were restricted in activity and subjects who developed orthostatic hypotension also had to remain supine for a specified time period (e.g. after the first Arip dose or dose increase of Arip). Subjects with poor tolerability (e.g. orthostatic hypotension that did not resolve within 12 hours after the dose titration in Study C...462) were withdrawn from the study. Therefore, subjects completing each study had received the assigned dose-level of each drug.

A Synopsis of Key Safety Findings

Phase 3 Major Depressive disorder (MDD) trials were not designed to allow for direct comparisons between antidepressant (ADT)-Arip treatment to each monotherapy condition (and ideally to a placebo-placebo condition). Consequently, the trials were not specifically designed for a systematic examination of potential ADT-Arip interaction effects on safety. However, the placebo controlled pivotal trials included an ADT monotherapy which allowed for comparisons between placebo-ADT and ADT-Arip groups, although ADT was given under OL conditions and not DB conditions. Given these study design limitations the primary focus of the safety review was to determine if the safety profile (the nature of adverse events or clinical parameter changes) in ADT-Arip treated subjects was unexpected (based on known AEs associated with either ADTs or Arip treatment alone). The studies did not reveal an unexpected safety profile. Also the safety results were reviewed to determine if the extent of any of the observed adverse effects was unexpectedly serious or clinically remarkable (based on known serious events associated with either drug alone). No serious and unexpected safety signal was revealed by the adjunctive Phase 3 MDD trials and the safety profile of adverse effects observed with adjunctive treatment was similar to that expected for either drug alone.

Subsections below summarize key safety findings that impact on recommendations provided in Section 9 of this review. Text below is identical to text in Section 9.2 of this review.

A Potential ADT-Arip Interaction Effect on Safety

The placebo controlled trials were designed to allow for a comparison between ADT-Arip and ADT-placebo groups on each safety parameter, but the interpretation of the results are limited given the study design, as previously discussed (the trials did not employ a DB design for both drugs and did not include at least a DB placebo-Arip monotherapy group). These safety results suggested a potential ADT-Arip interaction effect on some AEs that are known to be associated with each drug alone, as outlined below.

The results on the incidence of adverse events in the pivotal adjunctive MDD trials suggested an exaggerated effect of the combined ADT-Arip treatment over the ADT monotherapy group in these trials for some of the AEs that are known to be associated with each of these drugs given alone (and as suggested by comparing these results to those of the monotherapy Arip trials involving other patient populations, as described in approved labeling). The interpretation of these results is limited by the study design of the MDD trials, since the trials did not include DB monotherapy, placebo controlled groups (to allow for a direct comparison between each monotherapy condition against the combined treatment condition and ideally against a placebo-placebo condition). Yet the following observations are notable when contrasted to results of monotherapy trials for other indications described in approved labeling:

- Results on adverse events reported adjunctive major depressive disorder trials suggested an exaggerated effect of the combined antidepressant-Abilify™ treatment over the antidepressant-placebo group or in comparison to results of monotherapy trials for approved indications:
 - The incidence of adverse dropouts was 6% and 2% in adjunctive aripiprazole and placebo groups, respectively. Adverse dropouts due to akathisia and fatigue were most often reported (1.3% and 1.1%, respectively in the adjunctive aripiprazole group, and 0 placebo subjects with either adverse event). These results are compared to the incidence of ADOs in monotherapy as follows:
 - Schizophrenia monotherapy trials: 7% and 9% in Arip and placebo groups, respectively. Treatment groups were similar in the incidence of each type of ADO.
 - Bipolar monotherapy trials: 11% and 9% in Arip and placebo groups, respectively. Treatment groups were similar in the incidence of each type of ADO.
 - Common adverse events ($\geq 5\%$ incidence in Arip-ADT patients that was at least twice that of placebo-ADT patients) in the adjunctive MDD trials were akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision. Insomnia, fatigue and blurred vision were not among the common adverse events (with an incidence of $\geq 5\%$ and twice that of placebo) in monotherapy trials of Bipolar and schizophrenia patients. Yet other AEs meeting this criterion in the monotherapy trials also generally met this criterion in the adjunctive MDD trials or related AEs met this criterion (see section 9.4 of this review for a specific listing of these common AEs in the Bipolar, Schizophrenia and MDD trials).

- Akathisia showed the most exaggerated adjunctive treatment effect with 2D6 inhibitors (approximately 30% with paroxetine CR and fluoxetine adjunctive treatment). Yet, according to the sponsor no clinically relevant effects on PK were observed in the pivotal trials.
- Disturbance of attention was reported in 3% and 1% of adjunctive aripiprazole and placebo subjects, respectively. This AE was not among AEs meeting criteria for inclusion in the summary tables for monotherapy trials in approved labeling (refer to Table 3 in approved labeling specifying AEs showing an incidence of at least 1% in Abilify groups and an incidence that was greater than placebo).
- Disturbance of attention was most common with venlafaxine XR adjunctive treatment (6% and 1% in adjunctive aripiprazole and placebo groups, respectively and 0 to 3% of subjects receiving other antidepressants)

Also refer to Section 7.1.5.5 noting preliminary observations when comparing the incidence of AEs between the MDD All-Arip treated group (which represents the short-term and the ongoing longterm adjunctive MDD trials) with other diagnostic groups involving trials that generally did not involve adjunctive ADT treatment. Section 7.1.5.6 of this review also discusses these results but when comparing a Bipolar-depressed group to the MDD group in the All-Arip treated dataset. This Section also provides results of preliminary analyses of the incidence of AEs by ADT subgroups within the Arip and placebo DB groups in the short term Phase 3 MDD trials.

Key Observations in the Ongoing Longterm OL Adjunctive MDD Study -164

Key observations with longer-term adjunctive treatment in MDD patients and the potential for ADT-Arip interaction effects also require consideration. The following observations with longer term treatment are also outlined in Section 9.2 of this review (using identical text). These observations provide an additional rationale for recommendations in Section 9.3 of this review on postmarketing surveillance and Phase 4 requests for trials to examine for potential ADT-Arip interactions on safety.

ADOs of Disturbance of Attention

Disturbance of attention was among the above described AEs that had an incidence suggestive of an ADT-Arip interaction effect, particularly with venlafaxine in the short-term pivotal trials. Section 7.1.4.2 (under Other Search Strategies) lists cases of ADOs in the longterm study involving disturbance of attention and other AEs that were found by an attempt by the undersigned reviewer to find cases of serotonin syndrome (under subsection entitled “Reviewer Search for Serotonin Syndrome”).

Dyskinesia and Tardive Dyskinesia

Section 7.1.4.1 of this review also describes 12 cases of dyskinesia and TD in primarily the longterm study (under subsection on EPS). The total reported TD cases was 3 and occurred between 68 to 364 days (inclusive) of OL treatment in the longterm OL study. There are reports in the literature of these types of movement disorders induced by SSRIs and other ADTs (found by a pubmed search conducted by the undersigned reviewer). These reports are primarily of case reports in primarily psychiatric patients and also in neurological patients (e.g. Leo RJ, 1996 and others). Mechanistically such events may be anticipated (via indirect agonistic effects on

serotonergic systems projecting onto dopamine pathways in the extrapyramidal system, indirectly increasing dopamine release). Therefore, consideration needs to be given to a potential ADT-Arip interaction effect on these more serious EPS-related events.

Weight Gain

Section 7.1.5.6 of this review includes results based on additional analyses and explorations of AEs where the sponsor showed the incidence of AEs over time intervals in the All-Arip MDD dataset. Time-points beyond 42 days of treatment would correspond to treatment received during the ongoing OL Study -164. Weight increase was the only AE with an incidence of at least 5% at any given time interval beyond 42 days of treatment.

ADOs due to increased weight was reported in 2.7% (28/1055 subjects) in the All-Arip MDD group (of the All-Arip dataset) compared to only 0-0.3% of patients in any given non-MDD category (sample sizes/non-MDD category ranged from 593 to 8215 subjects). These results are summarized in section 7.1.3.2 of this review. Note that only 1 ADO due to increased weight occurred in Arip subjects in the short-term trials. This leaves 27 ADOs due to this event among subjects included in the All-Arip MDD dataset. Consequently, these remaining 27 ADOs would have been in the OL longterm, ongoing Study -164. Thus the incidence of ADOs due this event in this ongoing study is actually greater than 2.7% (the incidence would appear to be approximately 8% by using the sample size for only the OL study in the denominator). While weight gain is observed with Arip treatment (as described in approved labeling), the numerically greater incidence in the MDD group compared to other diagnostic groups could be reflecting an ADT by Arip interaction effect (as several ADTs are also associated with weight gain). Yet, it is difficult to interpret these results given a number of limitations with this dataset (as discussed elsewhere in this review, such as in Section 4.3 and in other sections). Yet, a greater combined effect of ADTs with Arip (for those ADTs that are known to increase weight) would not be a surprising finding.

Section 7.1.8.3.2 of this review shows results on outliers on weight gain (using the criterion of at least a 7% weight increase) over time intervals of ADT-Arip treatment. The incidence was numerically greater over each progressive time-interval of treatment as follows:

- 35% outliers among subjects receiving 36 weeks or greater of treatment
- 28% outliers during weeks 12-35 of treatment
- 6% outliers at weeks 11 or less of treatment.

Note that approved labeling provides results on the incidence of outliers on weight gain by BMI subgroups among subjects in longterm trials (subjects who were categorized into subgroups on the basis of their baseline BMI). Results for each baseline-BMI subgroup in the longterm adjunctive MDD trial (Study -164) could not be found in Module 2.7.4, as the study was specified in the NDA as ongoing (and a CSR was not provided for this study).

Metabolic Parameters

Given the above observations on weight gain, it is important to note the following results on metabolic parameters that may be potentially related (and indirectly related) to increases in weight gain (refer to Section 7.1.7.3.1 of this review for these results). The median change from

baseline to each time-interval in the All-Arip treated MDD dataset generally showed consistently greater numerical changes over time for most “metabolic” parameters such as glucose, HgB1Ac, LDL, HDL, triglyceride levels. Note that All-Arip-treated MDD group results for time-points beyond 6 weeks of treatment reflect those from the longterm safety study C...164. The magnitude of these changes was not clinically remarkable. The largest change occurred with fasting triglycerides at the last assessment time interval (>46 weeks of treatment) in which the median change from baseline values was 12.2 (units not shown). A change of 12.2 may have clinical relevance in a patient who has abnormal or borderline values on their lipid profile. Section 7.1.7.3.2 of this review summarizes results on outliers on these parameters. The longterm safety study was reported as an ongoing OL study and the interpretation of these results is further compromised by the absence of a placebo group with a DB study design.

7.1.1 Deaths

The following outlines deaths for each safety dataset.

2-Phase III MDD Trial Dataset: No deaths were reported.

All-Aripiprazole (Arip) Treated Safety Dataset Reported Since the October 2005 SUR and Blinded Studies Phase 2/3/4:

- No deaths occurred in MDD patients.
- 5 new deaths were reported in subjects in the all-arip safety dataset (since the October 2005 SUR) and
- 1 death was reported in the blinded study safety dataset.

Continued on the next page..

Deaths in the All-Aripiprazole Treated Safety Dataset Since the October 2005 SUR			
Subject Number	Patient Population	Treatment Received	Description
CN138006-73-189	Alzheimer disease	1856 Days Arip, discontinued 2 days prior to Cardiac Arrest	85 year old female receiving multiple concomitant medications who had a history of angina pectoris, obesity, hypertension, cardiac insufficiency, Alzheimer's disease and other psychiatric conditions who died of cardiac arrest .
CN138134-17-106	Bipolar I Disorder	On Day 365 of Arip 30 mg & Lithium 750 mg/day	A 49 year old female with a history of obesity and obstructive sleep apnea who died of pulmonary alveolar hypoventilation . She " accidentally overdosed " on lithium (1.05 mmol/l) and had respiratory distress, "severe" bradycardia, "severe" hypotension, "severe" pulmonary hypoventilation, and "moderate" syncope during here hospitalization. See additional details below.
CN138146-37-390	Bipolar I Disorder	On either Day 165 or 166 after discontinuing OL arip treatment (10 mg /day) & starting clonazepam treatment on Day 139 (for tremors&anxiety) and starting escitalopram on Day 155(for anxiety).	52 year old male had multiple concomitant medical illnesses was losing significant weight (dieting) with ketonuria with a week 34 ECG changes (TU fusion, anterior T notches & baseline and other abnormalities at baseline&week8). This patient died of a reported "cardiac disease." See details below.
CN138166-22-9	Schizophrenia	Not described in the in-text narrative	35 year old committed suicide (defenestration) that was reported to be "due to family conflict and the loss of her child."
CN138166-36-1	Schizophrenia	Day 120: OL Arip 15 mg/day started on Day 1, 25 mg/day started on Day 14	27 year old committed suicide (asphyxiation/suffocation) after 14 days of receiving concomitant escitalopram and clorazepate treatment.

Deaths in the Blinded Studies			
Subject Number	Patient Population	Treatment Received	Description
CN138162-3-433	Bipolar disease	Last dose was on Day 42: after 21 Days on 30 mg/day of Arip. Death occurred on Day 83.	69 year old with multiple pre-existing medical conditions who discontinued study drug on Day 42 due to increased mania and had SAEs of abdominal bleeding, perforated duodenal ulcer and died due to respiratory arrest and bronchopneumonia 41 days after Arip Treatment .

The following additional information in some of the above subjects is provided below (copied from pages 109-110 of Module 2.7.4):

Subject CN138134-17-106:

“The investigator considered the respiratory failure, pulmonary hypoventilation, bradycardia, hypotension and syncope to have a possible relationship to the study medication. After her admission to the intensive care unit, she developed type II respiratory failure, cardiac arrhythmias and mild cardiac failure. Obstructive sleep apnea and pulmonary hypoventilation were noted to have contributed to her death. A total of 4 ECGs were performed throughout the study and no ECG abnormalities were noted prior to the SAE.”

Reviewer comment on the above Bipolar patient:

The narrative of this subject was reviewed.

Based on the information found in the in-text Section 2.1.2.2 and upon review of the narrative of this subject appears to be an atypical case and warrants further consideration (with regard to a potential role of Arip and/or lithium), but this case alone does not in the opinion of the undersigned reviewer warrant any changes in labeling. The following paragraphs provide additional details and reviewer comments on this subject.

The following clinical observations (found in the narrative) are noted by the undersigned reviewer with some additional reviewer comments provided, as well.

The only reported medical condition at baseline was obesity. The patient first presented on Day 365 (while on 30 mg/day Arip and 750 mg lithium) due to a reported accidental lithium overdose (note in the above table that lithium levels revealed no clinically remarkable elevation in levels and that this overdose was reported as not being a suicide attempt). She was discharged after one day (only ongoing weight gain was described in the narrative and no concomitant medications were received within 14 days of the event).

Five hours after discharge the subject was readmitted (on Day 366) had respiratory failure, bradycardia, severe hypotension, “moderate syncope,” and cardiac arrhythmias as described in more detail in the narrative. The patient was treated with atropine and other specified drugs and received ventilation in the ICU (study drug was discontinued and lithium level was 0.7).

Sleep apnea was observed on Day 366. Refer to the narrative for more details and for additional events that followed.

This patient was suspected as having an undiagnosed underlying Pickwickian disease and possibly sick sinus syndrome (as specified in the narrative). These conditions are among several undiagnosed and potentially pre-existing conditions to consider in the differential diagnosis.

Mention of whether an autopsy was conducted cannot be found in the narrative.

One potential consideration is that Arip (and/or lithium) treatment contributed to the events or to the severity or nature of events in this patient (e.g. one consideration is the potential role of the drug on adversely affecting an undiagnosed sleep apnea, among other possibilities).

Subject CN138146-37-390:

Patient CN138146-37-390 was a 52-year-old male with history of Bipolar I Disorder, hypertension, obesity, asthma, gastroesophageal reflux disease, osteoarthritis, allergies, psoriasis and 1+ pitting edema who died of cardiovascular disease considered not related to study medication. The patient completed the 8-week double-blind phase of the study on Day 62 and began aripiprazole 10 mg during the open-label phase of the study on Day 63. The patient started a calorie-restricting diet and his weight decreased from approximately 327 pounds to 276 pounds between Days 56 and 155. During that time period he also experienced tremors in his right leg and foot, anxiety, and urine ketones (urine ketones 0 at baseline, 80 mg/dL on Day 139, 15 mg/dL on Day 155). On Day 139, the patient's leg tremors intensified and the patient reportedly went to the emergency room. The emergency room physician reportedly discontinued the patient's aripiprazole and started clonazepam to treat the anxiety and tremors. On Day 155, he was queried about his diet and reported caloric restriction, but not an overtly carbohydrate-restricted diet. In addition to being continued on clonazepam, the patient was prescribed escitalopram for anxiety. The patient's brother informed the investigator that the patient died sometime between night of Day 165 and morning of Day 166. The cause of death was reportedly cardiac disease. The investigator considered the fatal event very severe and not related to study medication. There were no potentially clinically relevant laboratory or vital sign abnormalities reported during the study period. ECG at baseline and Week 8 showed 1st degree A-V block and incomplete right bundle branch block, and for T-U fusion and anterior T notches at Week 34.

Continued on the next page.

The narrative of Subject CN...3-433:

Patient CN138162-3-433, a 62-year-old female with Bipolar I Disorder and a medical history of myocardial ischemia, atherosclerosis, chronic bronchitis, pneumosclerosis, chronic gastritis, chronic cystitis, cholecystitis, cholelithic disease, chronic cystitis, diabetes mellitus, anemia, and tobacco use, was randomized to receive placebo on Day 1 of the double-blind phase of the study. On Day 22 during the double-blind treatment, the patient began receiving aripiprazole 30 mg.

On Day 32 (Day 11 of aripiprazole 30 mg), the patient experienced an increase of manic symptoms. This was considered by the investigator to be moderate in intensity and possibly related to the study medication. The study medication was discontinued on Day 42 (Day 21 of aripiprazole 30 mg). The event resolved on Day 83, at the time of death.

Concomitant medications taken within 14 days prior to the start of the event included glyburide and trihexyphenidyl. Other events ongoing at the start of this event included akathisia and a tremor.

On Day 60 (18 days post aripiprazole therapy), per SAE report, "the patient complained of asthenia...the next day, she was noted to be hypotensive and tachycardic and continued to complain of asthenia. A consultation was obtained and the patient was felt to have abdominal bleeding and poorly controlled diabetes." The subject was hospitalized. At the time of hospital admission, the subject was diagnosed with right-sided pneumonia. Per supplemental report, "the patient was diagnosed with a perforated ulcer of the duodenum, and bilateral confluent bronchopneumonia. The perforated ulcer of duodenum was complicated with bleeding and penetration into hepatoduodenal ligament and head of the pancreas. Surgery was performed to excise the duodenum ulcer with duodenoplasty on Day 62." Relevant laboratory tests, per supplemental report, are listed below. The investigator considered gastric bleeding and the duodenal ulcer perforation severe in intensity and not related to the study medication; the events resolved on Day 60 and Day 62, respectively.

During the post-operative period (Day 62 to Day 83), "expansion of both lungs occurred, complicated with abscess formation and mortification," per SAE update. The subject experienced respiratory arrest and expired on Day 83. Per supplemental report, additional information was obtained from the investigator on February 13, 2007 as follows: findings on autopsy were pulmonary necrosis and lung abscess and were identified as the cause of death. The respiratory arrest was not associated with myocardial infarction; subject did have a pre-existing diagnosis of myocardial ischemia and cardiosclerosis. The investigator considered the respiratory arrest and bronchopneumonia (both ongoing at the time of subject's death) very severe in intensity and not related to study medication.

Concomitant medications taken within 14 days prior to the start of these events included glyburide and trihexyphenidyl. Other events ongoing at the start of this event included increase of manic symptoms and a tremor.

There were no additional potentially clinically relevant laboratory, vital sign, or ECG abnormalities during the study.

Phase I ADT-Arip Interaction Studies (C...462 and C...463)

No deaths were reported.

Additional Reviewer Comments and Overall Conclusion Regarding the Results of the Above Datasets

The following comments and conclusions are based on a review of information found in in-text Section 2.1.2 of Module 2.7.4 and a selected review of narratives.

No deaths were reported among MDD patients.

The deaths were reported in non-MDD patients and were generally of a nature that is expected of the given patient population. The patients who died for reasons other than completed suicide had multiple pre-existing and/or related conditions or had complications. Most of these subjects had been receiving study drug for months. While a potential role of study drug cannot be ruled out, these cases alone do not provide evidence for an unexpected and clinically remarkable drug-related safety signal for Arip (as described in approved labeling).

7.1.2 Other Serious Adverse Events

2-Phase III MDD Trial Dataset: The following table was copied from Module 2.7.4 summarizing results of SAEs.

Table 2.1.3.1: Incidence of Treatment-Emergent SAEs: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR SAE	366	371
NUMBER OF MALE PATIENTS	125	134
NUMBER OF FEMALE PATIENTS	241	237
NUMBER OF PATIENTS WITH ≥1 SAE	5 (1.4)	3 (0.8)
SYSTEM ORGAN CLASS		
PREFERRED TERM	INCIDENCE (%)	INCIDENCE (%)
INFECTIONS AND INFESTATIONS	1 (0.3)	3 (0.8)
CELLULITIS	1 (0.3)	1 (0.3)
CELLULITIS STAPHYLOCOCCAL	0	1 (0.3)
PNEUMONIA	0	1 (0.3)
STAPHYLOCOCCAL ABSCESS	1 (0.3)	0
GASTROINTESTINAL DISORDERS	1 (0.3)	0
GASTROESOPHAGEAL REFLUX DISEASE	1 (0.3)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (0.5)	0
ACCIDENT AT WORK	1 (0.3)	0
CONTUSION	1 (0.3)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.3)	0
EXOSTOSIS	1 (0.3)	0
SOCIAL CIRCUMSTANCES	1 (0.3)	0
PHYSICAL ASSAULT	1 (0.3)	0

MedDRA Version: 9.1

The sponsor notes a discrepancy between the numbers of SAEs in the CSRs compared to the numbers in Module 2.7.4 for this safety dataset, as described on page 13 of Module 2.7.4. 2 SAEs in placebo subjects (in the 2 MDD trials) were events with an onset prior to initiating treatment in the longterm OL Arip Study 164 or within the reporting time-window for the short-term phase in Study -134. The sponsor notes that the SAEs in Module 2.7.4 for these 2 trials are those that “are reported based on the onset date recorded rather than the study database in which the events were recorded.”

The sponsor does not describe any individual Arip treated subjects in this dataset (in in-text Section 2.1.3.1 of Module 2.7.4).

Reviewer Comments and Conclusion.

Based on a review of in-text Section 2.1.3.1 of Module 2.7.4, the above results are not considered as revealing a new safety signal (from that described in approved labeling) since the treatment groups were similar on the incidence of SAEs, as shown in the above table and occurred in less than 1% of subjects in each group in each system organ class category or Preferred Term.

All-Aripiprazole (Arip) Treated Safety Dataset. The sponsor notes that only 3.4% of MDD patients had SAEs compared to 16.3% of the total patients (all diagnostic groups combined) included in the All-Arip Safety Dataset. The summary table for these SAEs is provided below copied from Module 2.7.4.

Table 2.1.3.2A: Incidence of Treatment-Emergent SAEs That Occurred in at Least 0.5 Percent of Patients Within Any Indication: All Aripiprazole Data Set by Indication and Overall, Safety Sample

	MDD	BIPOLAR- MANIA	BIPOLAR- DEPRESSION	DEMENTIA	SCHIZO	ALL ARI*
NUMBER OF PATIENTS SCREENED FOR AES	1055	2008	593	894	8215	12925
NUMBER OF MALE PATIENTS	358	875	234	222	5092	6896
NUMBER OF FEMALE PATIENTS	697	1133	359	672	3123	6029
NUMBER OF PATIENTS WITH ≥1 AES	36(3.4)	193(9.6)	25(4.2)	396(44.3)	1452(17.7)	2107(16.3)
SYSTEM ORGAN CLASS						
PREFERRED TERM	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)
PSYCHIATRIC DISORDERS	2(0.2)	150(7.5)	10(1.7)	30(3.4)	1092(13.3)	1285(9.9)
PSYCHOTIC DISORDER	0	4(0.2)	1(0.2)	5(0.6)	411(5.0)	421(3.3)
SCHIZOPHRENIA	0	0	0	0	370(4.5)	370(2.9)
SUICIDAL IDEATION	1(0.1)	22(1.1)	4(0.7)	0	62(0.8)	89(0.7)
MANIA	0	58(2.9)	2(0.3)	0	9(0.1)	69(0.5)
DEPRESSION	1(0.1)	24(1.2)	1(0.2)	0	34(0.4)	60(0.5)
ANXIETY	1(0.1)	3(0.1)	0	0	51(0.6)	55(0.4)
AGGRESSION	0	0	0	5(0.6)	20(0.2)	25(0.2)
BIPOLAR DISORDER	0	18(0.9)	0	0	1(<0.1)	19(0.1)
BIPOLAR I DISORDER	0	13(0.6)	3(0.5)	0	0	16(0.1)
MENTAL STATUS CHANGES	0	0	0	9(1.0)	0	9(0.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	5(0.5)	10(0.5)	2(0.3)	84(9.4)	87(1.1)	188(1.5)
HIP FRACTURE	0	0	0	38(4.3)	0	38(0.3)
FALL	0	0	0	23(2.6)	3(<0.1)	26(0.2)
FEMORAL NECK FRACTURE	0	0	0	11(1.2)	0	11(0.1)
FEMUR FRACTURE	0	0	0	6(0.7)	1(<0.1)	7(0.1)

*:Includes all indications: bipolar depression, bipolar mania, dementia, schizophrenia, Psychosis associated with Parkinson's Disease, MDD, alcoholism.
 MedDRA Version: 9.1

Table 2.1.3.2A: Incidence of Treatment-Emergent SAEs That Occurred in at Least 0.5 Percent of Patients Within Any Indication: All Aripiprazole Data Set by Indication and Overall, Safety Sample

	MDD	BIPOLAR-MANIA	BIPOLAR-DEPRESSION	DEMENCIA	SCHIZO	ALL ARI*
NUMBER OF PATIENTS SCREENED FOR AES	1055	2008	593	894	8215	12925
NUMBER OF MALE PATIENTS	358	875	234	222	5092	6896
NUMBER OF FEMALE PATIENTS	697	1133	359	672	3123	6029
NUMBER OF PATIENTS WITH >=1 AES	36(3.4)	193(9.6)	25(4.2)	396(44.3)	1452(17.7)	2107(16.3)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)
NERVOUS SYSTEM DISORDERS	7(0.7)	19(0.9)	3(0.5)	79(8.8)	54(0.7)	163(1.3)
CONVULSION	2(0.2)	4(0.2)	0	7(0.8)	11(0.1)	24(0.2)
CEREBROVASCULAR ACCIDENT	1(0.1)	0	0	20(2.2)	0	21(0.2)
SYNCOPE	1(0.1)	3(0.1)	1(0.2)	8(0.9)	8(0.1)	21(0.2)
COMA	0	0	0	10(1.1)	2(<0.1)	12(0.1)
DEMENCIA	0	0	0	6(0.7)	1(<0.1)	7(0.1)
LETHARGY	0	0	0	5(0.6)	0	5(<0.1)
INFECTIONS AND INFESTATIONS	7(0.7)	2(0.1)	2(0.3)	101(11.3)	41(0.5)	155(1.2)
PNEUMONIA	2(0.2)	1(<0.1)	1(0.2)	37(4.1)	15(0.2)	56(0.4)
URINARY TRACT INFECTION	0	0	0	22(2.5)	1(<0.1)	24(0.2)
UROSEPSIS	0	0	0	11(1.2)	0	11(0.1)
SEPSIS	0	0	0	8(0.9)	0	8(0.1)
BRONCHITIS	0	0	0	7(0.8)	0	7(0.1)
CARDIAC DISORDERS	2(0.2)	3(0.1)	0	78(8.7)	32(0.4)	115(0.9)
MYOCARDIAL INFARCTION	2(0.2)	1(<0.1)	0	16(1.8)	7(0.1)	26(0.2)
CARDIAC ARREST	0	0	0	21(2.3)	3(<0.1)	24(0.2)
CARDIAC FAILURE	0	1(<0.1)	0	11(1.2)	2(<0.1)	14(0.1)

*:Includes all indications: bipolar depression, bipolar mania, dementia, schizophrenia, Psychosis associated with Parkinson's Disease, MDD, alcoholism.
 MedDRA Version: 9.1

Table 2.1.3.2A: Incidence of Treatment-Emergent SAEs That Occurred in at Least 0.5 Percent of Patients Within Any Indication: All Aripiprazole Data Set by Indication and Overall, Safety Sample

	MDD	BIPOLAR-MANIA	BIPOLAR-DEPRESSION	DEMENCIA	SCHIZO	ALL ARI*
NUMBER OF PATIENTS SCREENED FOR AES	1055	2008	593	894	8215	12925
NUMBER OF MALE PATIENTS	358	875	234	222	5092	6896
NUMBER OF FEMALE PATIENTS	697	1133	359	672	3123	6029
NUMBER OF PATIENTS WITH >=1 AES	36(3.4)	193(9.6)	25(4.2)	396(44.3)	1452(17.7)	2107(16.3)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)
CARDIAC DISORDERS	2(0.2)	3(0.1)	0	78(8.7)	32(0.4)	115(0.9)
CARDIAC FAILURE CONGESTIVE	0	0	0	9(1.0)	3(<0.1)	12(0.1)
ATRIAL FIBRILLATION	0	0	0	6(0.7)	0	6(<0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3(0.3)	6(0.3)	0	46(5.1)	48(0.6)	104(0.8)
CHEST PAIN	2(0.2)	4(0.2)	0	6(0.7)	21(0.3)	34(0.3)
PYREXIA	0	0	0	11(1.2)	2(<0.1)	13(0.1)
DEATH	0	0	0	6(0.7)	1(<0.1)	7(0.1)
GENERAL PHYSICAL HEALTH DETERIORATION	0	0	0	5(0.6)	0	5(<0.1)
SURGICAL AND MEDICAL PROCEDURES	2(0.2)	4(0.2)	0	3(0.3)	95(1.2)	104(0.8)
PSYCHOSOCIAL SUPPORT	0	1(<0.1)	0	3(0.3)	55(0.7)	59(0.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1(0.1)	1(<0.1)	1(0.2)	64(7.2)	23(0.3)	90(0.7)
DYSPNOEA	1(0.1)	0	0	9(1.0)	3(<0.1)	13(0.1)
PNEUMONIA ASPIRATION	0	0	0	9(1.0)	0	9(0.1)
RESPIRATORY DISTRESS	0	0	0	7(0.8)	1(<0.1)	8(0.1)
RESPIRATORY ARREST	0	0	0	7(0.8)	0	7(0.1)
LUNG DISORDER	0	0	0	5(0.6)	0	5(<0.1)

*:Includes all indications: bipolar depression, bipolar mania, dementia, schizophrenia, Psychosis associated with Parkinson's Disease, MDD, alcoholism.
 MedDRA Version: 9.1

Table 2.1.3.2A: Incidence of Treatment-Emergent SAEs That Occurred in at Least 0.5 Percent of Patients Within Any Indication: All Aripiprazole Data Set by Indication and Overall, Safety Sample

	MDD	BIPOLAR-MANIA	BIPOLAR-DEPRESSION	DEMENTIA	SCHIZO	ALL ARI*
NUMBER OF PATIENTS SCREENED FOR AES	1055	2008	593	894	8215	12925
NUMBER OF MALE PATIENTS	358	875	234	222	5092	6896
NUMBER OF FEMALE PATIENTS	697	1133	359	672	3123	6029
NUMBER OF PATIENTS WITH ≥1 AES	36 (3.4)	193 (9.6)	25 (4.2)	396 (44.3)	1452 (17.7)	2107 (16.3)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)
GASTROINTESTINAL DISORDERS	1 (0.1)	6 (0.3)	2 (0.3)	39 (4.4)	41 (0.5)	89 (0.7)
VOMITING	0	1 (<0.1)	1 (0.2)	7 (0.8)	7 (0.1)	16 (0.1)
GASTROINTESTINAL HAEMORRHAGE	0	0	0	6 (0.7)	0	6 (<0.1)
METABOLISM AND NUTRITION DISORDERS	0	2 (0.1)	1 (0.2)	33 (3.7)	28 (0.3)	65 (0.5)
DEHYDRATION	0	1 (<0.1)	0	18 (2.0)	4 (<0.1)	24 (0.2)
RENAL AND URINARY DISORDERS	2 (0.2)	0	1 (0.2)	11 (1.2)	5 (0.1)	19 (0.1)
RENAL FAILURE	0	0	0	6 (0.7)	2 (<0.1)	8 (0.1)

*:Includes all indications: bipolar depression, bipolar mania, dementia, schizophrenia, Psychosis associated with Parkinson's Disease, MDD, alcoholism.
 MedDRA Version: 9.1

Reviewer Comments. *The above summary table of SAEs is not complete since only those SAEs with an incidence of at least 0.5% in any given diagnostic group are shown, as specified in the title of the sponsor's summary table. Appendix 2.1.3.2 A of Module 2.7.4 provided the incidence of SAEs without this cut-off criterion. The undersigned reviewer found additional SAEs in the MDD group outlined below that were not included in the in-text summary table. The incidence of each of these additional SAEs was only 0 to 0.1% (occurred in no more than 1 out of the total of 1055 subjects) under any given Preferred Term or Organ System category except for the following Preferred Term or Organ System Categories:*

- *Psychiatric disorders category (0.2%, 2/1055 patients)*
- *Nervous System Category (0.7%, 7/1055 subjects)*
 - *Convulsions (0.2%, 2/1055 subjects)*
- *Injury, Poisoning and Procedural Complications category (0.5%, 5/1055 subjects)*
 - *Intentional Overdose (SAE Term) in 0.2% (2/1055 subjects)*
- *Infections and Infestations Category (0.7%, 7/1055 subjects)*
 - *Pneumonia (0.2%, 2/1055 subjects)*
 - *Cellulitis in 0.2% (2/1055 subjects)*
- *Cardiac Disorders Category (0.2%, 2/1055 subjects)*
 - *Myocardial infarctions (0.2%, 2/1055 subjects)*
- *Neoplasm Organ System Category of ADOs in 0.4% (4/1055 subjects)*
 - *Prostate cancer in 0.3% (1/358 male subjects)*
- *Musculoskeletal and Connective Tissue Disorder Organ System Category in 0.2% (2/1055 subjects)*
- *Renal Urinary Disorders Organ System Category in 0.2% (2/1055 subjects)*
- *Hepatobiliary Disorders Organ System Category in 0.2% (2/1055 subjects)*
- *General disorders and... Category (0.3%, 3/1055 subjects)*
 - *Chest Pain (0.2%, 2/1055 subjects)*

Refer to Appendix 2.1.3.2A for a further breakdown of the above organ/body system categories and for additional SAEs reported in the MDD patients and in other diagnostic groups.

The above additional events only occurred in 1 or 2 subjects except for neoplasm which occurred in 4 total subjects. These additional events showed an incidence that was generally similar to at least some of the other diagnostic groups.

The sponsor summarizes 3 subjects with SAEs of myocardial infarction or cerebrovascular accident in MDD patients in the OL longterm MDD study C...164, as follows (copied from page 115 of Section 2.1.3.2 of Module 2.7.4):

- Patient CN138163-16-5099 (CN138164-55-5099), a 52-year-old male with MDD and a relevant medical history of hypertension, a BMI of 29.2, diverticulosis, and headaches, suffered a myocardial infarction while receiving a daily dose of aripiprazole 2 mg and escitalopram 20 mg on Day 87 of the open-label study. Cardiac catheterization revealed multi-vessel disease and a coronary stent was placed. The investigator considered this event not likely related to the study medication.
- Patient CN138139-21-862 (CN138164-21-862), a 62-year-old male with MDD and an unremarkable medical history, was treated with aripiprazole 5mg and fluoxetine 40mg on Day 1. The patient discontinued aripiprazole on Day 223 and experienced a heart attack on Day 241. The patient required the placement of three coronary stents and the investigator considered this event to be severe in intensity and not related to the study medication.
- Patient CN138139-14-540 (CN138164-14-540), a 51-year-old female with MDD and a relevant medical history of hypertension, hypercholesterolemia, a BMI of 58.9, prior vascular thrombosis, type II diabetes mellitus, gastroesophageal reflux disease, arthritis, and asthma, experienced a cerebrovascular accident while receiving a daily dose of aripiprazole 5 mg and escitalopram 20 mg on Day 13 of the open-label study. There were no potentially clinically relevant laboratory, vital sign, or ECG abnormalities during the study. The investigator considered this event not likely related to the study medication.

Reviewer Comment on the above 3 subjects. *While the potential role of study drug cannot be ruled out in these 3 patients, they were all over 50 years old (2 male, 1 female) with multiple pre-existing and related conditions and generally occurred after months of Arip treatment (except the female patient who had 13 days of study drug in an OL study but was receiving a low dose of Arip).*

A line listing of SAEs in MDD patients was provided (in-text Table 2.1.3.2B of Module 2.7.4) that included the AE term, patient age, onset day and some additional information). The following additional SAEs (aside from the 3 above subjects) were found in this in-text listing that generally occurred in the OL Arip Study 164 (with a few exceptions) and only occurred in 1 subject unless otherwise specified: anxiety, suicidal ideation, suicide attempt with depression and movement disorder (all 3 AEs reported in 1 subject), overdose (2 subjects), convulsion (2 subjects), cholecystitis, decreased visual acuity, optic neuritis, pelvic deformity and pneumonia (both in 1 subject), pneumonia (in another subject), chest pain and dizziness (both AEs in 1 subject), chest pain in another subject, syncope and orthostatic hypotension (both in 1 subject), noncardiac chest pain, spontaneous abortion, excoriation and urinary retention (both in 1 subject), nephrolithiasis, menometrorrhagia, appendicitis and post-operational infection (both in 1 subject), cellulitis and animal bite (both in 1 subject), cellulitis in another subject, rectal prolapse repair and gastroenteritis (both in 1 subject), food allergy, disc protrusion, cancer or cancer-related SAEs (4 subjects).

The Reviewer Overall Conclusion of Results of the All-Arip Treated MDD Group.

The following overall conclusion is provided that is based on a review of the following information:

- *The in-text description of results and of selected individual subjects (as found in the in-text Section 2.1.3.2 of Module 2.7.4 and summarized above),*
- *The results of the in-text Table 2.1.3.2A (shown above)*
- *A review of Dictionary Derived Terms listed by each subject (in an in-text Table 2.1.3.2B that was reviewed in order to find any additional cases not found in the summary Table 2.1.3.2A)*
- *Appendix 2.1.3A (an appendix to Module 2.7.4 that was reviewed for the incidence of all SAEs reported in MDD patients in the All-Arip dataset since the in-text table on the incidence of SAEs only showed SAEs occurring in at least 0.5% of subjects).*

The overall conclusion is that the above results do not provide evidence for a new safety signal with Arip treatment.

Reviewer Caveat to the Above Conclusion: *It is important to note that it is difficult to interpret results in relation to potential drug-drug interaction effects or to other potentially drug-related factors (e.g. duration of treatment and other factors) given the small sample size of subjects. The longterm safety results for MDD are limited to one trial that employed OL treatment, such that it is difficult to interpret results of the OL trial with respect to a potential effect of duration of treatment on the reported SAEs. However, the overall incidence of SAEs for the MDD diagnostic group was small as discussed below.*

The Rationale for the Above Conclusion. *The following paragraphs provide the rationale for the above overall conclusion.*

The incidence of SAEs in the MDD diagnostic group only occurred in 1-2 subjects (for any given SAE preferred term that is shown in the table as occurring in the MDD group) and the incidence (for each SAE term) was generally similar to the incidence observed in other diagnostic groups for the given SAE term. See previous reviewer comments regarding the individual subjects described by the sponsor.

The line listing (that appears to show the Preferred SAE Terms and not the verbatim terms) did not reveal any evidence for a new safety signal that is not already described in approved labeling. Several SAEs were expected for the patient population or for Arip or ADTs, other events were isolated events or were highly suggestive of a non-drug related etiology or of a pre-existing condition.

Reviewer Comments and Conclusion Regarding SAEs in Other Diagnostic Groups

SAEs in other patient populations did not reveal any new safety signal relevant to approved indications and that are not already adequately addressed in approved labeling (based on a review of information previously described above).

Reviewer Caveat. *It is important to note that the interpretation of the results as presented by the sponsor are limited since trials of different study designs and treatment regimens were combined for each patient category.*

Blinded Studies Phase 2/3/4:

An in-text description of SAEs in the safety dataset cannot be found in Module 2.7.4 (in Section 2.1.3.3). The sponsor refers to a listing of SAEs in blinded studies provided in Appendix 2.1.3.3 of Module 2.7.4.

The sponsor notes that narratives were provided for subjects with SAEs in Studies -134 and -162 since these studies were unblinded subsequent after the cut-off date used for their blinded SAE line listing.

Reviewer Comment. *The above 2 studies from which narratives were provided (Studies -134 and -162) were not listed among MDD trials in Tables 1.A and 1.B in Module 2.7.4. Therefore, the narratives of these recently unblinded trials were not reviewed, since the focus of this review is on MDD patients.*

Only one MDD subject was found in the sponsor's line listing. This subject (subject 38165-17-20144) participated in the ongoing/blinded Phase III efficacy Study C...165 and was a 64 year old female patient on concomitant sertraline who had 36 days of blinded treatment. "Arterial occlusive disease" was the reported SAE in this subject.

Phase I ADT-Arip Interaction Studies (C...462 and C...463)

Only one subject was reported to have an SAE in the Phase I trials (subject C...463-1-17). This subject was also reported as having an ADO. The following summary was found in Section 5.3.6 of Module 2.7.4. This 43 year old black male had syncope on the first day of Arip 10 mg

(added to his ongoing SCT treatment of 10 mg daily) that occurred after “several hours” post-dose and resulted in a fall “from the bed onto the floor.” The SAE resolved on the same day. This subject also had additional AEs after this event (back and neck injury, nausea, hyperglycemia, leukocytosis and decreased blood potassium that resolved by Day 3).

Reviewer Comments. *For unclear reasons the sponsor does not describe this subject’s vital signs or any other clinically relevant assessments (e.g. EKG) before and after the syncopal event. It would appear from the description that this syncopal event was due to orthostatic hypotension and syncope is generally associated with orthostatic hypotension with Arip treatment as is described in labeling. The Phase I trials also employed multiple blood sampling for PK analyses that could increase the risk for syncope. Several of the post-syncope AEs were likely reflecting a stress response to the fall and other AEs were likely secondary to Arip treatment (e.g. nausea). The reason for decreased blood potassium is less clear.*

It can be difficult to extrapolate results from a Phase I study to the general MDD patient population, such that the one SAE (also an ADO) described above and the nature of this SAE/ADO does not provide evidence for a new and clinically remarkable safety signal that would warrant changing approved labeling.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

See Appendix 10.1 of this review for more details on disposition for each study phase of each pivotal study. The following summarizes observations for the DB phase (Phase C) of these trials.

Reviewer Comments on the Disposition of Subjects in the DB Phase (Phase C) of Pivotal Trials: *The majority of randomized subjects completed Phase C of each study (85% and 89% in Studies C...163 and C...139, respectively). As expected a slightly greater incidence of ADOs occurred in the Arip compared to placebo groups of each study (4% and 1%, respectively in Study C...163 and 3% and 2%, respectively in Study C...139). Approximately 1 or 2% of subjects withdrew due to lack of efficacy in each trial. These results and results of other disposition categories did not reveal any clinically remarkable findings that would alter overall conclusions on the efficacy or safety results of these 2 trials.*

The total number of randomized subjects was 360 subjects in Study -139 and 381 subjects in Study -163 (sample sizes in each treatment group of each study was similar).

The total number of subjects completing the DB phase (Phase C) was 160 subjects in each treatment group of Study -139 and 162 subject in each treatment group in Study -163.

7.1.3.2 Adverse events associated with dropouts

2-Phase III MDD Trial Dataset: 5.7% of Arip subjects (21 subjects) compared to 1.6% of placebo subjects (6 subjects) were ADOs. The following AEs resulted in ADOs in at least 1% of Arip subjects: akathisia (1.3%) and fatigue (1.1%). The sponsor notes (on page 125 of Module 2.7.4) discrepancies in the number of ADOs described in the CSRs compared to the number summarized in Module 2.7.4 as follows. The sponsor's summary in Module 2.7.4 includes ADOs that occurred in the longterm MDD Study C...164 since the AEs leading to these ADOs started during the short-term placebo controlled trials, C...139 and C...163 (10 Arip subjects and 1 placebo subject). The following table is a copy of the sponsor's summary table of ADOs in the MDD placebo controlled trials (including ADOs in the longterm MDD study C...164 if AEs began during the previous placebo controlled trials C...139 and C...163).

Table 2.1.4.1: Incidence of Treatment-Emergent AEs That Led to Discontinuation of Study Therapy: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	366	371
NUMBER OF MALE PATIENTS	125	134
NUMBER OF FEMALE PATIENTS	241	237
NUMBER OF PATIENTS WITH ≥1 AES	6(1.6)	21(5.7)
SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE(%)	INCIDENCE(%)
NERVOUS SYSTEM DISORDERS	1(0.3)	9(2.4)
AKATHISIA	0	5(1.3)
SOMNOLENCE	0	2(0.5)
COORDINATION ABNORMAL	0	1(0.3)
SEDATION	0	1(0.3)
RESTLESS LEGS SYNDROME	1(0.3)	0
PSYCHIATRIC DISORDERS	3(0.8)	6(1.6)
ANXIETY	0	2(0.5)
RESTLESSNESS	0	2(0.5)
ANORGASMIA	0	1(0.3)
INSOMNIA	0	1(0.3)
DEPRESSION	1(0.3)	0
LIBIDO DECREASED	1(0.3)	0
SUICIDAL IDEATION	1(0.3)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	5(1.3)
FATIGUE	0	4(1.1)
CHEST PAIN	0	1(0.3)
PAIN	0	1(0.3)

Continued on the next page

Table 2.1.4.1: Incidence of Treatment-Emergent AEs That Led to Discontinuation of Study therapy: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	366	371
NUMBER OF MALE PATIENTS	125	134
NUMBER OF FEMALE PATIENTS	241	237
NUMBER OF PATIENTS WITH ≥1 AES	6 (1.6)	21 (5.7)
SYSTEM ORGAN CLASS		
PREFERRED TERM	INCIDENCE (%)	INCIDENCE (%)
EYE DISORDERS	0	2 (0.5)
VISION BLURRED	0	2 (0.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	2 (0.5)
MUSCLE TWITCHING	0	1 (0.3)
MUSCULAR WEAKNESS	0	1 (0.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	2 (0.5)
HYPERHIDROSIS	0	1 (0.3)
RASH	0	1 (0.3)
GASTROINTESTINAL DISORDERS	1 (0.3)	1 (0.3)
HAEMATOCHEZIA	0	1 (0.3)
ORAL PAIN	1 (0.3)	0
INVESTIGATIONS	1 (0.3)	1 (0.3)
WEIGHT INCREASED	1 (0.3)	1 (0.3)
RENAL AND URINARY DISORDERS	0	1 (0.3)
URINARY HESITATION	0	1 (0.3)

Table 2.1.4.1: Incidence of Treatment-Emergent AEs That Led to Discontinuation of Study therapy: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	366	371
NUMBER OF MALE PATIENTS	125	134
NUMBER OF FEMALE PATIENTS	241	237
NUMBER OF PATIENTS WITH ≥1 AES	6 (1.6)	21 (5.7)
SYSTEM ORGAN CLASS		
PREFERRED TERM	INCIDENCE (%)	INCIDENCE (%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	1 (0.3)
SEXUAL DYSFUNCTION	0	1 (0.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.3)	0
PHARYNGOLARYNGEAL PAIN	1 (0.3)	0

Because studies employed a flexible dose design, potential dose-dependent effects on the incidence of ADOs was not examined.

In-text descriptions of individual subjects and a specification of which ADOs were also SAEs could not be found in in-text Section 2.1.4.1 of Module 2.7.4. Reference is made to a line listing in Appendix 2.1.4.1 but a designation of ADOs that were also SAEs could not be found in this line listing.

Reviewer Comments and Conclusion Regarding Results of this Dataset.

The following are reviewer conclusions and comments, based on a review of in-text results in Section 2.1.4.1 in Module 2.7.4.

The overall incidence of ADOs was greater in Arip compared to placebo subjects in the 2 Phase III MDD trials. The nature of preferred term AEs that showed a numerically greater incidence among Arip subjects than placebo subjects (for the Preferred Term AEs that occurred in at least 2 Arip ADOs) were generally not unexpected for Arip (as described in approved labeling for other patient populations). Other AEs reported as ADOs were only reported in a single Arip subject or were not unexpected for Arip (as described in approved labeling), for the ADTs employed or for the patient population. The sponsor does not note or describe any individual subject.

One potentially unexpected finding is that the numerical difference of the overall incidence of ADOs between Arip and placebo subjects was numerically greater than reported in approved labeling for other patient populations (for which treatment is approved). Other patient populations in approved labeling show little to no treatment groups on the overall incidence of ADOs. It is possible that the greater incidence of ADOs observed in MDD patients is, in part, due to concomitant ADTs. Yet only 2 preferred term AEs leading to ADOs occurred with an incidence of at least 1% which were fatigue (1.1%) and akathisia (1.3%) in Arip subjects. These events are expected of Arip and for several of the ADTs. An examination of ADOs by ADT was not described by the sponsor but the incidence of ADOs is small that it would be difficult to interpret results of the incidence ADOs by ADT assignment in the Arip and placebo groups.

All-Aripiprazole (Arip) Treated Safety Dataset Reported

The incidence of ADOs in MDD subjects of this safety dataset is 20.4% compared to 18 to 45% among other patient study populations. The most common preferred term AEs leading to ADOs among MDD patients in this safety dataset (incidence of at least 1%) were: anxiety (1.6%), akathisia (3%), somnolence (1.8%), fatigue (1.6%), weight increased (2.7%).

In-text descriptions of individual subjects and a specification of which ADOs were also SAEs could not be found in in-text Section 2.1.4.2 of Module 2.7.4. Reference is made to a line listing in Appendix 2.1.4.2B but a designation of ADOs that were also SAEs could not be found in this line listing.

The following MDD results were extracted from the sponsor's Table 2.14.2. The sponsor's table shows results for each diagnostic group in addition to the MDD group results shown below.

Reviewer Caveat: *The table below appears to be incomplete (does not include all ADOs occurring in MDD patients, as noted later in this section of this review).*

Table 2.1.4.2: Incidence of Treatment-Emergent AEs That Led to Discontinuation from Study Therapy: All Aripiprazole Data Set by Indication and Overall, Safety Sample

SYSTEM ORGAN CLASS PREFERRED TERM	MDD	INCIDENCE (%)
NUMBER OF PATIENTS SCREENED FOR AES	1055	
NUMBER OF MALE PATIENTS	358	
NUMBER OF FEMALE PATIENTS	697	
NUMBER OF PATIENTS WITH ≥1 AES	215 (20.4)	
<hr/>		
PSYCHIATRIC DISORDERS	54 (5.1)	
PSYCHOTIC DISORDER	0	
SCHIZOPHRENIA	0	
ANXIETY	17 (1.6)	
INSOMNIA	7 (0.7)	
DEPRESSION	7 (0.7)	
AGITATION	0	
RESTLESSNESS	9 (0.9)	
MANIA	0	
SUICIDAL IDEATION	3 (0.3)	
AGGRESSION	0	
CONFUSIONAL STATE	3 (0.3)	
BIPOLAR I DISORDER	0	
BIPOLAR DISORDER	0	
NERVOUS SYSTEM DISORDERS	97 (9.2)	
AKATHISIA	32 (3.0)	
DIZZINESS	4 (0.4)	
NERVOUS SYSTEM DISORDERS	97 (9.2)	
SOMNOLENCE	19 (1.8)	
TREMOR	6 (0.6)	
EXTRAPYRAMIDAL DISORDER	2 (0.2)	
SEDATION	9 (0.9)	
LETHARGY	3 (0.3)	
DISTURBANCE IN ATTENTION	7 (0.7)	
CEREBROVASCULAR ACCIDENT	1 (0.1)	
COMA	0	
DEMENTIA	0	
CONVULSION	0	
AMNESIA	1 (0.1)	
GASTROINTESTINAL DISORDERS	13 (1.2)	
NAUSEA	5 (0.5)	
VOMITING	3 (0.3)	
DYSPHAGIA	1 (0.1)	

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	23 (2.2)	
FATIGUE	17 (1.6)	
ASTHENIA	2 (0.2)	
IRRITABILITY	2 (0.2)	
GENERAL PHYSICAL HEALTH DETERIORATION	0	
GAIT DISTURBANCE	0	
PYREXIA	0	
DEATH	0	
INVESTIGATIONS	34 (3.2)	
WEIGHT INCREASED	28 (2.7)	
WEIGHT DECREASED	0	
CARDIAC DISORDERS	2 (0.2)	
CARDIAC ARREST	0	
MYOCARDIAL INFARCTION	2 (0.2)	
CARDIAC FAILURE	0	
CARDIAC FAILURE CONGESTIVE	0	
INFECTIONS AND INFESTATIONS	1 (0.1)	
PNEUMONIA	0	
URINARY TRACT INFECTION	0	
SEPSIS	0	
BRONCHITIS	0	
UROSEPSIS	0	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (0.4)	
DYSPNOEA	4 (0.4)	
PNEUMONIA ASPIRATION	0	
RESPIRATORY ARREST	0	
RESPIRATORY DISTRESS	0	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.1)	
FALL	0	
HIP FRACTURE	0	
METABOLISM AND NUTRITION DISORDERS	4 (0.4)	2 (0.1)
DEHYDRATION	0	0
EYE DISORDERS	5 (0.5)	13 (0.6)
VISION BLURRED	4 (0.4)	8 (0.4)
RENAL AND URINARY DISORDERS	3 (0.3)	0
RENAL FAILURE	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.1)	0
ANAEMIA	1 (0.1)	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	4 (0.4)	2 (0.1)
M ERECTILE DYSFUNCTION	3 (0.8)	0

(M) Incidence of AE adjusted for males (F) Incidence of AE adjusted for females

*:Includes all indications: bipolar depression, bipolar mania, dementia, schizophrenia, Psychosis associated with Parkinson's Disease, MDD, alcoholism.

MedDRA Version: 9.1

Reviewer Comments and Conclusions on Results of the All-Arip Treated Dataset.

The following overall conclusion is based on a review of the above results (in-text Section 2.1.4.2 of Module 2.7.4) and of Appendix 2.4.1.2 (on the incidence of ADOs), as described later. The results do not provide evidence for a new safety signal with Arip treatment for reasons that follow.

ADOs (by Preferred Terms) in the in-text Table 2.1.4.2.2 were generally reported in 0-9 out of 1055 subjects in the MDD group (0 to <1%). These ADOs were generally expected of the patient population or of Arip treatment (as described in approved labeling) noting that some of these ADOs are also expected of the ADTs employed in the trials.

The only potentially notable observation was on the incidence of ADOs due to weight increased (2.7%, 28/1055 subjects) which was only reported in 0-0.3% of patients in any given non-MDD category (sample sizes/non-MDD category ranged from 593 to 8215 subjects). While weight gain is observed with Arip treatment (as described in approved labeling), the numerically greater incidence in the MDD group compared to other diagnostic groups could be reflecting an ADT by Arip interaction effect, since several ADTs are also associated with weight gain. However, it is difficult to compare across diagnostic groups in this safety dataset given the limitations with this dataset (as discussed elsewhere in this review, such as in Section 4.3 and in other sections). See the last section of this review for further comment and recommendations

The ADOs (Preferred Term AEs) in the above in-text table of Module 2.7.4 that showed an incidence of <1% in MDD subjects were generally isolated events or were generally expected of the patient population or of Arip treatment, as described in approved labeling.

Additional ADOs found in Appendix 2.4.2.A of Module 2.7.4

The undersigned reviewer found that the sponsor's in-text summary table of ADOs (copied above in this review) did not include a number of additional ADOs that occurred in the MDD group. These additional ADOs were found by opening an additional table found in Appendix 2.1.4.2A (that was hyperlinked to the in-text section 2.1.4.2 of Module 2.7.4). The method for selecting which system organ class results and which preferred term results to show in the in-text summary table cannot be found. The incidence of these additional ADOs was small (generally ≤0.3% or no greater than 3/1055 subjects for each Preferred Term event and generally 0-0.9% for any organ system category in which the 0.9% incidence was observed in the musculoskeletal and connective tissue disorder categories, each). Moreover, the incidence for these additional organ system categories was generally similar to at least some of the diagnostic groups and generally did not include any Preferred Term ADO with an incidence that exceeded 0.3%.

The sponsor does not note or describe any specific individual subjects (in the in-text Section 2.1.4.1 of Module 2.7.4). Although, the undersigned reviewer notes that 3 ADOs subjects (1 CVA and 2 MIs) were found in a line listing as also having SAEs (refer to Section 7.1.2 of this review for a description of these subjects). The following provides more details on information found in the line listings. The subject number of each of these 3 ADOs was found in the sponsor's line listing of ADOs in Appendix 2.4.2B in Module 2.7.4 (while noting that the sponsor explains that subject C...-21-861 was miscoded and should have been listed as subject C...-21-862 instead, as described on page 115 of Module 2.7.4). The line-listing found in Appendix 2.4.2B was not otherwise reviewed since it was not anticipated to reveal any different or notable information that was not already revealed by an examination of the above tables of the incidence of ADOs (e.g. the line listing were of Preferred Term AEs as in the tables, the number of ADOs for any reported SAE term was too small to examine a potential role of the onset of the event relative to timing of dosing as a potential drug-related factor, and includes the previously

described short-term trial MDD Phase III dataset, while the remaining MDD patients were in an OL trial in which results are more difficult to interpret, among other reasons). It is also noted that it is not clear if any additional ADOs were also SAEs and a line listing with this information could not be found. A line listing of verbatim terms reported in the subjects with ADOs could also not be found in Module 2.7.4.

Reviewer Caveat. *The interpretation of results of the All-Arip MDD dataset are limited for reasons discussed elsewhere in this review and the focus of the review is on the MDD group and not on other diagnostic groups given the limitations with this dataset, as previously discussed (refer to Section 4.3 of this review).*

Blinded Studies Dataset

The sponsor does not provide an in-text description/summary of ADOs in this safety dataset but instead refers to appendices for listings and narratives.

Reviewer Comments. *A review of the line listing (Appendix 2.1.4.3) in Module 2.7.4) for ADOs in the single MDD trial (C...165) included in this safety dataset revealed 1 subject with SAE of “blocked arteries” leading to an ADO (previously mentioned under Section 7.1.2 of this review), 2 subjects with akathisia, 1 subject with “sensation of heaviness” and nausea (subjects 138165-17-20144, 138165-20-20415, 138165-24-20429, 138165-7-20267, respectively). A review of ADOs of other blinded trials was not conducted since they did not involve MDD patients and are results that are difficult to interpret (due to the data being blinded, multiple studies involving different study designs and treatment regimens were pooled for this safety dataset, among other limitations).*

Phase I ADT-Arip Interaction Studies (C...462 and C...463)

The following is a table of ADOs in both studies, as provided by the sponsor.

Continued in the next page

Table 5.3.7: Adverse Events That Led to Discontinuation, Clinical Pharmacology Studies (CN138462 and CN138463)

Subject Number	Age	Gender	Race	Date of AE Onset	Date of AE Resolution	Treatments Received	Severity	AE	Relationship to Study Medication
CN138462-1-17	33	Female	White	16-Sep-2006	17-Sep-2006	A, B, C (2 days) and B (7 days)	Moderate	Dystonia, neck and tongue	Probably
CN138462-1-27	31	Male	White	17-Sep-2006	29-Sep-2006	A, B, C (4 days) and B (3 days)	Moderate	Akathisia	Probably
CN138462-1-29	40	Male	White	14-Sep-2006	14-Nov-2006	A and B (3 days)	Moderate	Positional increase in blood pressure	Probably
CN138462-1-33	43	Female	White	17-Sep-2006	17-Sep-2006	A and B (3 days)	Mild	Headache	Possibly
CN138462-1-33	43	Female	White	19-Sep-2006	19-Sep-2006	A, B, C (4 days) and B (1 day)	Mild	Syncope	Possibly
CN138462-1-37	41	Female	White	17-Sep-2006	02-Oct-2006	A, B, C (4 days) and B (3 days)	Moderate	Anxiety	Probably
CN138462-1-38	41	Female	White	18-Sep-2006	24-Sep-2006	A, B, C (3 days) and B (4 days)	Moderate	Akathisia	Probably
CN138463-1-4	21	Male	White	19-Sep-2006	23-Sep-2006	A and B (2 days)	Mild	Increased Irritability	Probably
CN138463-1-4	21	Male	White	19-Sep-2006	23-Sep-2006	A and B (2 days)	Mild	Cognitive Impairment	Probably
CN138463-1-15	25	Male	White	20-Oct-2006	21-Oct-2006	A and B (1 day)	Mild	Orthostatic Hypotension	Probably
CN138463-1-17	43	Male	Black	20-Oct-2006	20-Oct-2006	A and B (1 day)	Moderate	Syncope (SAE)	Probably

Source: Supplemental Table S.6.4 in CN138462 and CN138463 clinical study reports

CN138462 Treatments: A = 75 mg venlafaxine XR, B = 10 mg aripiprazole + 75 mg venlafaxine XR, C = 15 mg aripiprazole + 75 mg venlafaxine XR, D = 20 mg aripiprazole + 75 mg venlafaxine XR

CN138463 Treatments: A = 10 mg escitalopram, B = 10 mg escitalopram + 10 mg aripiprazole

The sponsor provided an in-text summary of the ADO that was also reported as an SAE (subject C...463-1-17. Refer to Section 7.1.1 regarding this subject.

The subject with orthostatic hypotension in Study -463 is noted to have this AE for approximately 16 hours after the first dose of 10 mg Arip in which the AE was described as “mild” and “persistent.” This subject was discontinued from the study, according to the protocol (as a subject that was unable to tolerate Arip).

Reviewer Comments. *The following conclusion is based on a review of the in-text Section 5.3.7 of Module 2.7.4 (that included the above results).*

The ADOs are generally not atypical for this Phase I study given the study population, the study conditions (e.g. multiple blood sampling for PK analyses), and the drugs administered in these trials, while other events were isolated. Note that Study -462 employed higher dose-levels of Arip (using an up-titration phase) than in Study -463. Therefore, the results on ADOs do not yield evidence for a new safety signal that is not already adequately addressed in approved labeling for these drugs.

Caveat. *See Section 7.1 summarizing the study design of each study and other key aspects of the study design that were likely to influence the interpretation of the safety results in these 2 Phase I trials. It is generally difficult to extrapolate safety results from Phase I studies to psychiatric patient populations for a number of reasons (e.g. due Phase I study population and study conditions, differences in Phase I study populations and schizophrenia patients such as on past antipsychotic drug exposure, among other key factors).*

7.1.3.3 Other significant adverse events

Refer to other sections of this review for clinically remarkable or potentially clinically remarkable subjects since these subjects are described under subsections in which they apply.

7.1.4 Other Search Strategies

7.1.4.1 Search Strategies Conducted by the Sponsor

The sponsor searched their AE database for the following AEs of “special interest” in the 2 MDD Phase 3 trial dataset and in the All-Arip treated dataset:

- Extrapramidal Symptoms (EPS)
- Neuroleptic Malignant Syndrome (NMS)
- Seizures
- Orthostatic Hypotension
- Suicide
- Somnolence or sedation
- Metabolic and glucose measurement abnormalities: these results were of laboratory parameters and regarding individual subjects noted by the sponsor. These findings are addressed in the laboratory section of this review (Section 7.1.3 for routine laboratory parameters relevant to glucose and lipid profile parameters). Results of special laboratory parameters of glucose metabolism are summarized in Section 7.1.3.4. Results on body weight related measures are covered in Section 7.1.4 (vital sign measures).

Reviewer Comments. *Before summarizing the sponsor results please note the following for consideration.*

The selection of “special interest” AEs is not clear to the undersigned reviewer. The AEs selected are expected for the drug class. It appears that the sponsor’s search of “special interest” AEs was conducted for reasons that follow (but this is based on speculation):

- *To find cases or results based on the incidence of specific AEs within the AE search category (e.g. as with EPS-related AEs):*
- *That may suggest a clinically remarkable and new finding relevant to a given special interest AE category*
- *And that may warrant revision in corresponding sections of labeling (e.g. to determine if the incidence of seizures is unexpectedly high and to find individual subjects suggestive of an unexpected clinical presentation of a given special interest AE such as seizure due to events that could be suggestive of a unexpected and clinically remarkable drug-related effect).*

It is not clear if the sponsor conducted verbatim and/or preferred searches, although sponsor summarizes the incidence of special interest AEs by Preferred Terms. The interpretation of the results is limited by a number of factors that include several relevant to the given dataset being searched (and to the trial designs, among other factors) as discussed elsewhere in this review (e.g. refer to Section 4.3 of this review). Other limitations are inherent with the search methods employed (e.g. verbatim term searches for AEs typical of NMS may capture additional cases, yet the chance for false positive cases would also be expected to increase). Therefore, the interpretation of the results is limited but serves as an attempt to capture clinically meaningful cases with an AE of “special interest.”

Orthostasis.

Reviewer comments and conclusions. *A review of in-text information found in Section 2.1.5.4 of Module 2.7.4 (results based on orthostatic vital sign assessments and on AEs) failed to reveal any clinically remarkable and unexpected findings.*

Treatment groups of the 2 MDD trial dataset were similar on the incidence of outliers on orthostatic vital sign measures (Table 2.1.5.4A in Module 2.7.4) and on a “model” based mean change in orthostatic vital sign measures (Table 2.1.5.4B in Module 2.7.4 refer to the table footnote for details on the ANCOVA model employed). Refer to these summary tables showing the results that the sponsor incorporated into the corresponding Warning/Precaution subsection of proposed labeling.

Suicide.

Reviewer comments and conclusions. *A review of in-text information found in Section 2.1.5.5 failed to reveal any clinically remarkable and unexpected finding related to suicide. Current approved labeling for ADT and Arip includes a subsection on suicide (under Warnings and precautions). Note that the results found in Module 2.7.4 (on the basis of a several search methods) revealed no Arip subjects with this event in the 2 MDD trial dataset. This incidence of suicide-related AEs in the All-Arip treated MDD group was <0.02% and (a total of 5/1055 subjects). The sponsor did not describe any individual cases.*

Somnolence/Sedation

Reviewer comments and conclusions. *A review of in-text information found in Section 2.1.5.6 of Module 2.7.4 did not reveal any clinically remarkable and unexpected finding related to somnolence or sedation. The overall incidence of these events was 10.2% and 5.5% in the Arip and placebo groups in the 2-MDD trial dataset. The sponsor notes the incidence of ADOs due to somnolence or sedation in the Arip group of this dataset (only 0.5% and 0.3%, respectively). The sponsor did not describe any individual cases.*

Seizures.

The following is the sponsor’s summary of their search methods (on page 148 of Module 2.7.4):

A comprehensive search of the AE database for all Phase 2/3/4 studies was conducted to identify patients with a seizure-related AE using the following terms: seizure, convulsion, grand mal, petit mal, epilepsy, fits, electroencephalogram, EEG, and lobe. Terms were

then assessed to determine the appropriateness of the included entries.

The search revealed an incidence of $\leq 1\%$ in any diagnostic group of the All-Arip dataset (except for 1.7% in the dementia group, which a population with greater risk).

Reviewer comment.

2 MDD patients (CN138164-27-9171 and CN138164-34-9203) were found by the sponsor (reported as ADOs due to seizure). Both subjects had risk factors for seizures (history of seizure or history of alcohol use). These subjects were in study -164 (concomitant ADT was venlafaxine in 1 subject and escitalopram in the other subject).

The sponsor does not describe any results of a new and clinically remarkable safety signal that is not already addressed in ADT and Arip labeling.

See previous comments on potential limitations with search methods selected and with the databases searched, among other factors to consider. Note that the above search does not include a search of syncope. Searching for additional and potentially related AE terms may capture more seizure-related events but would also be expected to capture false positives. See search for syncope cases in the next subsection.

See subsection 7.1.4.2 of reviewer search strategies that includes a search for cases of syncope.

NMS: The sponsor summarizes results of a search of the All-Arip treated AE database for NMS and no MDD patient was identified (this dataset includes the short term pivotal trials -139 and -163 and the long term OL trial -164). Only 3 out of 12925 subjects were found (as described on page 147 of Module 2.7.4) who were subjects in non-MDD trials.

EPS

Section 2.1.5.1 of Module 2.7.4 provides the incidence of AEs (Preferred Term & Organ System) using a categorization system for grouping AEs into 5 categories: dystonic events, akathisia events, Parkinsonian event, Dyskinetic Events, Residual Events.

Reviewer Comment. *Any additional information on search methods could not be found in Section 2.1.5.1 of Module 2.7.4.*

2 Phase 3 MDD Trial dataset

The sponsor notes the results outlined below are from the 2 Phase 3 MDD Trial dataset. The sponsor includes these results under the EPS subsection in the Adverse Reactions section in proposed labeling.

- Results on the incidence of EPS-related AEs in Arip in placebo groups (in proposed labeling the incidence rate is rounded off to a whole number):
 - Non-akathisia EPS-related AEs: 8.4% and 5.5%, respectively (8% and 5% in proposed labeling)
 - Akathisia AEs: 24.8% and 4.4%, respectively (25% and 4% in proposed labeling)

- Results of treatment group comparisons on mean change from baseline to endpoint (of the DB phase) on clinically relevant rating scales:
 - The Simpson Angus Rating Scale (SAS) and Barnes Akathisia Scale: significant group differences were observed (Arip, 0.31, placebo, 0.03 and Arip, 0.22, placebo 0.02, respectively).
 - Assessments of Involuntary Movement Scales (AIMS) Total Score: treatment groups were similar in changes on this scale.

Reviewer Comment. *The manner of summarizing EPS-related AEs for the placebo-controlled trial (PCT) Phase 3 dataset in proposed labeling (e.g. in which the above results are described) is generally consistent with the manner used to summarize EPS-related AE results for other PCT Phase 3 datasets in approved labeling. The above results and conclusions are also consistent with results found in Table 2.1.5.1C and as summarized on page 136 of Module 2.7.4.*

The sponsor notes (on page 136 of Module 2.7.4) that their inspection of EPS-related AEs by ADT subgroups within the Arip treatment group revealed the following observations on the incidence of akathisia in subjects receiving CYP2D6 inhibitors compared to subjects receiving other ADTs:

- CYP2D6 inhibitor ADT-Arip subgroups: fluoxetine (34%), paroxetine (29%)
- Other ADT-Arip subgroups: venlafaxine (26%); escitalopram (21%); sertraline (20%)

The sponsor also notes an incidence of ADOs due to EPS-related AEs of 1.6% and 0% in Arip and placebo groups, respectively.

Reviewer Comment. *The sponsor notes that given the small sample size of subjects in the above subgroups that the interpretation of the above results is limited. OCPB input is recommended (e.g. consider potential PK-PD interactions). Refer to the last section of this review for further comment and recommendations.*

The sponsor also notes the following: ADOs due to EPS-related AEs occurred in 1.6% of Arip subjects compared to 0% of placebo subjects in which the most common AE leading to an ADO was akathisia (1.3%).

Table 2.1.5.1A shows the incidence of each EPS-related AE and of each PES category for each treatment group. The tables shows a numerically greater incidence in Arip compared to placebo subjects on the following additional AEs that had at least a 1% incidence in the Arip group (of AEs not already discussed above): Parkinsonism events (7% and 4%, in Arip compared to placebo patients; refer to the table for results for each AE under this category). Residual events (muscle twitching) were reported in <1% of subjects. Treatment groups were similar in the incidence of Dystonic Events (<2%/group),

No other results are summarized and no individual subjects are summarized for this safety dataset, other than noting the incidence of ADOs, as summarized above (refer to pages 136-140 of Module 2.7.4).

All-Arip Dataset

The sponsor summarizes results of EPS-related results for the All-Arip dataset as follows:

- Most events occurred within 42 days of treatment
- A MedDRA AE term search for dyskinesia or tardive dyskinesia (TD) was conducted in which the following observations are noted:
 - The incidence of dyskinesia and TD is 1.1% (12 subjects) and 0.28% (3 subjects) in the MDD diagnostic group (Arip treated subjects)
 - Among the above 12 subjects with dyskinesia or TD reported, the sponsor notes the timing of these reported AEs relative to days of Arip treatment as follows:
 - 6 subjects at >180 days of treatment
 - 3 subjects between 90 and 180 days
 - 2 subjects between 42 and 90 days
 - 1 subject < 42 days
 - Among the 12 subjects 3 were ADOs, 5 subjects had their Arip dose decreased, 1 subject received diphenhydramine, and 3 subjects had no intervention
 - The sponsor also notes the total and maximal/endpoint AIMS scores of the above 12 subjects in which the highest reported score at treatment endpoint was 2 (mild) in subjects CN13864-3-45, CN138164-20-148, CN138164-20-723

The above 3 subjects with TD were summarized on pages 141-142 in Module 2.7.4:

- CN138163-36-5842 (had mild TD on Day 68 leading to an ADO that resolved 31 days after the last dose)
- CN138139-9-477: “mild” TD reported on Day 311 leading to a decrease in Arip dose. This AE continued at study endpoint (AIMS scores are noted)
- CN138164-33-9107: “Rabbit Syndrome” reported on Day 236 (“mild”) leading to a dose reduction of Arip. The event resolved 1 day after the last Arip dose.

The sponsor also provides Tables 2.1.5.1D-E on the incidence of EPS-related AEs and a line listing of subjects (specifying the ADT treatment and other information) in the All-Arip MDD dataset (on pages 143—146 of Module 2.7.4).

Reviewer Comment: *Approved labeling has a TD section under Warnings/Precautions indicating that a TD (also describes dyskinesia) may develop in patients receiving antipsychotic (ATP) drugs. Approved labeling also notes that any potential differences between ATPs on developing these events remain unknown. It is not clear if subjects who were reported to have TD or dyskinesias had risk factors or previous ATP exposure. In conclusion, the above results on TD do not warrant a change in approved labeling. However, TD and dyskinesias should be monitored in the sponsor’s postmarketing safety surveillance and should include an examination of potential ADT-Arip interactions effects as discussed in Section 9.3.1 of this review.*

It is not clear why some EPS-related AEs (shown in Table 2.1.5.1D) would occur after chronic Arip treatment (e.g. dystonic events) or why some dyskinesias or TD were reported early in treatment (as early as Day 5 in 1 subject CN...164-29-9256 in Study -164 listed in Table 2.1.5.1E). The sponsor does not offer any explanations (in the section of Module 2.7.4 summarizing the All-Arip dataset results on EPS-related AEs). It is difficult to interpret these results given the small sample size and the nature of the dataset and study design employed.

Perhaps such events may be better characterized by conducting analyses of datasets from approved ATP trials (pooled in an appropriate, clinically relevant manner) and/or by an examination of postmarketing databases (e.g. for atypical and typical ATP pooled datasets). However, for the purposes of this NDA, the sponsor's results are sufficient and approved labeling describes events of TD and dyskinesias under Warnings/Precautions.

See Section 9 of this review for additional comments and recommendations.

Refer to Section 7.1.5.6 of this review for additional analyses and explorations of AEs.

7.1.4.2 Reviewer Search Strategies

Reviewer's Search for Syncope Cases (all searches were conducted for the term "syncope" using the "find" tool in Adobe Acrobat).

The following summarizes the results of a search for subjects with the AE of syncope. Based on search results described below, only 1 out of the 6 MDD Arip treated subject (with the AE of syncope) was found to have syncope reported as an SAE and/or as an ADO. That single subject also had orthostatic hypotension. Approved labeling already addresses the known drug effect of orthostatic hypotension and syncope associated with this event.

Examination by the undersigned reviewer of Appendices 2.1.A-1 and 2.1.B-1A (in Module 2.7.4) for AEs of syncope revealed the following observations:

- *2 MDD Phase 3 trial dataset (-139 and -163): 2 cases of syncope and no cases of placebo.*
- *All-Arip treated dataset): 6 (0.6%) in the MDD group (combines databases from the above 2 studies with the longterm OL study -164, such that if 2 cases were during the short-term trials, based on the above results, then the remaining 4 cases were in the longterm study). This incidence is generally comparable to the incidence in other diagnostic group categories.*

Line listings of SAEs or ADOs in the All-Arip dataset (Appendices 2.1.3.2B and 2.1.4.2B of Module 2.7.4) revealed the following syncope SAEs and ADOs in the MDD diagnostic group:

- *Subject ID numbers (1 subject): 138139-22-670 138164-22-670: SAE and ADO terms (found in both appendices) of syncope and orthostatic hypotension*

Reviewer Search for Serotonin Syndrome (SS):

Reviewer comments. *ADTs can be associated with SS. The following describes this syndrome under Warnings in Effexor labeling:*

The development of a potentially life-threatening serotonin syndrome may occur with Effexor XR treatment, particularly with concomitant use of serotonergic drugs (including SSRIs, SNRIs

and triptans) and with drugs that impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea)

The concomitant use of Effexor XR with MAOIs intended to treat depression is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS, Potential for Interaction with Monoamine Oxidase Inhibitors**).

If concomitant treatment of Effexor XR with an SSRI, an SNRI or a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **PRECAUTIONS, Drug Interactions**).

The concomitant use of Effexor XR with serotonin precursors (such as tryptophan supplements) is not recommended (see **PRECAUTIONS, Drug Interactions**).

Antipsychotics also act on serotonergic receptors. Therefore the undersigned reviewer conducted a search for SAEs or ADOs that may be suggestive of SS as described below that did not reveal any clear and clinically remarkable events that would suggest a new and unexpected safety signal that is not already addressed in approved labeling for either the given ADT or Arip treatment for each subject. Several events are more likely to be drug-related or study drug was a potential contributing factor (based on onset of events relative to treatment and/or a course suggesting a positive dechallenge) but the events were not considered as serious in nature (e.g. since they were mild in nature without any remarkable clinical parameter abnormalities or sequelae/complications and/or the events generally resolved after treatment cessation or occurred in elderly suggestive of greater sensitivity to CNS effects). See below for more details on search methods, results and key findings found in narratives.

Details on search methods and results:

A review of a cumulative listing of SAEs in the All-Arip dataset (Table 2.1.3.2B in Module 2.7.4) revealed no cases with a combination of SAE terms suggestive of SS (most SAE terms listed were involving other organ systems or were AE terms of a diagnosis while noting that 1 subject had an SAE of anxiety and 1 subjects had as SAE of gastroenteritis).

ADOs were found in Appendix 2.1.4.22B line listing. The listing was searched for AEs that may be suggestive of SS but does not include subjects with a single reported AE (as an ADO event) of an EPS-related AE (e.g. akathisia) or restlessness, since these events are more suggestive of EPS-related and/or are common or not atypical with ATPs or ADTs (e.g. restlessness). Subjects with dyskinesia were also not included with the below listing (since this event alone would not appear to be suggestive of SS). Tremor/tongue paralysis in one subject is likely an EPS-related event and is not listed below. Dyspnea in another as a single ADO-related event (not listed below). A subject with vision blurred and sedation listed is not included below. The following ADOs were found (note most subjects had 2 subject numbers since they participated in one of the short-term trials, -139 or -163 followed by the OL longterm MDD trial -164):

- *138139-8-227 138164-8-227 Mild disturbance in attention. Narrative revealed that this 58 year old had resolution of this event after discontinuation and that no clinical*

parameter abnormalities were described. The event was reported on Day 1 upon introducing his first Arip dose of 5 mg (added to escitalopram) from the short-term lead-in study -139. He also had other AEs (insomnia, tremor, irritability and delayed ejaculation. He was continued for 12 days on treatment before study drugs were discontinued.

- *138164-13-916: irritability, disturbance in attention, restlessness. Upon Day 11 after the addition of 10 mg Arip with 20 mg escitalopram in the OL extension study -164 these AEs were reported. The events resolved on Day 37 (except for irritability) after study drugs were discontinued (on Day 14). The only clinical parameter abnormality noted was the following ECG results: Lateral, anterior and inferior low T waves at baseline and flat T wave on day 48. This 46 year old female had a history of mild alcohol use.*
- *138139-13-760 138164-13-760; nausea and anxiety. This subject had elevations in glucose at baseline, Day -1, Day 57 and Day 78. No other clinical parameter abnormalities were described or clinical sequelae).*
- *138139-14-76 138164-14-76: nausea, salivary hypersecretion, tremor, disorientation, thinking abnormal*
- *138139-14-751 138164-14-751: blepharospasm, restlessness*
- *138139-15-752 138164-15-752: restlessness, vomiting, headache*
- *138139-15-752 138164-15-752: vision blurred, nausea, vomiting, sedation, cold sweat (27 year old Day 1 in Study 164 of 5 mg Arip and Venlafaxine)*
- *138139-22-820 138164-22-820: disturbance of attention in a 64 year old on day 58 with SCT and 10 mg Arip in Study -164.*
- *138163-17-5404 138164-56-5404: disturbance of attention in a 46 year old on day 61 with venlafaxine and 10 mg Arip in Study -164. The narrative review revealed “vivid dreams which began on Day 48; increased sweating on Day 56; and decreased coordination and hoarseness on Day 61.” No clinical parameter abnormalities were described except for elevated cholesterol levels.*
- *138163-18-5091: pain, hyperhidrosis, hematochezia, chest pain in a 46 year old on Day 1 or 2 of escitalopram and 5 mg of Arip CSR -163. The subject also had restlessness and urinary hesitation on Day 2. This subject is discussed in more detail in a subsection below on bleeding related events.*
- *138163-23-5020 138164-62-5020 54: hyperhidrosis on day 115 with venlafaxine and 20 mg of Arip in Study -164.*
- *138163-27-5247 138164-68-5247: disturbance of attention on Day 4 in 45 year old receiving sertraline and 5 mg Arip in Stud -164. No clinical parameter abnormalities were described in the narrative.*
- *138163-27-5856 138164-68-5856: Shock (mild) on Day 46 and 63 in 57 year old female with sertraline and 5 mg Arip in Study -164. The narrative revealed “shock like symptoms in the right upper limb. The subject was on Arip and sertraline in the preceding lead-in study -163 and she had not clinical parameter abnormalities described.*
- *138163-29-5455 138164-70-5455: A 62 year old with memory impairment and confusional state on day 87 with fluoxetine and 10 mg Arip in Study -164.*

- 138164-25-9318: *confusional state in a 70 year old male on Day 2 (escitalopram and 5 mg Arip) in study -164.*
- 138164-31-9214: *akathisia, paraesthesia, anxiety and dizziness on Day 115 or 125 in Study -164 with sertraline and 10 mg of Arip (or 5 mg of Arip on day 125 for the event of dizziness).*
- 138164-34-9331: *disturbance of attention in a 47 year old.*
- 138164-36-9127: *vomiting, somnolence and confusion state on Day 1 (fluoxetine and 5 mg Arip) in a 30 year old. Narrative review revealed “no clinically relevant” abnormalities on safety parameters except for elevated triglycerides.*

In light of the above findings regarding ADOs of disturbance of attention it is noted that the incidence of these ADOs was 0.7% (7/1055 subjects) in the MDD All-Arip diagnostic group compared to 0.1-0.2% in all other diagnostic groups in the All-Arip dataset (includes the dementia diagnostic group, Bipolar I-depressed, Bipolar I-mania, and schizophrenia diagnostic groups of samples sizes of generally approximately 1000 subjects per group except for 593 subjects in the Bipolar-depressed group).

Search for ADOs or SAEs of Hyponatremia.

Reports of a possible SIADH have been reported with some ADTs. A search was conducted for hyponatremia. The following is the only subject that was found by the undersigned reviewer among MDD patients based on line listings of SAEs and ADOs of the All-Arip dataset (Table 2.1.3.2B and Appendix 2.1.4.2B of Module 2.7.4):

- 138164-26-9076: *ADO-related AEs of Hyponatremia and disorientation in a 60 year old on day 209 and 210 respectively (venlafaxine and 10 mg Arip in Study -164). Review of the narrative revealed concomitant medications (hydrochlorothiazide), urinary frequency and weight loss (these AEs were not reported until after the onset of low sodium levels (sodium values were: (b) (4) at baseline, and ranged from (b) (4) on assessment days 50, 106, 182 and 191.*

Hypertension;

Hypertension is reported with venlafaxine (refer to labeling that includes a Warning/Precaution section). Several ADTs and antipsychotic drugs are associated with weight gain and some drugs are associated other metabolic effects (e.g. lipid profile effects, hyperglycemia-related events with antipsychotics). Since metabolic-like changes of this nature may also increase risk for hypertension, the undersigned reviewer conducted a special search for events of hypertension as follows. A search using search words of hypertension or blood pressure in the SAE and ADO line listings for the All-Arip MDD subjects Table 2.1.3.2B and Appendix 2.1.4.2B of Module 2.7.4) revealed the following subjects:

- *1 ADO due to hypertension on day 14 in Study -164 (venlafaxine with 5 mg Arip) in a 38 year old female (Subject numbers for this 1 subject: 138163-12-5127 138164-51-5127). A review of the narrative revealed that she was previously on placebo (and venlafaxine) in the lead-in Study -163. Her baseline blood pressure (BP at supine) was*

(b) (4) compared to (b) (4) on Day 14 after initiating Arip (5 mg on day 1, Day 14 venlafaxine dose was 225 mg/day). Treatment was stopped on Day 35 and on that day her BP was (b) (4). She was also receiving levothyroxine, flutin/salin, albuterol, and candesartan.

- IADO due to hypertension that was “mild” on day -71 of Study -164 and reported as “moderate” on Day 19 of venlafaxine and 5 mg Arip (138163-16-5439 138164-55-5439). Information found in the narrative included the following. This 36 year old female had a history of hypertension (baseline BP of (b) (4)) and was also receiving hydrochlorothiazide/valsartan when on Day 19 she had a “worsening” of hypertension and BP on Day was (b) (4) (Day 19 BP could not be found in the narrative).
- ADO due to hypertension in a 50 year old (138164-35-9052 138164-35-9052) on day 14 of sertraline and 5 mg Arip treatment in Study -164. A review of the narrative revealed that this male subject had a history of hypertension (was also receiving verapamil, hydrochlorothiazide, and potassium) and on Day 7 had a BP of (b) (4) (supine) compared to BP of (b) (4) (supine). His BP increased further up to (b) (4) on Day 46 and treatment was discontinued.

Two of the above cases had a history of hypertension. The other subject was on multiple concomitant medications that complicate the clinical picture. Venlafaxine is also associated with hypertension. A possible role of study drug or of a combination of Arip added to ADT treatment may exist in each of these cases. None of the cases were associated with more severe clinical sequelae. These cases alone do not suggest a new, clinically remarkable safety signal with Arip or with combining Arip with ADT treatment. Vital sign results, described in this review, also do not suggest a potentially new and clinically remarkable safety signal. Venlafaxine already adequately addresses hypertension reported with that drug.

Abnormal Bleeding

SSRIs are associated with abnormal bleeding, as follows (copied from Celexa™ labeling, which is a drug class labeling subsection under Warnings/Precautions):

Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see **Drug Interactions**). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Celexa with NSAIDs, aspirin, or other drugs that affect coagulation.

A review of line listings for SAEs and ADOs in the MDD All-Arip dataset revealed previously described cases of CVA and the following ADO:

- Subject 138163-18-5091: a 46 year old male with history of occasional constipation, diarrhea, arthritis and other conditions who developed intermitted blood in stool (started on Day 3 of Arip added onto escitalopram) leading to an ADO on Day 10 of DB treatment (body pain, increased perspiration and intermittent mid-chest pain and restlessness were also reported AEs leading to this ADO). The subject had no other

clinically remarkable abnormalities (on clinical parameters or assessments except for elevated triglycerides).

- See previously described in Section 7.1.2 of this review of one case of CVA in the longterm Study -164.
- One subject had an ADO (CN138164-64-464; 36 year old female) due to anemia (ADO on Day 212, anemia first detected on Day 3 of adding on Arip to venlafaxine treatment). She had ongoing events of heavy menstrual periods and was receiving acetaminophen and lansoprazole. The event was reported as “continuing” when the patient discontinued the trial. This subject was previously mentioned in this review (section 7.1.7). She had mild anemia at baseline and hemoglobin and HCT levels declined to as low as (b) (4) g/l and (b) (4)% respectively on Day 204.

Note that the overall hematology results of MDD trials described in this review do not show evidence for a safety signal relevant to bleeding. The above cases together with hematology results of MDD trials do not provide evidence suggesting a clinically remarkable new safety signal with Arip or Arip combined with ADT. Labeling for approved SSRIs adequately addresses the issue of bleeding for this drug class.

7.1.4.3 Concomitant disorders

The sponsor did not examine safety against concomitant disorders and eligibility criteria employed in the MDD trials generally involved criteria for including healthy non-elderly adults.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Generally standard methods for monitoring and reporting for adverse events (AEs) were employed in the sponsor’s trials. Any special rating scales that might be considered as elicited AEs are also described, elsewhere, in the appropriate subsection of this review.

Reviewer Comment on Review Strategy. *In-text Section 2.1A of Module 2.7.4 summarizes results of AEs reported in Phase C of the pooled placebo controlled MDD trial dataset (pooled data from Studies C...139 and C..163) since this study phase was the DB Arip and placebo treatment phase of these trials for most subsections below, unless otherwise specified in the applicable subsection.*

For the purposes of this review, only results of the MDD placebo controlled trial, pooled safety dataset were reviewed and are shown in this section of the review.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The MedDRA classification system was used. The version used for each pivotal MDD trial was the version that was available at the time of the database lock.

Reviewer Comments. *Each AE categorization system has its inherent limitations. The MedDRA system is now considered the preferred categorization system by the Agency at this time, to the knowledge of the undersigned reviewer.*

Line listings of preferred terms with corresponding verbatim terms could not be found. However subject descriptions (as found in in-text sections and in selected narratives reviewed) used terms that were consistent with the clinical presentation that was described. A review of selected CRFs with narrative descriptions was reviewed that did not reveal any inconsistencies between verbatim terms used in CRFs and AE terms found in the narratives (refer to Section 4.4 of this review).

7.1.5.3 Incidence of common adverse events

2-Phase III MDD Trial Dataset

The following shows the sponsor's results as found in Module 2.7.4 (the table below is Table 2.1.A-1 in Module 2.7.4).

Continued on the next page

Table 7.1.5.3.1

Incidence of Treatment-Emergent AEs That Occurred in at Least 2 Percent of Patients in the Aripiprazole Group: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	366	371
NUMBER OF MALE PATIENTS	125	134
NUMBER OF FEMALE PATIENTS	241	237
NUMBER OF PATIENTS WITH ≥1 AES	233 (63.7)	307 (82.7)
SYSTEM ORGAN CLASS		
PREFERRED TERM	INCIDENCE (%)	INCIDENCE (%)
NERVOUS SYSTEM DISORDERS	98 (26.8)	184 (49.6)
AKATHISIA	16 (4.4)	92 (24.8)
HEADACHE	40 (10.9)	29 (7.8)
SOMNOLENCE	14 (3.8)	23 (6.2)
TREMOR	14 (3.8)	18 (4.9)
SEDATION	6 (1.6)	15 (4.0)
DIZZINESS	7 (1.9)	14 (3.8)
DISTURBANCE IN ATTENTION	4 (1.1)	12 (3.2)
EXTRAPYRAMIDAL DISORDER	0	8 (2.2)
PSYCHIATRIC DISORDERS	49 (13.4)	99 (26.7)
RESTLESSNESS	7 (1.9)	45 (12.1)
INSOMNIA	9 (2.5)	30 (8.1)
ABNORMAL DREAMS	9 (2.5)	9 (2.4)
GASTROINTESTINAL DISORDERS	68 (18.6)	78 (21.0)
CONSTIPATION	7 (1.9)	17 (4.6)
NAUSEA	18 (4.9)	15 (4.0)
DIARRHOEA	16 (4.4)	12 (3.2)
DRY MOUTH	15 (4.1)	11 (3.0)
GASTROINTESTINAL DISORDERS	68 (18.6)	78 (21.0)
FLATULENCE	6 (1.6)	8 (2.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	33 (9.0)	61 (16.4)
FATIGUE	15 (4.1)	31 (8.4)
FEELING JITTERY	2 (0.5)	11 (3.0)
INFECTIONS AND INFESTATIONS	44 (12.0)	58 (15.6)
UPPER RESPIRATORY TRACT INFECTION	16 (4.4)	22 (5.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	40 (10.9)	46 (12.4)
ARTHRALGIA	10 (2.7)	15 (4.0)
MYALGIA	4 (1.1)	10 (2.7)
BACK PAIN	6 (1.6)	8 (2.2)
EYE DISORDERS	8 (2.2)	35 (9.4)
VISION BLURRED	5 (1.4)	21 (5.7)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	28 (7.7)	23 (6.2)
HYPERHIDROSIS	10 (2.7)	8 (2.2)
INVESTIGATIONS	20 (5.5)	18 (4.9)
WEIGHT INCREASED	9 (2.5)	12 (3.2)
METABOLISM AND NUTRITION DISORDERS	12 (3.3)	13 (3.5)
INCREASED APPETITE	6 (1.6)	10 (2.7)

The incidence of AEs for a particular System Organ Class is the incidence of all AEs in that System Organ Class.
 MedDRA Version: 9.1

It is generally difficult to interpret results between patient populations and between independent studies or datasets. Since the studies did not include placebo control groups for ADT treatment (e.g. placebo-Arip group) it is also difficult to determine if an ADT-Arip combination effect was observed.

Given the above caveat the following AEs yielded potentially notable results (when numerically compared to results of the incidence of AEs in approved labeling) that may suggest a greater effect of the combination of ADT with Arip treatment over a placebo-ADT treatment effect on the incidence of AEs:

- *Akathisia,*
- *Restlessness,*
- *Insomnia*
- *Blurred vision*
- *Possibly fatigue/somnolence and sedation*
- *Disturbance of attention*
- *Increased appetite*
- *Increased weight*

The overall safety profile is not unexpected for Arip treatment or for some of the ADTs, but may suggest a greater effect of ADT combined with Arip on the above AEs. See the below results on AEs in placebo controlled Phase 3 trials described in approved labeling (copied from labeling) for comparison to the above results.

Note below that increased appetite, increased weight, disturbance of attention, and insomnia were among AEs (listed above) that did not meet the at least 2% incidence criterion in Bipolar trials.

Schizophrenia short-term Phase 3 trials

Commonly Observed Adverse Events

The only commonly observed adverse event associated with the use of aripiprazole in patients with schizophrenia (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) was akathisia (placebo 4%; aripiprazole 8%).

Continued on the next page

Bipolar-mania short-term Phase 3 Trials

Table 3: Treatment-Emergent Adverse Events in Short-Term, Placebo-Controlled Trials in Patients Treated with Oral ABILIFY

System Organ Class Preferred Term	Percentage of Patients Reporting Event ^a	
	Aripiprazole (n=1523)	Placebo (n=849)
Eye Disorders		
Blurred Vision	3	1
Gastrointestinal Disorders		
Nausea	16	12
Vomiting	12	6
Constipation	11	7
Dyspepsia	10	8
Dry Mouth	5	4
Abdominal Discomfort	3	2
Stomach Discomfort	3	2
Salivary Hypersecretion	2	1
General Disorders and Administration Site Conditions		
Fatigue	6	5
Pain	3	2
Peripheral Edema	2	1
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	5	4
Pain in Extremity	4	2
Nervous System Disorders		
Headache	30	25
Dizziness	11	8
Akathisia	10	4
Sedation	7	4
Extrapyramidal Disorder	6	4
Tremor	5	3
Somnolence	5	4
Psychiatric Disorders		
Anxiety	20	17
Insomnia	19	14
Restlessness	5	3
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal Pain	4	3
Cough	3	2
Nasal Congestion	3	2
Vascular Disorders		
Hypertension ^b	2	1

^a Events reported by at least 2% of patients treated with oral aripiprazole, except events which had an incidence equal to or less than placebo.

^b Including blood pressure increased.

See additional analyses and explorations of AEs in Section 7.1.5.6 of this review.

7.1.5.4 Common adverse event tables

See the previous section of this review.

7.1.5.5 Identifying common and drug-related adverse events

The undersigned reviewer notes the following treatment group comparisons (using specified criteria) on the incidence of AEs, for the 2-MDD Phase 3 trial dataset.

Based on the tabular results on AEs shown in Section 7.1.5.3 of this review regarding the 2-MDD Phase 3 Trial dataset, the most common AEs in Arip treated subjects (at least 5% incidence when rounding off the nearest whole number) and that had twice the rate than the incidence in the placebo subjects were (refer to Table 7.1.5.3.1 in Section 7.5.3 of this review):

- Akathisia,
- Restlessness,
- Insomnia,
- Constipation,
- Fatigue
- Blurred vision.

The sponsor notes on page 65 of Module 2.7.4 that most patients reporting akathisia did not also report restlessness or vice versa.

Reviewer Comments. *Compare the incidence and treatment group differences of the above AEs to that described in approved labeling. A numerical comparison shows a greater treatment group difference in the MDD trials for akathisia and restlessness in schizophrenia and Bipolar short-term, placebo controlled trials. Insomnia, blurred vision and fatigue were not among common AEs in the Bipolar and Schizophrenia trials that also showed at least a greater than twice the incidence observed in the placebo group. Although sedation met these criteria in the Bipolar trials (8% and 3% in Arip and placebo groups).*

Additionally it is potentially notable that akathisia and restlessness showed numerically larger treatment group differences (between Arip and placebo subjects) in the MDD trial dataset (based on results of the above table) compared to the schizophrenia and Bipolar trial datasets that are described in approved labeling. For example akathisia showed an incidence of only 3% and 6% in placebo and Arip subjects in the Schizophrenia trials (and only 4% and 10% in the combined, Bipolar and schizophrenia trial dataset in labeling) compared to an incidence of 4% and 25%, respectively in the MDD trial dataset. Note placebo group rates are similar across the 3 datasets yet a remarkably, numerically larger incidence of akathisia is reported in Arip subjects in the MDD dataset. The sponsor notes in Section 2.1.A of Module 2.7.4 that most patients that had the AE of restlessness or akathisia reported only one of these AEs reported rather than having both AEs reported in a given subject.

The following less common AEs (with an incidence of 2% to <5%) in Arip subjects that had twice the rate than the incidence in the placebo subjects were (based on results of Table 7.1.5.3.1 in Section 7.1.5.3 of this review regarding the 2-MDD Phase 3 trial dataset):

- Sedation
- Dizziness
- Disturbance in attention
- Extrapyramidal disorder
- Feeling jittery
- Myalgia

Reviewer Comments.

Among these less common AEs, as previously defined note that the above AEs generally did not meet the above specified criteria in the Bipolar trials in labeling (in which labeling provides the incidence for AEs with at least a 2% incidence, as specified in Table 3 of labeling)). Although Bipolar trials did have several related AEs showing a greater incidence in Arip compared to placebo subjects (see Table 3 in approved labeling, also previously shown in this review). Yet, the following AEs did not even meet the at least 2% criterion in the Bipolar trials:

- *Disturbance of attention*
- *Increased appetite*

Reviewer Comments on a Comparison between MDD patients and Other Diagnostic Groups in the All-Arip Dataset

In light of the above observations regarding insomnia, blurred vision, akathisia and restlessness the following diagnostic group comparisons are noted.

Akathisia, restlessness and fatigue each showed a similar incidence rates in the MDD and Bipolar-depressed groups but showed numerically lower rates in the other diagnostic groups in the All-Arip treated safety dataset (schizophrenia, Bipolar-manic, dementia and others based on results of Table 2.1B-1 in Module 2.7.4). These results were most notable given that the incidence was large in magnitude (>10%) in MDD and Bipolar-depressed groups (e.g. akathisia which had the highest incidence rates showed a 26% incidence in the MDD group, 25% incidence in the Bipolar-depressed group compared to 16%, 0.4%, 7% in the Bipolar-manic, dementia and schizophrenia diagnostic groups, respectively).

Blurred vision showed a similar pattern across diagnostic groups except that the Bipolar-manic group also showed a similar incidence to that of the Bipolar-depressed and MDD groups.

Perhaps the similar incidence rates in the Bipolar-depression and the MDD groups suggest an Arip-ADT interaction effect at least for these 2 groups. Note that the Bipolar-manic group generally showed intermediate incidence rates on the above AEs compared to lower rates in other diagnostic groups.

Several ADTs are known to be associated with akathisia and restlessness, as well as other AEs that are also associated with Arip and other antipsychotic drugs. However, mood stabilizers are commonly used during both the manic and depressed episodes of Bipolar disorder that may also be a potential factor in the results since the Bipolar manic group showed intermediate incidence rates. However, it is not clear if this interpretation would explain the results of the Bipolar manic group in the absence of more information or data.

A potential interaction effect of Arip and ADT treatment on akathisia, restlessness and fatigue (or sedation) would not be surprising given the known effects of both drug classes (for at least the SSRI ADT drug class since akathisia is generally not reported with Ven monotherapy). However, the magnitude of the incidence of akathisia, restlessness and fatigue in the MDD group (and in the Bipolar-depressed group) may be surprising and in the magnitude of the treatment

group differences on the incidence of these AEs between Arip and placebo groups in the short-term, placebo controlled trial safety dataset. Additional AEs showed a numerically greater incidence in the MDD diagnostic group compared to other diagnostic groups, as described in the Section 7.1.5.6 below. See the last section of this review for additional comments and recommendations.

The next subsection describes 7.1.5.6 discusses diagnostic group comparisons on the incidence of AEs in the All-Arip dataset in more detail. This subsection 7.1.5.6 also summarizes results of exploratory analyses of the results on the incidence of AEs by ADT subgroups. However, these are generally difficult to interpret due to reasons discussed later.

Reviewer Comments of Treatment Group Comparisons on Less Common AEs (2 to <5% incidence)

As previously shown a number of AEs met the at least greater than twice that of placebo criterion among the less commonly reported AEs in Arip subjects (incidence of 2 to <5%) in the 2-MDD Phase 3 Trial dataset. Note that several of these AEs include AEs expected of Arip such as extrapyramidal disorder, increased appetite, and sedation, among others.

7.1.5.6 Additional analyses and explorations

Analyses of AEs by ADT Subgroups in the 2-Phase III MDD Trial Dataset

The sponsor showed the incidence of AEs by DB treatment group for each ADT subgroups in Tables 2.1.A-1 of Module 2.7.4 (these results are also provided in Table 10.4.1 in Appendix 10.4 of this review). The sponsor concludes that ADT subgroups showed similar overall safety profiles.

Reviewer Comments. *The basis or criteria used for making ADT subgroup comparisons on potential differences between Arip and placebo treatment groups cannot be found in Module 2.7.4 (e.g. no statistical comparisons were employed, some subgroups showed greater numerical DB treatment group differences than others on a given AE but the methods for determining that these group differences were not relevant cannot be found). Consequently, the basis for the sponsor's conclusion is not clear to the undersigned reviewer. In the opinion of the undersigned reviewer, the results provided are difficult to interpret for a number of reasons. Several key factors were not controlled for in the results, such as potential effects of the dose-level of either or both Arip and ADT (different subjects received different dose levels within any given subgroup). The sample sizes of several subgroups were small such that the interpretation of the results is further compromised (e.g. only approximately 30 subjects/DB treatment group were in the paroxetine subgroup). Moreover, the sponsor did not employ a DB, placebo control-group study design with respect to ADT treatment in the study. These and other factors limit the interpretation of comparing ADT subgroups on safety results.*

See additional observations on ADT subgroup differences in the next subsection.

Diagnostic Group Differences on the Incidence of AEs

2-MDD Phase 3 Trial Dataset

Reviewer Comments. *The following observations are based on results of AEs that had an incidence of at least 2% in the Arip group that was also numerically greater than the incidence in the placebo group. When these results are compared to results of the Schizophrenia and Bipolar placebo controlled trials the following observations are noted by the undersigned reviewer:*

- *The overall safety profile among the diagnostic groups is generally similar (note that labeling only describes common AEs for the schizophrenia group) except that the following AEs meet the >2% criteria (and greater than placebo) for the following possible differences:*
 - *Akathisia shows a larger treatment group difference on the incidence of this AE in the MDD trials (21% group difference: 25% and 4% in Arip and placebo groups respectively) compared to the Bipolar (9% group difference: 15% and 6%, respectively) and to the Schizophrenia trials (4% difference: 8% and 4%, respectively). Refer to approved Abilify labeling.*
- *Blurred vision is a common AE in the Arip group in the MDD trials (6%) but is not a common AE in the Arip group of the Schizophrenia or the Bipolar trials. MDD trials may also show a greater treatment group difference in the incidence of this AE in the MDD trials (6% and 1% in Arip compared to placebo groups) compared to the Bipolar trials (3% and 1%, respectively) and in the schizophrenia trials.*
- *Disturbance of Attention is not described for the schizophrenia trials and is not among AEs in Bipolar trials that met the criteria of having an incidence of $\geq 2\%$ in the Arip group that is numerically greater than the incidence in the placebo group. However, this AE met this criterion in the MDD trials (3% and 1%, respectively).*

ADT Subgroup Differences of Selected AEs in the 2 MDD trial Safety dataset

In light of the above observations the following ADT subgroup differences are noted (based on results in Table 2.1.A-2 in Module 2.7.4):

- *Akathisia showed the largest numerical treatment subgroup difference (between Arip and placebo groups) in the fluoxetine ADT subgroup (approximately 30%) compared to other ADT subgroups (treatment group differences ranged from approximately 15 to 22%).*
- *The sponsor also notes a higher incidence of akathisia in the paroxetine and fluoxetine subgroups of Arip treated subjects (2D6 inhibitors showing a 34% and 29% incidence, respectively) than in the other ADT-Arip subgroups (20-26%/ADT group) in the 2 MDD trial dataset. See section 7.1.4 of this review.*
- *Disturbance of Attention was a common AE in the Arip group in the Venlafaxine subgroup and not in the other ADT subgroups. Treatment group differences were also greater in the venlafaxine subgroup (6% and 1%, in Arip and placebo groups, respectively) compared to the other ADT subgroups. Each of the other ADT groups (the SSRI groups) had an incidence of only 0-1.9% in the Arip groups, except for the sertraline group that had an incidence of 3.4% in the Arip group and a 1% incidence in the placebo group.*

- *Treatment group differences (Arip compared to placebo groups) on the incidence of blurred vision were generally similar across each ADT group (6-8%) except for escitalopram (2% differences: 4.2% and 2.0% in Arip and placebo groups, respectively).*
- *Venlafaxine XR subgroup did not show treatment group differences on AEs of increased weight or appetite, while SSRI ADT subgroups did generally show a greater incidence in Arip compared to placebo subjects for increased weight and to a lesser extent for increased appetite. The results of the venlafaxine subgroup are not surprising based on known effects of this drug.*

All-Arip Treated Safety Dataset

The sponsor shows the incidence of AEs for diagnostic groups of the All-Arip treated safety dataset (for MDD, schizophrenia, Bipolar-mania, Bipolar-depression and dementia diagnostic groups) in Table 2.1B-1 in Module 2.7.4. The sponsor notes that the following more frequently reported AEs, showed a higher incidence in the MDD diagnostic group compared to the other approved indications (Bipolar-mania and Schizophrenia) in the All-Arip treated safety dataset:

- Akathisia,
- Restlessness,
- Fatigue,
- Somnolence,
- Weight increase,
- Increased appetite,
- Blurred vision,
- Disturbance of attention,
- Upper respiratory infection.

Any other diagnostic group differences were considered as disease specific AEs by the sponsor. Given the higher incidence of upper respiratory infection, the sponsor indicates that the incidence of AEs of potentially related events of a potentially serious nature (e.g. pyrexia, pneumonia, bronchitis and cough) were low.

Reviewer Comments.

Comments on the sponsor's conclusions

Given the observations on upper-respiratory tract infection, Table 2.1B-1 in Module 2.7.4 was reviewed for results on the incidence of upper respiratory tract infection in other diagnostic groups and for potentially related AEs in the MDD group. As noted by the sponsor the incidence of each AE of cough, pneumonia, bronchitis and pyrexia is low (2.7% for cough, 1.5% for bronchitis and 1% or less for the other AEs). These observations would suggest that the high incidence of upper respiratory tract infection AEs (10%) in MDD patients do not appear to reflect events of a more clinically serious nature. The incidence of upper respiratory tract infections was approximately 2% for schizophrenia and Bipolar mania groups, 6% for the Bipolar depressed group, and 11% for the dementia group. Note that the previously summarized short-term trial dataset (of the 2 pivotal trials, combined) showed an incidence of 5.9% and 4.4% in Arip and placebo subjects, respectively which only suggests a possible trend for a

potential drug effect on this AE. The incidence of potentially related AEs of cough, bronchitis, pneumonia or others did not meet the at least 2% in Arip treated criteria in the short-term trial dataset (as shown in Table 7.1.5.3.1 of this review). The above MDD All-Arip treated subject results can only be considered preliminary in the absence of a placebo group.

Comments on Comparing MDD and Bipolar-depressed Diagnostic Groups (in the All-Arip Treated Dataset) on the Incidence of Common AEs (≥5% incidence)

See previous reviewer comments and noted observations in Section 7.1/5/5 regarding potential differences in observations of AEs in the MDD trials compared to other diagnostic groups in the placebo controlled trial (when comparing to observations described in approved labeling for approved indications) and when comparing diagnostic groups in the All-Arip dataset. The following paragraphs discuss in more detail, observations based on numerical comparisons (on the incidence of common AEs) between the MDD diagnostic group and a similar psychiatric group (Bipolar-depressed) to other diagnostic groups in the All-Arip dataset.

The observations discussed below are based on a review of Table 2.1.B1 in Module 2.7.4 of only those AEs with at least 5% incidence in the MDD group that was also at least twice that of other diagnostic groups, unless otherwise specified. The following paragraphs describe AEs that showed a higher incidence in both the MDD and the Bipolar-depressed groups compared to all other diagnostic groups of the All-Arip treated safety dataset. These events are noted because the MDD and Bipolar-depressed groups share similar clinical features both symptomatically and in some Bipolar-depressed patients also in the concomitant treatment with ADTs.

It is also important to note that most of the AEs identified below were not only common AEs (≥5%) in Arip treated subjects but were also AEs in the Arip group that had at least twice the incidence observed in the placebo subjects in the short-term MDD trial safety dataset. Akathisia, restlessness, fatigue, blurred vision, constipation and insomnia were previously noted Section 7.1.5.5 of this review as common AEs in Arip subjects (had an incidence of ≥5%) in the short-term, placebo controlled MDD trial dataset and also showed an incidence of at least twice the incidence in placebo subjects in this short-term trial dataset.

The following AEs showed a similar incidence between the MDD group and the Bipolar-depressed groups that were reported at lower rates in the other diagnostic groups (using the above specified criteria of showing at least a 5% incidence in the MDD group that was at least twice that of all other groups except for the Bipolar-depressed group):

- *Akathisia, restlessness and fatigue:* *These AEs showed the most remarkably high incidence rates in the MDD and Bipolar-depressed groups (e.g. akathisia was reported in approximately 25% in each of these 2 diagnostic groups, as previously summarized). The Bipolar-mania subgroup showed intermediate incidence rates of each of the AEs of akathisia and restlessness (e.g. 16% for akathisia) while other diagnostic groups showed the lowest incidence rates for each of these 2 AEs (e.g. 0.4 and 7 % in Dementia and Schizophrenia diagnostic groups). The incidence of fatigue in each diagnostic group was: 17% in MDD and 13% in Bipolar-depressed groups, compared to 3-7% in each of the other diagnostic groups).*

- *Increased Appetite (6% and 5% in MDD and Bipolar depressed groups, respectively compared to <1%-2% in other diagnostic groups).*

Blurred Vision which showed at least twice the incidence in the Arip group compared to placebo treated subjects in the short-term MDD trial dataset (and was a common AE in the Arip group) showed the following incidence rates in diagnostic groups of the All-Arip treated dataset: in 6% of MDD patients, 4% in the Bipolar-depressed group, 4% in the Bipolar-manic group while numerically lower rates were reported in the other 2 diagnostic groups (1% or less).

The incidence of constipation or insomnia in the MDD diagnostic group of the All-Arip treated dataset was generally similar to, or lower than, the incidence observed in other diagnostic groups of the All-Arip treated safety dataset.

The following are additional comments regarding results of AEs that are potentially related to the above described AEs of fatigue and increased appetite:

- *Somnolence:* Given the above results on fatigue it is important to note that somnolence showed a high incidence (over 5%) in all diagnostic groups and several groups showed a similar or higher incidence of somnolence as follows: 13% of MDD subjects, in 9% in the Bipolar depressed group, 16% in the Dementia group, 5% in the Schizophrenia group and 6% in the Bipolar-mania group.
- *Increased appetite:* Given the above results on increased appetite, results on increased weight are noted as follows: 14% incidence in the MDD group compared to only 3% in the Bipolar depression group and a similar incidence of 2-3% in the other diagnostic groups.

Relatedness to Duration of Treatment

The sponsor did not systematically evaluate the effect of duration of Arip treatment on AEs since the longterm safety dataset is from Study C...164 which was an OL study. However, the sponsor shows results of the incidence of AEs by time-intervals for the All-Arip treated safety dataset for the MDD diagnostic group in Table 2.1.B-2 (<42 days, 42 to <90 days, 90 to <180 days, 180 to <270 days and >270 days; corresponding samples sizes for each interval are 1055, 873, 630, 426 and 264 subjects). Note that Study C...164 was the only MDD study that employed treatment beyond 42 days such that the results of treatment durations exceeding 42 days in the MDD All-Arip treated dataset should be reflecting results from this longterm safety data.

The sponsor indicates that weight increase was the only AE that had did not show the highest incidence over the first 42 day-interval compared to later time-intervals. Weight increase showed higher incidence rates through 180 days based on results of Table 2.1.B-2.

Reviewer Comments. Upon review of Table 2.1.B-2 for AEs with an incidence of at least 5% at any time-interval beyond the initial 42 day time-interval weight increase was the only AE to meet this criterion (note that the incidence of common AEs in 6-weeks trials were previously discussed in this review and are not reiterated here). The incidence of weight increase over each time-

interval was 4, 5, 6, 3 and <1% for each time interval, respectively (for the time intervals of <42 days, 42 to <90 days, 90 to <180 days, 180 to <270 days and >270 days, respectively). Note that time-intervals reflecting these results are not equal in duration, such that the 4 and 5% rates were only for 42 and 48 day time-intervals, respectively compared to the next 2 time-intervals which were 90 day intervals (and the final time-interval was >270 days). Also sample sizes decrease over each time interval. These and other factors confound the interpretation of the results (see previous discussions on limitations with the All-Arip dataset). Although results of this safety dataset are difficult to interpret it is not surprising that weight increases would continue over time. Since a similar trend was not observed for other AEs that met the $\geq 5\%$ cut-off criterion, the results suggest a drug by duration of treatment effect. Weight increase is not unexpected for ADT and Arip. However, the magnitude of the effect may be larger than with ADT or Arip monotherapy, as discussed elsewhere in this review. Also consider the effects of ADOs on interpreting these results (e.g. such that ADOs due to AEs that occur early in treatment versus ADOs that may occur late in treatment). Moreover, without the use of a DB, placebo control group study design, definitive conclusions cannot be made regarding these results over increasing time-intervals.

Refer to the last section of this review for recommendations.

Dose-Relatedness

The placebo controlled MDD trials did not employ a fixed dose, parallel group study design to explore dose-dependent effects on safety or efficacy.

Demographic Interactions in the 2 MDD Trial Pooled Safety Dataset

Results of Gender Subgroups

The sponsor concludes that there are no statistically significant gender subgroup differences on the incidence of AEs (that had at least 5% incidence in the Arip group), based on an analyses of results from the pooled, placebo controlled, MDD trial safety dataset (using Breslow-Day tests) as summarized in Section 2.1.12 of Module 2.7.4.

Reviewer Comments. *The rationale for the approach in analyzing gender results using the methods described is not clear to the undersigned reviewer and cannot be found in Module 2.7.4. A review of the results on the incidence of AEs with at least 2% the incidence in Arip subjects shown in Table 2.1.1.2 of Module 2.7.4 (for the 2-MDD trial, pooled safety dataset) was conducted. Among common AEs (incidence of $\leq 5\%$) within any given gender subgroup the following criteria was used by the undersigned reviewer to identify AEs that may be showing DB treatment group differences that may differ between men and women.*

- *An AE that had an incidence in the Arip group within a gender subgroup that was at least twice the incidence of placebo group within that same gender and that also*
- *Did not meet this criterion in the other gender subgroup (did not have an incidence of at least twice that of placebo, even if the incidence in this subgroup was less than 5%).*

The following AEs were identified by the undersigned review for meeting the above criteria suggesting gender differences as follows:

- *Somnolence and sedation each showed similar incidence in placebo compared to Arip groups in men (the incidence did not meet the greater than twice that of placebo group and the incidence was less than 5% for both treatment group). The women showed a greater incidence in the Arip compared to the placebo group for each of these events (Arip treated subjects had an incidence of at least 5% that was also at least twice that of placebo).*
- *Constipation showed a greater incidence in Arip compared to Placebo treated subjects among women but not men.*
- *Diarrhea showed a greater effect of Arip treatment for a lower incidence of this event compared to placebo in men that was not observed in women (7% compared to 3% in Arip and placebo treated men compared to 3 and 3% in each treatment group, respectively in women).*
- *Arthralgia showed a greater incidence in Arip treated compared to placebo treated subjects among women (5 and 2%, respectively) but not among men (2 and 4 %, respectively).*
- *Increased appetite showed a greater incidence in Arip treated compared to placebo treated subjects among men (5 and 2%, respectively) but not among women (2 and 2 %, respectively).*

Among the above AEs note that (as previously shown in Section 7.1.5.3 of this review) constipation and somnolence were common AEs in Arip subjects not stratified by gender subgroups. Constipation met the at least twice that of placebo criterion while somnolence did not quite make this criterion when subjects were not stratified (6.2% and 3.8% in Arip and placebo groups, respectively).

It is difficult to interpret or explain the above observations of AEs with potential gender subgroup differences, as specified above.

Results of “Race” Subgroups

Reviewer Comments. *The sponsor conducted a subgroup analyses on the incidence of AEs in each treatment group of the following “race” categories: White, Black, Asian and Other. The results are described in Section 2.1.1.3 of Module 2.7.4. The sample sizes are insufficient to yield interpretable results (sample sizes were 4 to 29 subjects in each treatment group of each “race” category except for the “White” category).*

Refer to the last section of this review for additional comments and recommendations.

Results of Age Subgroups

The sponsor concludes that there are no statistically significant age subgroup differences (for the 2 age-group categories of 18-50 year old and over 51 year old age-groups) on the incidence of AEs (that had at least 5% incidence in the Arip group). This conclusion is based on an analysis

of results from the pooled, placebo controlled, MDD trial safety dataset using Breslow-Day tests (as summarized in Section 2.1.12 of Module 2.7.4).

Reviewer Comments. *The rationale for the approach in analyzing gender results using the methods described in Module 2.7.4 cannot be found and are not clear to the undersigned reviewer. Upon review of the results on the incidence of AEs with at least 2% the incidence in Arip subjects shown in Table 2.1.1.1 of Module 2.7.4 (for the 2-MDD trial, pooled safety dataset) the following observations were made by the undersigned reviewer.*

For AEs with at least a 5% incidence in any age-group subgroup in the Arip treatment group the following AEs showed DB treatment group differences between men and women (based on the criteria that the Arip treated subgroup showed at least twice the incidence of placebo group within that same age-group but that this criterion was not met for the other subgroup, even if the incidence in the other subgroup was less than 5%):

- *Sedation showed a greater incidence in Arip treated compared to placebo treated subjects in the younger age-group (6 and 2%, respectively) but not in the older age-group (1 and 2 %, respectively).*
- *Somnolence showed a greater incidence in Arip treated compared to placebo treated subjects in the older age-group (9 and 4%, respectively) but not in the younger age-group (4 and 4 %, respectively).*
- *Fatigue showed a greater incidence in Arip treated compared to placebo treated subjects in the older age-group (7 and 3%, respectively). The younger age-group did not meet the criteria for demonstrating DB treatment group differences. However, upon rounding off the numbers for the incidence in each treatment group, similar group differences were also observed for the younger age-group (10 and 5%, for Arip and placebo treated subjects, respectively).*

Among the above identified AEs (as showing potential age-group differences on treatment group effects, somnolence was the only common AE ($\leq 5\%$) for the Arip treated subjects (unstratified by age group). As previously shown in this review the unstratified treatment groups, showed an incidence of somnolence of 6.2% compared to 3.8% in the Arip compared to placebo treated subjects. Sedation was reported in 4.0% and 1.6% of each unstratified treatment group, respectively.

It is difficult to interpret and explain the above potential age-group differences on AEs.

7.1.6 Less Common Adverse Events

Refer to sections of this review for less common AEs reported as SAEs, ADOs, found as a result of conducting special search strategies on AEs of conducted by the sponsor (unless otherwise specified in this review), and on subsections on clinical parameter results.

No additional less common AEs were found that were considered as serious AEs based on the following review. The review of the MDD diagnostic group in Appendix 2.1.A-1A was selected

for review since this was the integrated placebo-controlled MDD dataset (the table showed the incidence of Preferred term AEs for Studies 139 and 163, combined). This table was reviewed for any additional AEs in the Arip group that would be considered by the undersigned reviewer as serious AEs and that would not otherwise be adequately captured by results described elsewhere in this review (which showed the incidence of Preferred Term AEs).

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Hematology, chemistry, prolactin levels, and urinalyses were scheduled to be obtained at screening, the end of the final week of the 8-week ADT-placebo Prospective Treatment Phase and at the end of the final week of the 6-week DB Phase or upon early withdrawal (as shown in the “FlowChart/Schedule of Events” table found in the CSR of each study C...139 and C..163). A copy of the study flow chart table found in the CSRs is provided in Appendix 10.1 of this review.

Reviewer Comments. *The sponsor generally showed results on “measures of central tendency” using a median change from the baseline value for Phase C (the value obtained at the end-of-Phase B) or by using a % median change in value (using the LOCF dataset). This information could not be found for the All-Arip dataset, unless otherwise specified in this review.*

Results of mean change, standard deviations and range of values were generally not found in the sponsor’s summary tables and summary of results, unless otherwise specified in this review (as found in in-text sections of Module 2.7.4).

This review summarizes the results as found in Module 2.7.4 (in in-text sections).

Statistical analyses of the results of outliers or on “measures of central tendency” could generally not be found in the in-text sections of Module 2.7.4 unless otherwise specified in this review. Therefore, comparisons of results across groups or over time-intervals are based on numerical comparisons, unless otherwise specified.

The incidence of outliers on a given parameter (as found in in-text summary tables of Module 2.7.4) generally was based on results of subjects having either normal baseline values or baseline values that did not meet outlier criteria. It is not clear how the sponsor selected one of these methods over the other method for presenting these results in the in-text table.

As previous discussed in this review, the primary focus of the review of safety results was on information found in in-text sections of Module 2.7.4, unless otherwise specified below.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Refer to Sections 4 and 7.1 of this review.

It is important to note that the Annotated Clinical Review template (as part of the MAPP) clearly indicates the following regarding the examination of longterm laboratory results for section 7.1.7 of this review:

Placebo-controlled trials are generally short term, and unsuitable for assessing late-developing abnormalities; therefore, longer-term data need to be examined also.

Therefore, longterm safety results are described in Sections 7.1.7, 7.1.8 and 7.1.9 review.

7.1.7.3 Standard analyses and explorations of laboratory data

In accordance with the general guidelines specified in the Clinical Review Template in the MAPP subsections below are to include controlled trial results as well as longterm safety results, even though longterm results are not placebo controlled.

7.1.7.3.1 Analyses focused on measures of central tendency

2-Phase III MDD Trial Dataset

Descriptive statistical results could not be found in Module 2.7.4 except for results on the median percent change from baseline to treatment endpoint on each parameter, as shown below. The following table provides the results (copied from Module 2.7.4).

Continued on the next page

Median Percent Change from Baseline to Endpoint, Serum Chemistry and Electrolyte Measurements: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

Laboratory Test	Placebo		Aripiprazole	
	N	Median % Change	N	Median % Change
AST (SGOT)	331	0.0	351	6.5
ALT (SGPT)	332	0.0	351	11.1
Alkaline Phosphatase	332	1.0	351	0.0
LDH	332	0.0	350	1.4
Total Protein	332	0.0	351	0.0
Blood Urea Nitrogen	332	-0.0	351	0.0
Creatinine	333	0.0	351	0.0
Uric Acid	332	2.2	350	3.5
Bilirubin (Total)	332	0.0	351	0.0
CPK	332	0.0	351	5.5
Prolactin	332	0.0	350	-18.3
Sodium	332	0.0	351	0.0
Potassium	332	0.0	351	0.0
Chloride	333	0.0	351	0.0
Calcium	332	0.0	350	0.0

Median Percent Change from Baseline to Endpoint, Hematology Measurements: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

Laboratory Test	Placebo		Aripiprazole	
	N	Median % Change	N	Median % Change
Hematocrit	333	0.0	344	-0.2
Hemoglobin	333	0.0	344	-1.3
WBC	333	-2.2	344	3.4
Eosinophils (relative)	298	-0.0	301	-6.6
Neutrophils (absolute)	331	-3.5	344	6.5
Platelet Count	326	1.8	339	2.7

The sponsor notes the following observations in the Arip group and that these parameters were also showed greater changes in the Arip compared to placebo subjects (in Sections 3.1.1.3) of Module 2.7.4:

- AST and levels increased
- ALT and levels increased
- Prolactin and levels increased
- CPK and levels decreased

The sponsor notes that the greatest observed change was in ALT (11.1%) and Prolactin (-18.3%) and notes that these changes were “not consistent with the abnormalities of potential clinical relevance.

Reviewer Comment.

The above results do not show evidence for a clinically remarkable effect of Arip on the above laboratory parameters, yet limitations with the interpretation of the results exist (based on median percent change, may not reflect potential time-dependent drug effects among other potential confounding variables). Also note that baseline values were obtained while subjects were receiving ADT treatment. A decrease in Prolactin is not expected for Arip and could possibly be reflecting an adjunctive treatment effect. But this is only speculative. The sponsor notes in another section of Module 2.7.4 (Section 3.1.2.1) that a study, described in the literature (Papakostas et al., 2006) observed elevations of serum prolactin in MDD patients associated with fluoxetine treatment during the acute phase of the study.

Regarding results on AST and ALT, note that the trials excluded subjects with AST or ALT values that were greater than three times the upper limit of normal at baseline/screening.

Elevations in CPK are not clinically remarkable.

See subsequent sections on outliers and potentially clinically remarkable subjects.

Continued on the next page

The following table on “metabolic” parameters was copied from Module 2.7.4.

Median Percent Change from Baseline to Endpoint, Metabolic and Glucose Laboratory Measurements: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

Laboratory Test	Placebo		Aripiprazole	
	N	Median % Change	N	Median % Change
Cholesterol Total				
Fasting	243	1.7	241	0.6
Non-Fasting	58	1.1	67	1.8
HDL Cholesterol				
Fasting	243	0.0	241	1.7
Non-Fasting	58	0.7	67	1.5
LDL Cholesterol				
Fasting	243	2.0	241	-1.0
Non-Fasting	58	4.8	67	-3.2
Triglycerides				
Fasting	243	0.0	241	4.9
Non-Fasting	58	2.2	67	6.6
Glucose				
Fasting	243	0.0	241	0.0
Non-Fasting	57	0.0	67	2.3
HbA1c	333	0.0	344	0.0

Reviewer Comment. *The largest numerical group differences are observed on the triglyceride and LDL parameters. Note group differences on the incidence of outliers on similar and additional parameters described in the next subsection of this review. Refer to the last section of this review for additional comments and recommendations.*

All Arip Treated MDD Dataset

Reviewer Comments. *Median change from baseline to each time-interval in the All-Arip treated MDD dataset (noting that results beyond 6 weeks of treatment reflect those from the longterm safety study C...164) showed generally showed consistently greater changes over time for most “metabolic” parameters such as glucose, HgB1Ac, LDL, HDL, triglyceride levels that were of a magnitude of change that was clinically unremarkable. The largest change occurred with fasting triglycerides at the last assessment time interval (>46 weeks of treatment) in which the median change from baseline values was 12.2 (units not shown). A change of 12.2 may have clinical relevance in a patient who has abnormal or borderline values on their lipid profile. However, the longterm safety study was an OL study such that the interpretation of the results is limited by the absence of a placebo group with a DB study design. See the last section of this review for additional comments.*

Results on measures of “central tendency” cannot be found for hematology and chemistry parameters in Module 2.7.4.

7.1.7.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

Outlier criteria employed for laboratory parameters are shown in Table 10.4.2 in Appendix 10.4 of this review.

2-Phase III MDD Trial Dataset

The following table provides the results (copied from Module 2.7.4).

TABLE 3.1.1.1A

TABLE 3.1.1. Clinical Summary of Safety

Table 3.1.1.1A: Incidence of Treatment-Emergent Serum Chemistry Measurements of Potential Clinical Relevance: Placebo Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

Number of Patients with Potentially Clinically Relevant Abnormality (a)/Number Assessed (%) (b)			
#PTS IN SAFETY SAMPLE LAB MEASUREMENT	CRITERION	Placebo 366 INCIDENCE (%)	Aripiprazole 371 INCIDENCE (%)
AST (SGOT)	≥ 3xULN	1/ 314 (0.3)	0/ 350 (0.0)
ALT (SGPT)	≥ 3xULN	1/ 306 (0.3)	0/ 339 (0.0)
Alkaline Phosphatase (ALP)	≥ 3xULN	0/ 316 (0.0)	0/ 336 (0.0)
Lactate Dehydrogenase (LD)	≥ 3xULN	0/ 314 (0.0)	0/ 340 (0.0)
Blood Urea Nitrogen	≥ 30mg/dL	0/ 315 (0.0)	0/ 336 (0.0)
Creatinine	≥ 2.0mg/dL	1/ 331 (0.3)	0/ 353 (0.0)
Uric Acid	Abnormal (c)	1/ 306 (0.3)	1/ 322 (0.3)
Bilirubin, Total	≥ 2.0mg/dL	0/ 336 (0.0)	0/ 356 (0.0)
Creatine kinase (CK)	≥ 3xULN	0/ 300 (0.0)	2/ 309 (0.6)
Prolactin	> ULN	18/ 317 (5.7)	23/ 329 (7.0)

(a) Criteria for identifying potentially clinically significant laboratory values are based on guidelines suggested by the FDA Division of Neuropharmacological Drug Products (see Appendix 1.1C).
 (b) Includes only patients with a baseline value within normal limits.
 (c) Uric acid: Abnormal: ≥ 10.5 mg/dL (men); ≥ 8.5 mg/dL (women).

Table 3.1.1.1B: Incidence of Treatment-Emergent Electrolyte Measurements of Potential Clinical Relevance: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

Number of Patients with Potentially Clinically Relevant Abnormality (a)/Number Assessed (%) (b)			
#PTS IN SAFETY SAMPLE LAB MEASUREMENT	CRITERION	Placebo 366 INCIDENCE (%)	Aripiprazole 371 INCIDENCE (%)
Sodium (Low)	≤ 126 mEq/L	0/ 339 (0.0)	0/ 359 (0.0)
Sodium (High)	≥ 156 mEq/L	0/ 339 (0.0)	0/ 359 (0.0)
Potassium (Low)	≤ 2.5 mEq/L	0/ 339 (0.0)	0/ 359 (0.0)
Potassium (High)	≥ 6.5 mEq/L	0/ 339 (0.0)	0/ 358 (0.0)
Chloride (Low)	≤ 90 mEq/L	1/ 340 (0.3)	0/ 359 (0.0)
Chloride (High)	≥ 118 mEq/L	0/ 340 (0.0)	0/ 359 (0.0)
Calcium (Low)	≤ 8.2 mg/dL	0/ 338 (0.0)	0/ 358 (0.0)
Calcium (High)	≥ 12 mg/dL	1/ 339 (0.3)	0/ 358 (0.0)

(a) Criteria for identifying potentially clinically significant laboratory values are based on guidelines suggested by the FDA Division of Neuropharmacological Drug Products (see Appendix 1.1C).
 (b) Includes only patients not meeting criteria at baseline

Reviewer Comments. *The above results fail to show any new and clinically remarkable safety signal (that differs from that described in approved labeling). However, 2 subjects in the Arip group were outliers for high CK for unclear reasons (while no placebo subjects showed elevations). Since elevations in ALT, AST and CK were observed either in the above results or in previously shown results on the % median change in levels the undersigned reviewer reviewed results found in Appendix 3.1.1.A showing the incidence of outliers on chemistry parameters for each subgroup of subjects categorized by baseline values, as shown below (extracted from the sponsor's appendix). Only the results showing an incidence of at least 1% in the Arip group for any given parameter are shown below (no Arip subjects were outliers on almost all other parameters for any given category).*

Appendix 3.1.1.1A:
 Incidence of Serum Chemistry Measurements of Potential Clinical Relevance, by Baseline Level:
 Placebo Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

Number of Patients with Potentially Clinically Relevant Abnormality(a)/Number Assessed (%)				
#PTS IN SAFETY SAMPLE LAB MEASUREMENT	CRITERION	BASELINE	Placebo 366 INCIDENCE (%)	Aripiprazole 371 INCIDENCE (%)
Uric Acid	Abnormal (c)	All patients	6/ 339(1.8)	7/ 358(2.0)
		<= ULN	1/ 306(0.3)	1/ 322(0.3)
		> ULN	5/ 33(15.2)	6/ 36(16.7)
		Missing	0/ 0	0/ 0
Creatine kinase (CK)	>= 3xULN	All patients	1/ 339(0.3)	6/ 358(1.7)
		<= ULN	0/ 300(0.0)	2/ 309(0.6)
		> 1-3XULN	1/ 35(2.9)	3/ 46(6.5)
		>=3XULN	0/ 4(0.0)	1/ 3(33.3)
		Missing	0/ 0	0/ 0
Prolactin	> ULN	All patients	30/ 340(8.8)	33/ 358(9.2)
		<= ULN	18/ 317(5.7)	23/ 329(7.0)
		> ULN	12/ 23(52.2)	10/ 29(34.5)
		Missing	0/ 0	0/ 0

(a) Criteria for identifying potentially clinically significant laboratory values are based on guidelines suggested by the FDA Division of Neuropharmacological Drug Products (see Appendix 1.1C).

(c) Uric acid: Abnormal: >= 10.5 mg/dL (men); >= 8.5 mg/dL (women).

High CK would generally not be expected among MDD patients and is not described as a drug effect in approved labeling. An explanation for any of the above cases of elevated CK could not be found in Module 2.7.4 (in in-text sections of Section 3 on results from this safety dataset). Yet, CK can be elevated in highly agitated patients which can sometimes occur in a MDD patient. Akathisia was among more commonly reported AEs in these trials. Perhaps this AE and possibly other extrapyramidal related AEs may account for some of these cases of elevated CK. Note the number of subjects with elevated CPK levels at baseline in both treatment groups and the incidence of these subjects was similar between the treatment groups prior to receiving DB treatment (39/339 placebo subjects and 47/358 Arip subjects). A search for "CK" in the patient-line-listings for the 2 MDD trials in Appendix 3.1.1.1B of Module 2.7.4 revealed the following subjects and a review of the information on these subjects revealed the following observations:

- Subject 138163-16-5216 (a second number for this subject is listed as:138164-55-5216) who was receiving escitalopram as their ADT had the following values (copied from the listing):

Lab Date	Lab Time	Lab Value	ULN Value	Base Line Value	Lab Protocol	Period When Lab Taken	Actual Treatment When Lab Taken
05MAY2005	08:40	(b)	179	(b)	CN138-163	Pre-Treat	
12JUL2005	10:00	(4)	179	(4)	CN138-163	Pre-Treat	
23AUG2005	10:10	* (b)	179		CN138-163	Initial Ph Ari	
31AUG2005	09:40		179		CN138-163	Initial Ph Ari	
15SEP2005	09:15		179		CN138-164	Initial Ph Ari	
30NOV2005	10:30		179		CN138-164	Post-Treat	
22FEB2006	09:45		179		CN138-164	Post-Treat	

- Subject 138163-4-5270 who was receiving venlafaxine as their ADT had the following values (copied from the listing):

Lab Date	Lab Time	Lab Value	ULN Value	Base Line Value	Lab Protocol	Period When Lab Taken	Actual Treatment When Lab Taken
03JUN2005	09:30	(b)	197	(b)	CN138-163	Pre-Treat	
02AUG2005	13:50	(4)	197	(4)	CN138-163	Pre-Treat	
23AUG2005	09:10	* (b)	197		CN138-163	Initial Ph Ari	
26AUG2005	11:55		197		CN138-163	Initial Ph Ari	

Yet transient elevations in CPK occurred in the following subjects during either placebo treatment or the elevation first occurred at pre-treatment while these subjects also had abnormal values at baseline (or pretreatment) prior to meeting outlier criteria in the study as follows:

- Subject 138139-2-687 (also had the subject number of (138164-2-687) with the following elevations (copied from the listing):

Lab Date	Lab Time	Lab Value	ULN Value	Base Line Value	Lab Protocol	Period When Lab Taken	Actual Treatment When Lab Taken
07SEP2005	12:43	(b)	197	(b)	CN138-139	Pre-Treat	
10NOV2005	10:02	(4)	197	(4)	CN138-139	Pre-Treat	
17NOV2005	09:31		197		CN138-139	Initial Ph Placebo	
22DEC2005	10:10	* (b)	197		CN138-139	Initial Ph Placebo	
03JAN2006	10:30		197		CN138-164	Ext/Maint. Ari	
16FEB2006	10:03		197		CN138-164	Ext/Maint. Ari	
09MAR2006	09:35		197		CN138-164	Ext/Maint. Ari	

- Subject 138139-15-169 (138164-15-169) with elevations as follows:

Lab Date	Lab Time	Lab Value	ULN Value	Base Line Value	Lab Protocol	Period When Lab Taken	Actual Treatment When Lab Taken
14OCT2004	16:12	(b)	221	(b)	CN138-139	Pre-Treat	
14DEC2004	15:55	(4)	221	(4)	CN138-139	Pre-Treat	
26JAN2005	15:05	* (b)	197		CN138-139	Initial Ph Ari	
23MAR2005	16:50	* (b)	197		CN138-164	Ext/Maint. Ari	
28MAR2005	09:25		197		CN138-164	Ext/Maint. Ari	
04MAY2005	16:35		197		CN138-164	Ext/Maint. Ari	
01AUG2005	16:10		197		CN138-164	Ext/Maint. Ari	
17AUG2005	16:05		197		CN138-164	Ext/Maint. Ari	

- Additional placebo and Arip subjects were found in the line listing to be outliers that also had abnormal values at baseline.

Reviewer Comments.

The above cases show that transient elevations occurred in a few MDD subjects who were not assigned to Arip treatment or occurred at time-points prior to receiving Arip. Consequently, the results in the summary table may be reflecting non-Arip treatment related elevations in CK. Yet, while treatment groups were similar in the incidence of subjects with abnormal baseline CK (for each specified category) the incidence of outliers during the DB phase was greater in the Arip than in the placebo group (1.7% compared to 0.3%), as previously shown, and is consistent with a numerically greater group mean increase in CK in the Arip compared to the placebo group, as previously discussed. This may not be clinically remarkable finding but warrants some consideration. Note that in section 7.1.7.3.3 no ADOs in Arip subjects were due to elevated CPK levels. Also note that in Section 7.1.2 of this review that none of SAEs were due to elevated CPK or events that would be suspected to increase CK levels.

In conclusion the results on the incidence of outliers fail to reveal a new and clinically remarkable safety signal that is not already described in approved labeling.

The following are results on hematology parameters copied from Module 2.7.4.

Number of Patients with Potentially Clinically Relevant Abnormality(a)/Number Assessed (%) (b)			
#PTS IN SAFETY SAMPLE LAB MEASUREMENT	CRITERION	Placebo 366 INCIDENCE (%)	Aripiprazole 371 INCIDENCE (%)
Hematocrit	Abnormal (c)	2/ 331 (0.6)	1/ 340 (0.3)
Hemoglobin	Abnormal (d)	0/ 321 (0.0)	0/ 329 (0.0)
WBC (Low)	<= 2800/mm3	0/ 340 (0.0)	0/ 351 (0.0)
WBC (High)	>= 16000/mm3	0/ 322 (0.0)	0/ 338 (0.0)
Eosinophils (relative)	>= 10%	3/ 335 (0.9)	2/ 348 (0.6)
Neutrophils (absolute)	< 1000/mm3	0/ 338 (0.0)	0/ 351 (0.0)
Platelet Count (Low)	< 100000/mm3	0/ 333 (0.0)	0/ 346 (0.0)
Platelet Count (High)	>= 700000/mm3	0/ 324 (0.0)	0/ 336 (0.0)

(a) Criteria for identifying potentially clinically significant laboratory values are based on guidelines suggested by the FDA Division of Neuropharmacological Drug Products (see Appendix 1.1C).

(b) Includes only patients with a baseline value within normal limits.

(c) Hematocrit: Abnormal: <= 37% (men) and <= 32% (women) and >= 3% decrease from baseline.

(d) Hemoglobin: Abnormal: <= 11.5 g/dL (men); <= 9.5% g/dL (women).

Reviewer Comment. *No new clinically remarkable finding was revealed by the above hematology results.*

The following results on “metabolic” parameters were copied from Module 2.7.4.

Number of Patients with Potentially Clinically Relevant Abnormality(a)/Number Assessed (%) (b)			
#PTS IN SAFETY SAMPLE LAB MEASUREMENT	CRITERION	Placebo 366 INCIDENCE(%)	Aripiprazole 371 INCIDENCE(%)
Cholesterol Total	>= 240 mg/dL	25/ 193 (13.0)	25/ 188 (13.3)
Fasting		8/ 45 (17.8)	6/ 47 (12.8)
Non-Fasting			
HDL Cholesterol	<= 30 mg/dL	5/ 248 (2.0)	1/ 248 (0.4)
Fasting		2/ 57 (3.5)	0/ 68 (0.0)
Non-Fasting			
LDL Cholesterol	>= 160 mg/dL	17/ 213 (8.0)	13/ 204 (6.4)
Fasting		4/ 51 (7.8)	2/ 58 (3.4)
Non-Fasting			
Triglycerides	>= 160 mg/dL (M) , >=120 mg/dL (F)	16/ 128 (12.5)	30/ 131 (22.9)
Fasting		6/ 21 (28.6)	12/ 26 (46.2)
Non-Fasting			
Glucose			
Fasting	>= 115 mg/dL	9/ 241 (3.7)	5/ 235 (2.1)
Non-Fasting	>= 200 mg/dL	0/ 58 (0.0)	1/ 68 (1.5)
HgB A1C	> 6.0 %	8/ 300 (2.7)	11/ 318 (3.5)

(a) Criteria for identifying potentially clinically significant laboratory values are based on guidelines suggested by the FDA Division of Neuropharmacological Drug Products (see Appendix 1.1C).
 (b) Includes only patients not meeting criteria at baseline.

Reviewer Comments. Note above that HDL, LDL (non-fasting) and triglyceride parameters show treatment group differences in the incidence of outliers (a difference is defined as an incidence of at least 1% in a given group that is also at least two times the incidence observed in the other group). Note group differences observed on some of these parameters described in the previous Section 7.1.7.3.1 on results of “central tendency” measures.

Refer to the last section of this review for additional comments and recommendations.

Results on the incidence of outliers on urinalysis parameters could not be found but rather a listing of subjects who were outliers was provided in the appendix of Module 2.7.4 which was summarized in the in-text section of Module 2.7.4 as showing only a low incidence of outliers in each treatment group and that clinically meaningful treatment group differences were not observed.

All-Arip Treated MDD Dataset

The sponsor notes that the incidence of outliers in MDD patients for several metabolic parameters were higher for the MDD group compared to other diagnostic groups as shown in Table 2.1.5.7 in Module 2.7.4 (incidence of outliers exceeded 10% on most parameters and reached an incidence of 36% and 51% for fasting and nonfasting triglyceride levels, respectively while other diagnostic groups were generally consistently lower and were generally lower by at least 10% on a few of the parameters).

The results of outliers over time-intervals shown in Table 2.5.7.I of Module 2.7.4 generally showed trends for greater changes over time on several metabolic parameters. Fasting glucose shows an incidence of 7.2% of high outliers at the >46 week time-interval compared to only 3.3% at baseline and HgB1Ac shows values of 8.4% compared to 4% at each of these time-points, respectively. Fasting triglyceride shows an incidence of 30% compared to 23% at each of these time-points respectively. The table shows other changes over time.

The results on the incidence of chemistry parameters (Table 3.1.2.1 of Module 2.7.4) shows an incidence of less than 1% in the MDD group except for prolactin (10%) and CPK (1.6% 14/869 subjects). The sponsor notes that this incidence of Prolactin was greater than that observed in other diagnostic groups (incidence ranged from 0% to 6.4% among the diagnostic groups). The sponsor notes that concomitant SSRIs may account for the higher incidence of Prolactin in the MDD group. Note that these results (from Table 3.1.2.1 are of only the subjects with baseline values within normal limits).

The sponsor notes that among the 14 subjects with elevated CPK (for those subjects with normal baseline values) that 7 showed a resolution of abnormal values and 2 showed transient CPK elevations and none of the 14 subjects had concurrent AEs “that suggest a serious medical condition.”

The sponsor also summarizes some LFT findings among the 6 patients who were outliers on LFT parameters (in subjects with normal baseline values). 4 out of 5 subjects who were outliers on ALT or AST values showed transient increases that normalized by the final assessment. None of the 6 subjects showed concurrent elevations in transaminases and bilirubin levels. No ADOs occurred due to elevated AST, ALT or bilirubin.

The incidence of outliers on hematology parameters was less than 1% on each parameter except for relative eosinophil count which as only 1.3%. The sponsor summarizes on ADO due to anemia in a female who was having menorrhagia (and had a history of this condition).

Reviewer Comments. *The interpretation of results of OL trials and the interpretation of results based on comparisons between diagnostic groups and between safety datasets of pooled data from different trials are limited. In light of CPK results in the short term trials and given additional subjects in the OL extension trial noted above the following results are shown (extracted from Appendix 3.1.2.1A which was reviewed given the elevations in CPK or LFTs that were observed in some subjects). Prolactin results are shown, noting a numerically higher incidence in the MDD group compared to other diagnostic groups. However, this observation is considered preliminary, given the limitations with this dataset as discussed elsewhere in this review (e.g. Section 4.3)*

Continued on the next page

Appendix 3.1.2.1A:
 Incidence of Serum Chemistry and Electrolyte Measurements of Potential Clinical Relevance,
 by Baseline Level: All Aripiprazole Data Set, Safety Sample

#PTS IN SAFETY SAMPLE LAB MEASUREMENT BASELINE	Number of Patients with Potentially Clinically Relevant Abnormality(a)/Number Assessed (%)					
	MDD 1055	BIPOLAR- MANIA 2008	BIPOLAR- DEPRESSION 593	DEMENTIA 894	SCHIZO 8215	ALL ARI* 12925
	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)
Creatine kinase (CK)						
All patients	19/ 987(1.9)	62/1565(4.0)	10/ 490(2.0)	20/ 876(2.3)	555/6267(8.9)	668/10334(6.5)
<= ULN	14/ 869(1.6)	26/1266(2.1)	7/ 438(1.6)	17/ 831(2.0)	320/4935(6.5)	386/ 8443(4.6)
> 1-3XULN	4/ 107(3.7)	27/ 247(10.9)	2/ 48(4.2)	1/ 38(2.6)	168/ 866(19.4)	202/ 1319(15.3)
>=3XULN	1/ 6(16.7)	9/ 34(26.5)	1/ 4(25.0)	1/ 1(100.0)	54/ 110(49.1)	66/ 155(42.6)
Missing	0/ 5(0.0)	0/ 18(0.0)	0/ 0	1/ 6(16.7)	13/ 356(3.7)	14/ 417(3.4)
Prolactin						
All patients	124/ 983(12.6)	146/1596(9.1)	39/ 488(8.0)	0/ 0	266/3186(8.3)	576/ 6266(9.2)
<= ULN	91/ 904(10.1)	75/1163(6.4)	28/ 455(6.2)	0/ 0	96/2025(4.7)	290/ 4558(6.4)
> ULN	33/ 75(44.0)	63/ 311(20.3)	11/ 33(33.3)	0/ 0	163/1065(15.3)	270/ 1485(18.2)
Missing	0/ 4(0.0)	8/ 122(6.6)	0/ 0	0/ 0	7/ 96(7.3)	16/ 223(7.2)
Sodium(mEq/L)						

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

2-Phase III MDD Trial Dataset

The sponsor notes in Sections 3.2.1.1, 3.1.1.1 and 2.1.5.7 of Module 2.7.4 that no ADOs occurred due to laboratory parameter abnormalities. It is also noted in Section 3.1.1 that no Arip-treated subject had a simultaneous elevation in AST or ALT with an elevation of total bilirubin levels.

A description of individual subjects with clinically remarkable (or potentially clinically remarkable) events or SAEs involving abnormal laboratory measures (or potentially related adverse events) could not be found in the in-text sections of Module 2.7.4 except for the following 2 subjects with hyperglycemia (in Sections 2 and 4 of the module).

Subjects C...163-17-5497 and C...163-4-5188 were summarized on page 167 of Module 2.7.4 as having abnormal hemoglobin A1C or fasting glucose prior to Arip treatment who were later diagnosed with diabetes. The in-text descriptions of these subjects do not describe any new and clinically remarkable events that occurred during Arip treatment (one subject is described as starting glyburide treatment during the study). Fasting glucose and hemoglobin A1C levels either remained unchanged or improved during Arip treatment. The subject descriptions do not describe any clinical abnormalities of diabetic ketoacidosis. Fasting glucose values provided on these subjects were generally only mildly to moderately elevated (the highest level described was a value of 166 mg/dl and the highest hemoglobin A1C value was 6.8, of which both values were reported prior to Arip treatment).

Both of the above subjects were also receiving venlafaxine XR. One subject had multiple medical conditions and a history of alcohol/drug use. Both subjects completed the study and enrolled in the OL longterm Study C...164.

Reviewer Comments. *These subjects had pre-existing hyperglycemia. The absence of any worsening of their pre-existing hyperglycemia may be reflecting the effect of treatment for diabetes type II (e.g. by diet and/or glyburide treatment of which the latter was reported to be given to one of the subjects during Arip treatment). Current labeling includes a section under Warnings on “Hyperglycemia and Diabetes. The subject descriptions do not suggest any new and clinically remarkable safety signal that is not already described in current approved labeling for Abilify.*

Also refer to Sections 7.1.2-3 on ADOs and SAEs in this review.

All Arip Treated MDD Dataset

Section 2.1.5.7 indicates that no SAEs were hyperglycemia-related events.

Individual subject descriptions could not be found in the in-text laboratory-related sections 2.1.5.7 and 3 of Module 2.7.4 regarding the All-Arip Treated MDD dataset except for subjects summarized below.

2 ADOs occurred due to this reason among Arip treated MDD patients (C...-32-9032 and C...-10-898) who were overweight or obese at baseline who had increased fasting glucose levels and HgB1Ac levels leading to ADOs (on Day 74 in one subject, the day of the ADO in the other subject is not found in the in-text description). One of the subjects was an overweight young female (27 years old) with normal baseline values, but during treatment had a fasting glucose of (b) (4) mg/dl and HgB1Ac of (b) (4) at baseline). The other subject was an obese 53 year old male subject who had hyperglycemia and elevated HgB1Ac that increased on Day 74 of treatment. Fasting glucose returned to baseline values by Day 128 in this subject.

Only one individual subject description was found in in-text laboratory parameter section 3 of Module 2.7.4 for the All-Arip treated MDD dataset. The subject is patient C...64-464 with a history of menorrhagia who developed anemia associated with “heavy menstrual bleeding” (Hgb was (b) (4) g/dl at baseline, at the study time-point with the lowest value, and at the end of the study, respectively).

Also refer to Sections 7.1.2-3 on ADOs and SAEs in this review.

7.1.7.4 Additional analyses and explorations

Additional Glucose-related Metabolic Parameters

The following summarizes results on parameters using a model that is believed to assess pancreatic beta-cell function (referred by the sponsor as HOMA2-%B or %B in this review) and insulin resistance (HOMA2-IR or IR in this review). Data on these parameters was analyzed in the All-Arip Treated dataset and described for the MDD diagnostic group in Section 2.1.5.7 of Module 2.7.4. The sponsor concludes that “no clinically important changes” in the median

percent changes from baseline for each parameter. The sponsor notes that results “are confounded by large variance and diminishing sample size over time.” Several fasting glucose values were considered by the sponsor as being strongly suspicious of blood samples that were not collected under fasting conditions. The sponsor reanalyzed the data excluding “implausible” values from the analyses (i.e. glucose <3.0 or >25.0 mmol/l or insulin <20 or >400 pmol/l). This reanalysis yielded similar results.

Reviewer Comments. A review of in-text Table of 2.1.5.7J-2 was conducted. This table showed median percent changes from baseline to each time-interval on the IR (a normal value is 1) and %B (a normal value is 100%) parameters over time-intervals in the All-Arip MDD dataset (time-points beyond 6-weeks reflects results of the longterm safety study C...164). These results show a wide variance (based n % quartile median values or median % change values that were also provided in the table) and inconsistent numerical increases and decreases in values for IR. %B values appeared to show a numerical decline over time as shown in the sponsor’s table below.

Median Percent Change from Baseline By Time Period, HOMA2 Measurements: Aripiprazole-Treated Patients in Major Depressive Disorder Studies, Safety Sample Excluding Patients who Took Antihyperglycemic Agents

Laboratory Test (b, c)	Study Weeks (a)					
	Baseline	Weeks <=11	Weeks 12-20	Weeks 21-35	Weeks 36-46	Weeks >46
	Median N (25p, 75p)	Median [±] Change N (25p, 75p)	Median [±] Change N (25p, 75p)	Median [±] Change N (25p, 75p)	Median [±] Change N (25p, 75p)	Median [±] Change N (25p, 75p)
HOMA2-IR	426 1.2 (0.8, 2.1)	374 8.0 (-23.1, 49.7)	51 22.5 (-27.9, 89.6)	212 -0.8 (-37.7, 49.2)	139 1.7 (-33.2, 78.6)	123 -3.7 (-40.3, 53.9)
HOMA2 Percent Beta	426 106.9 (78.1, 149.6)	374 5.8 (-16.3, 34.6)	51 3.2 (-16.1, 47.0)	212 -7.2 (-30.6, 28.6)	139 -10.1 (-29.6, 31.6)	123 -12.2 (-33.9, 19.0)

(a) Patients must have had at least 1 fasting laboratory evaluation within the period and that was assessed within at least 30 days of the last known day of study medication to be included in the period evaluation.
 (b) Laboratory evaluations were performed at Weeks 6, 14, 32, 44, 58 for patients continuing on aripiprazole from CN138139 and CN138163, and Weeks 8, 26, 38, 52 for patients initiating treatment with aripiprazole in CN138164.
 (c) (25p, 75p) = (25th percentile, 75th percentile)
 Patient is only counted once within each time category but can appear in multiple time categories.

7.1.7.5 Special assessments

See the previous section.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The “Flow Chart/Schedule of Events” in the CSRs of each of the 2 completed, placebo controlled MDD trials (C...139 and C...163) indicates that vital sign assessments were conducted at screening, baseline, at the end of weeks 1, 4, 8 during the ADT-placebo prospective treatment phase, at the end of weeks 9, 10, 11, 12, 13 and 14 during the DB phase (or upon early withdrawal). A copy of the study flow chart table found in the CSRs is provided in Appendix 10.1 of this review.

Weight and waist circumference measures appear to have been obtained during physical examinations which were conducted at screening and at the end of Phase B and C of the pivotal MDD trials and as shown in the study flow chart in Appendix 10.1 of this review (a description of the specific timing of these measurements cannot be found in the study flow chart tables and safety assessment section of the CSRs or in Module 2.7.4).

The sponsor generally showed results on “measures of central tendency” using a mean change from the baseline value for Phase C (the value obtained at the end-of-Phase B) using the LOCF dataset. Results of the median change and range of values were generally not found in the sponsor’s summary tables and summary of results, unless otherwise specified in this review (as found in in-text sections of Module 2.7.4). This review summarizes the results as found in Module 2.7.4 (in in-text sections).

Statistical analyses of the results of outliers or on “measures of central tendency” could generally not be found in the in-text sections of Module 2.7.4 unless otherwise specified in this review.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Refer to Sections 4 and 7.1 of this review. Also refer to Section 7.1.7.2 of this review regarding the inclusion of results from the longterm MDD safety dataset (the All-Arip Treated MDD dataset).

7.1.8.3 Standard analyses and explorations of vital signs data

In accordance with the general guidelines specified in the Clinical Review Template in the MAPP subsections below are to include controlled trial results as well as longterm safety results, even though longterm results are not placebo controlled.

7.1.8.3.1 Analyses focused on measures of central tendencies
 2-Phase III MDD Trial Dataset

The following tables summarize the results (as provided by the sponsor).

Table 4.1.1.3: Mean and Median Change from Baseline to Endpoint, Vital Sign Measurements: Placebo-Controlled Studies Major Depressive Disorder (CN138139, CN138163), Safety Sample

Vital Sign Measurement	Placebo			Aripiprazole				
	N	Mean	(SE)	Median	N	Mean	(SE)	Median
Heart Rate (bpm)								
Standing	354	-0.18	(0.50)	0.00	365	1.88	(0.55)	2.00
Supine	347	0.14	(0.42)	0.00	358	1.71	(0.50)	1.50
Diastolic Blood Pressure (mmHg)								
Standing	354	0.08	(0.43)	0.00	365	0.19	(0.47)	0.00
Supine	346	0.08	(0.43)	0.00	358	-0.28	(0.43)	0.00
Systolic Blood Pressure (mmHg)								
Standing	354	0.80	(0.62)	0.00	365	1.10	(0.58)	1.00
Supine	346	0.26	(0.56)	0.00	358	0.37	(0.58)	0.00

Table 2.1.5.4B: Model-Based Mean Change from Baseline in Orthostatic Blood Pressure Measurements: Placebo Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

Variable	Systolic Blood Pressure Difference, Supine to Standing (mmHg)							
	Placebo			Aripip			Ari. vs. Pbo	
	N	Mean	SE	N	Mean	SE	p-value	@
Mean Baseline	345	-1.10	0.42	356	-0.86	0.4		0.659
Mean Change from Baseline at Endpoint(a)	345	0.34	0.42	356	0.82	0.4		0.389

(a) Change = [standing systolic BP at endpoint - supine systolic BP at endpoint] - [standing systolic BP at baseline - supine systolic BP at baseline].
 @ ANCOVA model with adjustment for baseline systolic blood pressure difference, gender, age group (18-50, >=51) and protocol was utilized to evaluate change at endpoint using the LOCF observation. No statistically significant differences between treatment groups.

Reviewer Comments. Note that the mean and median change in supine heart rate results suggest a greater increase in Arip compared to placebo subjects (based on numerical comparisons) but the magnitude of this change is small. Also note in subsections below that the incidence of outliers for increased heart rate and tachycardia on ECG assessments is 0% among Arip subjects in this MDD safety dataset. Consequently, the above results on supine heart rate are not considered clinically remarkable and do not warrant a description of these findings in labeling.

Approved labeling describes orthostatic hypotension effects of Arip such that the above results on standing or orthostatic vital sign measures do not yield any clinically remarkable new findings.

The following tables show results on weight related measures (as provided in Module 2.7.4).

Adjusted Mean Change from Baseline to Endpoint of Phase C (Week 14) in Body Weight: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

Variable [b]	Week	Body Weight (kg)								
		Placebo			Aripiprazole			Treatment Comparison [a] Aripiprazole - Placebo		
		N	Mean	SE	N	Mean	SE	Difference	(95% CI)	p-value
Baseline		330	87.48	(1.17)	347	86.15	(1.14)	-1.33	(-4.53, 1.86)	0.414
Change	14 (OC) [c]	305	0.44	(0.13)	315	1.73	(0.12)	1.29	(0.95, 1.64)	< 0.001
	14 (LOCF) [c]	330	0.38	(0.12)	347	1.73	(0.12)	1.35	(1.02, 1.68)	< 0.001

- [a] ANOVA model, with double-blind treatment as main effect with Study as a stratification effect, is used for Baseline comparisons. ANCOVA model, with double-blind treatment as main effect with Study as a stratification effect, and Baseline assessment as covariate, is used for mean change from Baseline comparisons using the OC and the LOCF dataset. Means, treatment differences comparisons and placebo, 95% confidence intervals for the differences and the p-values for pairwise comparisons are based on ANOVA/ANCOVA model.
- [b] Baseline was the last weight measured in Phase B (Week 8). Phase C was 6 weeks in duration with Week 14 being the last week of Phase C.
- [c] End-of-Phase C was Week 14 of the study and Week 6 of Phase C (double-blind aripiprazole vs placebo).

Median Change from Baseline to Endpoint of Phase C in Body Mass Index and Waist Circumference, Analyses of Ranked Change: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

Variable	Week	CN138139, Safety Sample						
		Placebo		Aripiprazole		Treatment Comparison		
		N	Median [a]	N	Median [a]	p-value [b]		
Body Mass Index [c]	Baseline	329	29.59	347	29.20	0.374		
	Change	14 (OC) [d]	304	0.14	315	0.62	< 0.001	
		14 (LOCF) [d]	329	0.13	347	0.59	< 0.001	
Waist Circumference	Baseline	325	96.50	341	96.00	0.616		
	Change	14 (OC) [d]	301	0.00	311	1.30	< 0.001	
		14 (LOCF) [d]	325	0.00	341	1.30	< 0.001	

- [a] Median baseline and median change from baseline value at Week 6 and Week 6 LOCF of Phase C.
- [b] P-values are based on ranked ANOVA/ANCOVA model. ANOVA model, with double-blind treatment as main effect, is used for ranked baseline comparisons. ANCOVA model, with double-blind treatment as main effect, and rank of baseline assessment as covariate, is used for ranked change from baseline comparisons using the OC and the LOCF dataset.
- [c] BMI = weight (kg)/[height (m)]².
- [d] End of Phase C was Week 14 of the study and Week 6 of Phase C (double-blind aripiprazole vs placebo).

Weight Change by Baseline BMI: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

	Weight (in kg)					
	BMI < 23		BMI 23 - 27		BMI > 27	
	Placebo	Aripiprazole	Placebo	Aripiprazole	Placebo	Aripiprazole
Sample Size [a]	46	44	69	80	214	223
Mean Baseline (SE) [b]	59.18 (1.02)	59.74 (1.16)	72.06 (1.01)	72.30 (1.00)	98.31 (1.26)	96.36 (1.14)
Mean Change from Baseline at Endpoint (Phase C) (SE) [b]	0.72 (0.17)	1.48 (0.30)	0.73 (0.19)	2.03 (0.31)	0.19 (0.15)	1.68 (0.16)
	Number of Patients/Number Assessed (%)					
>=7% increase at anytime on-treatment (Phase C) [c]	0/48 (0.0)	2/46 (4.3)	0/71 (0.0)	10/81 (12.3)	2/219 (0.9)	6/227 (2.6)

- [a] Includes all patients with both a baseline and an endpoint measurement.
- [b] Raw unadjusted mean.
- [c] Includes all patients with both a baseline and an on-study measurement.

Mean Change in Weight at Endpoint, by Endpoint Dose: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

	Placebo	Aripiprazole Endpoint Dose (mg)		
		< 7.5 mg	7.5 - 12.5 mg	> 12.5 mg
Sample Size [a]	330	111	89	146
Mean Baseline Weight in kg (SE) [b]	87.49 (1.22)	84.67 (1.87)	86.54 (2.16)	86.98 (1.71)
Mean Change from Baseline at Endpoint in kg (SE) [b]	0.38 (0.11)	1.89 (0.25)	1.36 (0.26)	1.86 (0.18)
Number of Patients/Number Assessed (%)				
>=7% increase at endpoint from baseline [a]	2/330 (0.6)	4/111 (3.6)	5/89 (5.6)	9/146 (6.2)

[a] Includes all patients with both a baseline and an endpoint measurement.
 [b] Raw unadjusted mean.

Reviewer Comment. *As expected for Arip and for ADT concomitant treatment the above results show evidence for an effect of Arip on weight gain. These results are consistent with results shown in the next subsection below.*

The last table shows results on mean change and on the incidence of outliers by Arip endpoint dose that show greater effects on the incidence of outliers with increasing dose-level at treatment endpoint. These results suggest a dose-dependent effect on weight gain but since the studies were not fixed dose studies, this interpretation should be considered a preliminary finding, yet the finding is consistent with the known of effect of antipsychotic drugs on weight.

The MDD trials were not designed to examine potential Arip-ADT treatment interaction effects on safety. Therefore it is difficult to make definitive conclusions on a potential Arip-ADT interaction effect on weight.

See the last section of this review for additional comments and recommendations.

All-Arip MDD Dataset

Descriptive statistical vital sign results of this safety dataset cannot be found in Section 4 of Module 2.7.4 except for results on weight-related parameters as found Section 2.1.5.7 which provides the following table. The table shows a generally consistent mean increase on each parameter over time interval of treatment.

Mean Change from Baseline By Time Period in Body Weight, BMI, and Waist Circumference Measurements: Aripiprazole Treated Patients in Major Depressive Disorder Studies, Safety Sample

Vital sign	Study Weeks															
	Baseline				Weeks <=11			Weeks 12-35			Weeks >=36					
	N	Mean	(SE)	Median	N	Mean Change	(SE)	Median Change	N	Mean Change	(SE)	Median Change	N	Mean Change	(SE)	Median Change
Body Weight (a)	927	87.3	0.7	85.5	476	1.6	0.1	1.4	605	3.3	0.2	3.4	264	3.9	0.4	3.6
BMI	926	30.7	0.2	29.5	475	0.6	0.0	0.5	605	1.2	0.1	1.2	264	1.4	0.2	1.3
Waist Circumference	875	97.6	0.6	96.5	457	1.2	0.2	1.2	565	2.3	0.6	1.5	247	1.8	1.0	2.5

(a) Weight and waist circumference measurements were performed at Weeks 6, 32, and 58 for patients continuing on aripiprazole from CN138139 and CN138163, and Weeks 26 and 52 for patients initiating treatment with aripiprazole in CN138164.
 Patient is only counted once within each time category but can appear in multiple time categories.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

2-Phase III MDD Trial Dataset:

Outlier criteria employed for vital sign parameters are shown in Table 10.4.2

The following tables are copied from Module 2.7.4.

Table 4.1.1.1: Incidence of Vital Sign Abnormalities of Potential Clinical Relevance: Placebo-Controlled Studies Major Depressive Disorder (CN138139, CN138163), Safety Sample

# of Patients in Safety Sample Vital Sign Measurement	Placebo N = 366 Number of Patients with Potentially Clinically Relevant Abnormality(a) / Number Assessed (%)	Aripiprazole N = 371 Number of Patients with Potentially Clinically Relevant Abnormality(a) / Number Assessed (%)
Systolic Blood Pressure		
Supine increase	0/ 350 (0.0)	0/ 361 (0.0)
Supine decrease	4/ 350 (1.1)	1/ 361 (0.3)
Standing increase	2/ 358 (0.6)	0/ 369 (0.0)
Standing decrease	3/ 358 (0.8)	5/ 369 (1.4)
Diastolic Blood Pressure		
Supine increase	0/ 350 (0.0)	0/ 361 (0.0)
Supine decrease	3/ 350 (0.9)	2/ 361 (0.6)
Standing increase	1/ 358 (0.3)	3/ 369 (0.8)
Standing decrease	2/ 358 (0.6)	0/ 369 (0.0)
Heart Rate		
Supine increase	1/ 350 (0.3)	0/ 361 (0.0)
Supine decrease	1/ 350 (0.3)	1/ 361 (0.3)
Standing increase	2/ 358 (0.6)	2/ 369 (0.5)
Standing decrease	0/ 358 (0.0)	0/ 369 (0.0)

(a) Criteria for identifying potentially clinically significant vital sign measurements are based on guidelines suggested by the FDA Division of Neuropharmacological Drug Products (see Appendix 1.1D).

Table 2.1.5.4A: Incidence of at Least 20-mmHg Decrease and at Least 25-bpm Increase in Heart Rate (Supine to Standing): Placebo Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

	Placebo n / N (%)	Aripiprazole n / N (%)	Ari. vs. Pbo p-value @
>=20 mmHg Decrease in Systolic Blood Pressure and >= 25 bpm Increase in Heart Rate Measurements n/N (%)	0/350	3/361 (0.8)	0.249

@ Aripiprazole vs. placebo incidence tested using Fisher's Exact test.

	Placebo n / N (%)	Aripiprazole n / N (%)	Ari. vs. Pbo p-value @
>=20 mmHg Decrease in Systolic Blood Pressure and >= 25 bpm Increase in Heart Rate Measurements n/N (%)	0/350	3/361 (0.8)	0.249

@ Aripiprazole vs. placebo incidence tested using Fisher's Exact test.

Reviewer Comments. The above results (copied from Module 2.7.4) do not yield any new or clinically remarkable findings that are not already adequately addressed in approved labeling.

The following table shows results on weight-related parameters (as provided in Module 2.7.4).

Numbers and Percentages of Patients with Clinically Relevant Weight Gain or Weight Loss during Phase C: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

Variable	Week	Number (%) of Patients with Clinically Relevant Weight Values [a]/Number Assessed (%)		Treatment Comparison [b]		
		Placebo	Aripiprazole	RR [c]	95% CI	p-value
Weight Gain	14(OC) [d]	2/305 (0.7)	17/315 (5.4)	8.34	(1.94 ,35.81)	0.001
	14(LOCF) [d]	2/330 (0.6)	18/347 (5.2)	8.68	(2.02 ,37.17)	<0.001
Weight Loss	14(OC) [d]	0/305 (0.0)	0/315 (0.0)	.		
	14(LOCF) [d]	1/330 (0.3)	0/347 (0.0)	0.00		0.310

[a] Clinically relevant weight gain (loss) is an increase (decrease) of at least 7% from Baseline.
 [b] CMH General Association Test stratified by Study.
 [c] RR = Ratio of Response Rates (Aripiprazole/Placebo).
 [d] End-of-Phase C was Week 14 of the study and Week 6 of Phase C (double-blind aripiprazole vs placebo).

Reviewer Comment. *As expected for Arip and for ADT concomitant treatment the above results show evidence for an effect of Arip on weight gain in patients that were also receiving ADT as part of the protocol. In the absence of a placebo-placebo group, any conclusions on a potential Arip-ADT interaction effect on weight cannot be made.*

See the previous subsection of one of the sponsor’s table showing results that included the incidence of outliers on weight gain relative to the Arip endpoint dose-level that suggest a dose-dependent effect on weight gain.

See the last section of this review for additional comments and recommendations.

All-Arip Treated MDD Dataset

The sponsor provided an in-text table of the incidence of vital sign outliers for the All-Arip treated safety dataset for each diagnostic group (e.g. Bipolar mania, Bipolar depression, Schizophrenia and others). The incidence among the All-Arip MDD group was reviewed since this included subjects from the longterm safety study (combined with subjects from the 2 previously described short-term trials).

The incidence of vital sign outliers in the MDD group on any given parameter (except for weight gain) was 1% or less, except for standing systolic blood pressure which was only 2% among a total of 1055 subjects. The incidence of outliers on orthostatic hypotension cannot be found for the All-Arip treated safety dataset (as provided for the short-term MDD trial dataset in Section 2.1.5.4 of Module 2.7.4 and as previously summarized in this review). However, the incidence of outliers on standing vital sign measures were found with results of other vital sign measures, as described in the preceding paragraph (as found in Section 4.1.2.1 of the Module 2.7.4).

The overall incidence of outliers on weight increase in the MDD group was 23.4%. The table below shows that the incidence of outliers for weight gain and to a less extent weight loss increases over each assessment interval during chronic treatment (the table was provided in Module 2.7.4).

Incidence of Potentially Clinically Relevant Weight Change by Time: Aripiprazole Treated Patients in Major Depressive Disorder Studies, Safety Sample

Vital Sign Measurement	Weeks <=11	Weeks 12-35	Weeks >=36
Number of Patients with Potentially Clinically Relevant Abnormality(a) / Number Assessed (%)			
Weight			
Weight increase	28/ 476(5.9)	167/ 605(27.6)	91/ 264(34.5)
Weight decrease	1/ 476(0.2)	18/ 605(3.0)	15/ 264(5.7)

(a) Criteria for identifying potentially clinically significant vital sign measurements are based on guidelines suggested by the FDA Division of Neuropharmacological Drug Products (see Appendix 1.1D).

Reviewer Comment. Results from the longterm safety data combined with the 2 MDD short-term trials do not show any clinically remarkable new safety finding that is not already described in approved labeling for Arip, except for longterm safety results on weight gain over time that show a remarkably high incidence of outliers on weight gain at the week ≥36 category. Because of the observed overall incidence of 23% among MDD patients and the incidence of 27% and 34.5% in the two later time-intervals with chronic treatment the following is a discussion on the interpretation of these results which is seriously limited given that the results reflect results from a single, OL longterm safety study involving concomitant ADT.

It is difficult to determine the extent of the role of Arip, MDT treatment and the combined treatment of Arip with ADT on the increase in the incidence of outliers over time, since the longterm safety results are derived from a single OL study (that was not DB and did not include placebo controls for Arip and ADT).

The sponsor notes that results on the incidence of weight gain in the All-Arip treated group show a greater incidence in the MDD group than in the other diagnostic groups (as shown in Table 2.1.5.7K on page 184 of Module 2.7.4). Yet the undersigned reviewer notes a similar incidence of outliers on weight gain (20%) in schizophrenia patients. However, the incidence of outliers on weight loss in the schizophrenia group is 18% compared to only 3.3% in the MDD group.

It is difficult to compare results across diagnostic groups since the dataset is derived from trials that differ in key aspects of the study design employed among these trials (e.g. in duration of treatment, dose-level, OL versus DB design, among other key differences in the study design among different trials). It is also difficult to compare results across independent trials regarding the magnitude of a potential drug effect. Moreover, the proportion of subjects receiving longterm Arip exposure is likely to differ remarkably between the MDD group and other diagnostic groups. For example the schizophrenia group most likely had a greater proportion of subjects from short-term trials in contrast to the MDD group (as can be estimated from information in Appendix 1A of Module 2.7.4 which outlines trials with corresponding sample sizes that were included in the safety datasets). Another key limitation with interpreting results

across diagnostic groups are potential confounding factors specific to a given diagnostic group (e.g. the proportion of women versus men, concomitant medication use, differences in comorbidity, among other factors).

Reviewer Comment. *Note that approved labeling includes longterm trial results on weight gain for other patient populations for approved indications based on BMI categories (mean change and % with at least 7% weight gain for each BMI <23, 23-27 and >27 category).*

Approved labeling shows the incidence of outliers on weight gain (defined as $\geq 7\%$ increase in weight) in a 52 week OL schizophrenia trials for each BMI category <23, 23-27 and >27 as follows: 30%, 19% and 8%. Since Study -164 in ongoing this information was not found in Module 2.7.4. It is difficult to extrapolate these results to those above for the MDD group although they may suggest a similar overall incidence in the schizophrenia study to the incidence reported for the MDD group (if one assumes the majority of schizophrenia patients were in the 2 lower BMI categories).

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

2-Phase III MDD Trial Dataset

In section 4.1.1.1 of Module 2.7.4 the sponsor notes the following ADOs in Arip treated subjects:

- One ADO occurred due to weight gain (subject number and an in-text description of this subject cannot be found in Section 4.1.1.1. or in Section 2.1.4.1 on ADOs)
- No other ADOs occurred due to vital sign abnormalities.

A description of individual subjects with potentially clinically remarkable, clinically remarkable events or SAEs involving abnormal vital sign measures or cardiovascular system-related events could not be found in the in-text sections of Module 2.7.4 (in Sections 2 and 4 of the module).

Also refer to Sections 7.1.2-3 on ADOs and SAEs in this review.

All-Arip MDD Dataset

Aside from that previously described regarding the 2 short-term MDD trials that were also included in the All-Arip treatment MDD Dataset, the sponsor does not describe any subjects with clinically remarkable or potentially remarkable vital sign related events (in the in-text section of Section 4.1 of Module 2.7.4).

Reviewer Comments. *There were no SAEs or ADOs among MDD patients in the short-term and longterm safety datasets due to AEs of vital sign abnormalities (under the “Investigations” Organ System Class category). However, there were a few subjects with Cardiac System AEs leading to an ADO (in 2 subjects with myocardial infarction reported as the Preferred term event) and 1 subject with the event of cerebrovascular accident (preferred term) that led to an ADO. Refer to sections 7.1.2 and Section 7.1.3 of this review.*

In light of the findings on weight gain over chronic treatment in MDD patients as noted by the sponsor, it is also noted by the undersigned reviewer that the incidence of ADOs due to weight gain was 2.7% (34 out of 1055 total subjects), while none of the 10055 subjects were ADOs due to weight loss. It appears that only 1 of these ADOs occurred during the short-term trials while the remainder occurred during the longterm safety study (by comparing results from Table 2.1.4.1 for the combined short-term trial dataset to result from table 2.1.4.2 on the combined All-Arip Treated MDD dataset in Module 2.7.4). Furthermore, the incidence of ADOs due to weight in other diagnostic groups in the All-Arip treated safety dataset was only 0 to 0.3%. However, see the previous discussion on the limitations with interpreting results of different diagnostic subgroups involving different trials using different study designs in this safety dataset.

While major limitations exist with interpreting the All-Arip results, the following results on the incidence of ADOs due to weight gain of the non-MDD diagnostic groups are notable since few if any subjects were reported as an ADO due this event in each diagnostic group despite the large total number of subjects in each group:

- *Bipolar Mania: 0/2008 subjects*
- *Bipolar Depression: 4/593 subjects (0.2%)*
- *Dementia: 0/894 subjects*
- *Schizophrenia: 6/8215 subjects (0.1%)*

The above results of other diagnostic groups are contrasted to an incidence of 2.7% (28/1055 subjects) in the MDD group.

Also refer to Sections 7.1.2-3 on ADOs and SAEs in this review.

7.1.8.4 Additional analyses and explorations

Refer to Section 7.1.4 of this review for a summary of results of the sponsor's special searches for AEs "by Organ System or Syndrome," and for any other special AE searches conducted for the purposes of this review.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

The 2 placebo controlled MDD studies had ECG assessments scheduled at screening, and at the end of each study phase (the 8-week Prospective ADT-placebo Phase and the 6-week DB phase, as shown in the "Flow Chart/Schedule of Events" table found in the CSR of each of these studies

(Study C...139 and Study C...163). A copy of this study flow chart table is provided in Appendix 10.1 of this review.

The sponsor indicates in Section 4.2.1.4 that they calculated QTc values (from which results shown in in-text sections of Module 2.7.4 were generated) by using a method “recommended by FDA’s Neuropharmacological Drugs Division.” A fractional exponent correction method was employed using baseline measurements from all Phase 2/3/4 trials (excluding dementia and pediatric trials). These data were used to determine a value of the exponent k in the equation of QT/RR^k that would yield a slope closest to 0.

The sponsor generally showed results on “measures of central tendency” using a mean change from baseline value for Phase C (the value at the end of Phase B) using the LOCF dataset. Results of the range of values were generally not found in the sponsor’s summary tables and summary of results, unless otherwise specified in this review (as found in in-text sections of Module 2.7.4). This review summarizes the results as found in Module 2.7.4 (in in-text sections).

Statistical analyses of the results of outliers or on “measures of central tendency” could generally not be found in the in-text sections of Module 2.7.4 unless otherwise specified in this review.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Refer to Sections 4 and 7.1 of this review. In accordance with the general guidelines specified in the Clinical Review Template in the MAPP subsections below are to include controlled trial results as well as longterm safety results, even though longterm results are not placebo controlled (as previously discussed in Section 7.1.7.2 of this review).

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

2-Phase III MDD Trial Dataset:

The following table summarizes the results (copied from Module 2.7.4).

Table 4.2.1.3: Mean and Median Change from Baseline for the Minimum, Maximum, and Endpoint On-Treatment ECG Value: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

ECG Parameter	Placebo			Aripiprazole		
	N	Mean	(SE) Median	N	Mean	(SE) Median
PR (msec)						
Maximum	335	1.09	(0.77) 0.00	352	0.80	(0.72) 0.00
Endpoint	325	0.90	(0.77) 0.00	341	0.61	(0.74) 0.00
QRS (msec)						
Maximum	335	-0.49	(0.43) 0.00	352	-0.03	(0.41) 0.00
Endpoint	325	-0.36	(0.44) 0.00	341	-0.20	(0.41) 0.00
RR (msec)						
Maximum	335	8.68	(6.02) 0.00	352	-18.09	(6.44) -20.00
Minimum	335	3.94	(5.86) 0.00	352	-20.60	(6.43) -20.00
Endpoint	325	6.66	(6.01) 0.00	341	-18.02	(6.46) -20.00
Heart Rate (bpm)						
Maximum	335	-0.17	(0.44) 0.00	352	1.74	(0.46) 1.00
Minimum	335	-0.44	(0.45) 0.00	352	1.53	(0.46) 1.00
Endpoint	325	-0.34	(0.44) 0.00	341	1.57	(0.47) 1.00

Reviewer Comment. *The mean and median decrease in RR interval in the Arip group is associated with a mean and median increase in heart rate in this group and is not observed in the placebo group. However, the magnitude of these changes in the Arip group is clinically unremarkable.*

The following table summarizes the incidence of outliers on QTc interval (copied from Table 4.2.1.4A in Module 2.7.4). Refer to Section 7.1.9.1 for the methods in calculating QTc interval values.

Analysis of QTc (Fractional Exponent Correction): Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

	Fractional Exponent Correction [a]		
	Placebo	Aripiprazole	p-value [e]
Sample Size [b]	325	341	
Mean Baseline QTcE (msec)	405.9	404.5	0.353
Mean Change at Endpoint (SE)	-0.23 (0.85)	-0.47 (0.83)	0.840
Mean Change at Max QTcE (SE)	-0.16 (0.83)	-0.23 (0.81)	0.964

- [a] QTcE=Fractional exponent correction (QT/RR*0.36).
- [b] Includes all patients with both a baseline and an endpoint measurement.
- [c] Includes all patients with an on-study measurement.
- [d] Includes all patients with both a baseline and an on-study measurement.
- [e] Comparisons of means were done by ANCOVA controlling for baseline QTc. Comparisons of proportions were done by Fisher's exact test.

The sponsor reports no statistical difference between the treatment groups on QTc for QTcE, QTcF and QTcB (ANCOVA controlling for baseline values was employed for treatment group comparisons).

The sponsor conducted additional analyzes on QTc interval data in which subjects of each treatment group were categorized into subgroups with respect to gender, age and “race,” respectively. These results are summarized in Section 7.1.9.4.

The All-Arip Treated MDD Dataset

Results on measures of “central tendency” on ECG and QT interval data could not be found in the in-text section 4 of Module 2.7.4 for the All-Arip MDD dataset.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Outlier criteria employed for ECG parameters are shown in Table 10.4.4 in Appendix 10.4 of this review.

2-Phase III MDD Trial Dataset:

The following table was copied from Module 2.7.4 of the submission.

Table 4.2.1.1: Incidence of Treatment-Emergent ECG Abnormalities of Potential Clinical Significance: Placebo Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

# of Patients in Safety Sample ECG Measurement	Placebo N = 366 Number of Patients with Potentially Clinically Relevant Abnormality(a) / Number Assessed (%)	Aripiprazole N = 371 Number of Patients with Potentially Clinically Relevant Abnormality(a) / Number Assessed (%)
Rate		
Tachycardia	0/ 343 (0.0)	0/ 357 (0.0)
Bradycardia	2/ 343 (0.6)	0/ 357 (0.0)
Rhythm		
Sinus tachycardia	0/ 343 (0.0)	0/ 357 (0.0)
Sinus bradycardia	2/ 343 (0.6)	0/ 357 (0.0)
Supravent. premature beat	0/ 343 (0.0)	1/ 357 (0.3)
Vent. premature beat	0/ 343 (0.0)	1/ 357 (0.3)
Supravent. tachycardia	0/ 343 (0.0)	0/ 357 (0.0)
Vent. tachycardia	0/ 343 (0.0)	0/ 357 (0.0)
Atrial fibrillation	0/ 343 (0.0)	0/ 357 (0.0)
A. fib with rapid vent. response	0/ 343 (0.0)	0/ 357 (0.0)
Atrial flutter	0/ 343 (0.0)	0/ 357 (0.0)
Conduction		
1st deg A-V block	0/ 343 (0.0)	0/ 357 (0.0)
2nd deg A-V block	0/ 343 (0.0)	0/ 357 (0.0)
3rd deg A-V block	0/ 343 (0.0)	0/ 357 (0.0)
LBB block	0/ 343 (0.0)	0/ 357 (0.0)
RBB block	0/ 343 (0.0)	0/ 357 (0.0)
Pre-excitation syndrome	0/ 343 (0.0)	0/ 357 (0.0)
Other intravent. conduction	1/ 343 (0.3)	0/ 357 (0.0)
Infarction		
Acute infarction	0/ 343 (0.0)	0/ 357 (0.0)
Subacute (recent) infarction	0/ 343 (0.0)	0/ 357 (0.0)
Old infarction	0/ 343 (0.0)	0/ 357 (0.0)
Myocardial ischemia	0/ 343 (0.0)	0/ 357 (0.0)
Symmetrical T-wave inversion	0/ 343 (0.0)	0/ 357 (0.0)

(a) Criteria developed from a previous BMS filing based upon discussions with the FDA Division of Neuropharmacological Drug Products (see Appendix 1.1E).

Reviewer Comment. The incidence in Arip subjects is 0% to almost all parameters with only 2 exceptions in which the incidence is only 0.3% (only 1/371 subjects).

The following table summarizes the incidence of outliers on QTc interval (copied from Table 4.2.1.4A in Module 2.7.4).

Analysis of QTc (Fractional Exponent Correction): Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

	Fractional Exponent Correction [a]		
	Placebo	Aripiprazole	p-value [e]
	Number of Patients/Number Assessed (%)		
>450 msec [c]	4/343 (1.2)	6/357 (1.7)	0.753
>500 msec [c]	0/343 (0.0)	0/357 (0.0)	1.000
≥30 msec increase [d]	10/335 (3.0)	14/352 (4.0)	0.537
≥60 msec increase [d]	0/335 (0.0)	1/352 (0.3)	1.000

- [a] QTcE=Fractional exponent correction (QT/RR**0.36).
 [b] Includes all patients with both a baseline and an endpoint measurement.
 [c] Includes all patients with an on-study measurement.
 [d] Includes all patients with both a baseline and an on-study measurement.
 [e] Comparisons of means were done by ANCOVA controlling for baseline QTc. Comparisons of proportions were done by Fisher's exact test.

The sponsor notes no statistically significant treatment group differences on the above parameters using a Fisher's exact test. No significant group differences were observed when using outlier criteria for QTcF or QTcB correction methods (using Fisher's exact test).

The sponsor conducted additional analyzes on QTc interval results in which subjects in each treatment group were categorized into subgroups with respect to gender, age and "race," respectively. These results are summarized in Section 7.1.9.4.

All-Arip Treated MDD Dataset

The incidence of outliers on ECG parameters in the MDD diagnostic group in the All-Arip Treated safety dataset was generally 0 to .4% (but did not exceed 0.7% for any given parameter) based on results of Table 4.2.2.1A in Module 2.7.4.

Results on outliers on QTc (fraction exponent correction method) showed an incidence of 2.1% for outliers in the over 450 msec category, 0% for the over 500 msec category, 6.5% in the ≥30 msec category and 0.1 % (1/968 subjects) in the ≥60 msec category.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

2-Phase III MDD Trial Dataset

In section 4.2.1.1 of the submission the sponsor notes that no ADOs occurred among Arip subjects due to an abnormal ECG finding.

A description of individual subjects with potentially clinically remarkable, clinically remarkable events or SAEs involving ECG abnormalities or cardiovascular system-related events could not be found in the in-text sections of Module 2.7.4 (in Sections 2 and 4 of the module).

Also refer to Sections 7.1.2-3 on ADOs and SAEs in this review.

All-Arip Treated MDD Dataset

The sponsor does not describe any subjects with clinically remarkable or potentially remarkable ECG related events (or ADOs or subjects with SAEs involving ECG related events), except for the single patient who was the only outlier in the ≥ 60 msec QTc category.

The subject showing an over 60 msec QTc change was subject CN138163-23-5282 who was reported as being asymptomatic. QTc values described by the sponsor did not exceed 434 msec. The following description provides more details as provided by the sponsor. This subject was 40 year old female who received concomitant escitalopram and other concomitant medications (glucosamine, ascorbic acid, acetaminophen and propranolol for akathisia). QTc values noted by the sponsor were 434 msec QTc value at the end of the study (Day 42). The pre-Arip treatment ECGs showed values of 423 msec at stud entry (Day -75) and 362 msec at randomization (Day1). The sponsor notes that this subject had no other potentially clinically relevant laboratory or vital sign abnormalities.

Also refer to Sections 7.1.2-3 on ADOs and SAEs in this review.

7.1.9.4 Additional analyses and explorations

Subgroup Analyses of QTc Interval Results for Gender, “Race,” and Age Subgroups in the 2-Phase III MDD Trial Dataset

The sponsor conducted additional analyses on QTc interval data in which subjects of each treatment group were categorized into subgroups with respect to gender, age and “race,” respectively.

The following tables were provided in Module 2.7.4 and summarize results on the basis of gender and age-group, respectively.

Analysis of QTc (Fractional Exponent Correction) by Gender: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

	Fractional Exponent Correction [a]			
	Placebo		Aripiprazole	
	Men	Women	Men	Women
Sample Size [b]	109	216	122	219
Mean Baseline QTcE (msec)	397.3	410.3	396.3	409.1
Mean Change at Endpoint (SE)	0.93 (1.39)	-0.86 (1.04)	-2.35 (1.31)	0.62 (1.03)
Mean Change at Max QTcE (SE)	0.81 (1.33)	-0.69 (1.03)	-2.19 (1.28)	0.84 (1.01)
	Number of Patients/Number Assessed (%)			
>450 msec [c]	1/116 (0.9)	3/227 (1.3)	0/128 (0.0)	6/229 (2.6)
>500 msec [c]	0/116 (0.0)	0/227 (0.0)	0/128 (0.0)	0/229 (0.0)
≥ 30 msec increase [d]	4/114 (3.5)	6/221 (2.7)	5/124 (4.0)	9/228 (3.9)
≥ 60 msec increase [d]	0/114 (0.0)	0/221 (0.0)	0/124 (0.0)	1/228 (0.4)

[a] QTcE=Fractional exponent correction (QT/RR^{0.36}).

[b] Includes all patients with both a baseline and an endpoint measurement.

[c] Includes all patients with an on-study measurement.

[d] Includes all patients with both a baseline and an on-study measurement.

Analysis of QTc (Fractional Exponent Correction) by Age: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

	Fractional Exponent Correction [a]			
	Placebo		Aripiprazole	
	18-50 years	>=51 years	18-50 years	>=51 years
Sample Size [b]	215	110	210	131
Mean Baseline QTcE (msec)	405.3	407.2	404.2	405.0
Mean Change at Endpoint (SE)	-0.04 (1.06)	-0.58 (1.42)	-0.41 (1.07)	-0.58 (1.30)
Mean Change at Max QTcE (SE)	-0.05 (1.04)	-0.42 (1.39)	-0.25 (1.05)	-0.22 (1.27)
	Number of Patients/Number Assessed (%)			
>450 msec [c]	1/231 (0.4)	3/112 (2.7)	4/222 (1.8)	2/135 (1.5)
>500 msec [c]	0/231 (0.0)	0/112 (0.0)	0/222 (0.0)	0/135 (0.0)
≥30 msec increase [d]	6/224 (2.7)	4/111 (3.6)	9/218 (4.1)	5/134 (3.7)
≥60 msec increase [d]	0/224 (0.0)	0/111 (0.0)	1/218 (0.5)	0/134 (0.0)

[a] QTcE=Fractional exponent correction (QT/RR**0.36).

[b] Includes all patients with both a baseline and an endpoint measurement.

[c] Includes all patients with an on-study measurement.

[d] Includes all patients with both a baseline and an on-study measurement.

Reviewer Comments. A statistical analyses of the above results could not be found in the in-text tables or sections of Module 2.7.4 that provided the above results. The following is a summary of observations noted by the undersigned reviewer based on numerical comparisons of the treatment subgroups on results shown the above tables.

As expected, women showed a greater incidence of high or increased QTc interval values for the over 450 msec and the over 30 msec increase categories. These parameters also showed a numerically greater incidence in Arip compared to placebo women subjects on these 2 parameters, that was generally not observed among men (although note that the sample sizes of women in each treatment group is larger than the treatment groups among men). The incidence among women for QTc of >500 msec and for ≥30 msec increase categories is 2.6% and 3.9%, respectively in Arip subjects compared to only 1.3% and 2.7%, respectively in placebo women subjects.

Also note the greatest numerical incidence for high or increased QTc interval values among 18-50 year old Arip treated subjects for values of >450msec and ≥30 msec increased values which showed an incidence of 1.8% and 4.1%, respectively compared to an incidence of 0.4% and 2.7%, respectively among placebo subjects in this age-group. Failure to show similar treatment group differences among the over 50 year old age-group may be due to greater variance of QTc values within a given individual upon retesting or over time and between subjects (e.g. older subjects may show greater fluctuations in QTc interval values than younger adults).

The descriptive statistical results did not yield similar gender and age-group differences but generally showed little to no mean changes in values. Furthermore, the results of outliers on over 500 msec values and over 60 msec increases showed only 1 single subject as an outlier (a women who was in the 18-50 year old age-group) based on results from the above tables.

Refer to the last section of this review for additional comments and recommendations.

The results from the sponsor's analysis of "race" by treatment subgroups is not discussed in this review since sample sizes in the non-"white" subgroups (which were "black" and "other" subgroups) were insufficient to yield interpretable results (sample sizes ranged from 8 to 19 subjects in a given non-"white" subgroup).

Subgroup Analyses of QTc Results for Each DB Treatment Group for Each ADT Subgroup

The sponsor also analyzed QTc results (using the fractional exponent correction method) for each ADT subgroup in the placebo controlled, short-term MDD trial dataset (Studies C..139 and C..163, combined). No statistically significant group differences were observed between Arip and Placebo groups on each QTc dependent variable within each ADT subgroup. The following paragraphs provide more details.

Appendices 4.2.1.4A-E showed results on several dependent variables for each DB treatment group within each ADT subgroup as follows:

- The mean change of QTc from baseline (at Phase B endpoint) to each of the following time-points in Phase C:
 - To endpoint
 - To the maximum QTc value for each given subject
- The incidence of outliers was also provided for each QTc outlier category (<450 msec, >500 msec, ≥ 30 msec increase, and ≥ 60 msec increase categories).

Because the interpretation of the results is influenced by sample sizes which in some subgroups were small, the following summarizes the sample sizes of each DB group within each ADT subgroups:

- The largest sample sizes were in the SCT and Ven subgroups (approximately 90-100 subjects in each DB treatment group of each of these ADT subgroups)
- The smallest sample sizes were in the paroxetine subgroup (26 Placebo subjects and 29 Arip subjects)
- The Fluoxetine and Sertraline subgroups were intermediate in size (approximately 47 to 64 subjects/DB treatment group for each these 2 ADT subgroups, respectively).

No statistically significant group differences were observed between Arip and placebo groups for each of the ADT treatment groups on each of the above dependent variables (using Fishers Exact test for comparisons of proportions and using ANCOVA controlling for baseline QTc for comparisons of means).

Refer to Section 7.1.4 of this review for a summary of results of the sponsor's special searches for AEs "by Organ System or Syndrome," and for any other special AE searches conducted for the purposes of this review.

7.1.10 Immunogenicity

Abilify is not a therapeutic protein.

7.1.11 Human Carcinogenicity

Human carcinogenicity was not systematically evaluated in clinical trials included in this NDA submission and MDD trials were short-term trial, except for one ongoing trial that is an open-label 52-week Study C...164. Appendix 2.1B-1A in Module 2.7.4 showing the incidence of Treatment Emergent AEs for the All Arip safety dataset for each patient diagnostic subgroup (MDD, Bipolar-mania, Bipolar-depression, Dementia, and Schizophrenia) and for all subjects combined. The table shows the following results under the Neoplasms...and unspecified” category (copied from the sponsor’s table).

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Incidence of Treatment-Emergent AEs: All Aripiprazole Data Set by Indication and Overall, Safety Sample

	MDD	BIPOLAR- MANIA	BIPOLAR- DEPRESSION	DEMENTIA	SCHIZO	ALL ARI*
NUMBER OF PATIENTS SCREENED FOR AES	1055	2008	593	894	8215	12925
NUMBER OF MALE PATIENTS	358	875	234	222	5092	6896
NUMBER OF FEMALE PATIENTS	697	1133	359	672	3123	6029
NUMBER OF PATIENTS WITH >=1 AES	961(91.1)	1607(80.0)	502(84.7)	849(95.0)	6309(76.8)	10372(80.2)
SYSTEM ORGAN CLASS						
PREFERRED TERM	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)	INCIDENCE (%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	9(0.9)	5(0.2)	3(0.5)	27(3.0)	54(0.7)	99(0.8)
BASAL CELL CARCINOMA	1(0.1)	1(<0.1)	0	4(0.4)	4(<0.1)	10(0.1)
SKIN PAPILLOMA	0	1(<0.1)	0	3(0.3)	6(0.1)	10(0.1)
F UTERINE LEIOMYOMA	0	0	1(0.3)	0	3(0.1)	4(0.1)
F OVARIAN CANCER	1(0.1)	0	0	0	2(0.1)	3(<0.1)
LIPOMA	1(0.1)	0	0	1(0.1)	3(<0.1)	5(<0.1)
MELANOCYTIC NAEVUS	0	0	0	0	4(<0.1)	4(<0.1)
SQUAMOUS CELL CARCINOMA	0	0	1(0.2)	3(0.3)	0	4(<0.1)
M PROSTATE CANCER	1(0.3)	0	0	1(0.5)	0	2(<0.1)
BREAST CANCER	0	1(<0.1)	0	1(0.1)	1(<0.1)	3(<0.1)
NEOPLASM SKIN	0	0	0	0	3(<0.1)	3(<0.1)
SKIN CANCER	0	0	1(0.2)	0	2(<0.1)	3(<0.1)
F CERVIX CARCINOMA STAGE 0	0	0	0	0	1(<0.1)	1(<0.1)
F OVARIAN NEOPLASM	0	0	0	0	1(<0.1)	1(<0.1)
ACROCHORDON	0	0	0	0	2(<0.1)	2(<0.1)
COLON NEOPLASM	0	0	0	0	2(<0.1)	2(<0.1)
FIBROMA	0	0	0	0	2(<0.1)	2(<0.1)
HEPATIC NEOPLASM	0	0	0	2(0.2)	0	2(<0.1)
LUNG NEOPLASM	1(0.1)	0	0	1(0.1)	0	2(<0.1)
LUNG NEOPLASM MALIGNANT	0	0	0	0	2(<0.1)	2(<0.1)
METASTASES TO CENTRAL NERVOUS SYSTEM	0	0	0	1(0.1)	1(<0.1)	2(<0.1)
OCULAR NEOPLASM	0	0	0	1(0.1)	1(<0.1)	2(<0.1)
SEBORRHOEIC KERATOSIS	0	0	0	2(0.2)	0	2(<0.1)
THYROID NEOPLASM	1(0.1)	0	0	0	0	2(<0.1)
M PROSTATIC ADENOMA	0	1(0.1)	0	0	0	1(<0.1)
M TESTICULAR NEOPLASM	0	0	0	0	1(<0.1)	1(<0.1)
M TESTIS CANCER	0	0	0	0	1(<0.1)	1(<0.1)
ABDOMINAL NEOPLASM	0	0	0	0	1(<0.1)	1(<0.1)
ADENOCARCINOMA	0	0	0	1(0.1)	0	1(<0.1)
ADENOMA BENIGN	0	0	0	0	1(<0.1)	1(<0.1)
BENIGN NEOPLASM	0	0	0	0	1(<0.1)	1(<0.1)
BLADDER CANCER	0	0	0	0	1(<0.1)	1(<0.1)
BLADDER NEOPLASM	0	0	0	0	1(<0.1)	1(<0.1)
BOWEN'S DISEASE	1(0.1)	0	0	0	0	1(<0.1)
BRAIN NEOPLASM	0	0	0	0	1(<0.1)	1(<0.1)
CARCINOID TUMOUR OF THE GASTROINTESTINAL TRACT	0	0	0	0	1(<0.1)	1(<0.1)
CHONDROMA	0	0	0	0	1(<0.1)	1(<0.1)
COLON CANCER	0	0	0	1(0.1)	0	1(<0.1)
COLON CANCER STAGE III	0	0	0	0	1(<0.1)	1(<0.1)
GASTROINTESTINAL CARCINOMA	0	0	0	1(0.1)	0	1(<0.1)
HEMANGIOMA	0	0	0	0	1(<0.1)	1(<0.1)
LEIOMYOMA	0	1(<0.1)	0	0	0	1(<0.1)

LEUKAEMIA	0	0	0	0	1(<0.1)	1(<0.1)
LYMPHOMA	0	0	0	1(0.1)	0	1(<0.1)
MALIGNANT MELANOMA	0	0	0	0	1(<0.1)	1(<0.1)
MALIGNANT PALATE NEOPLASM	0	0	0	0	1(<0.1)	1(<0.1)
METASTASES TO LIVER	0	0	0	0	1(<0.1)	1(<0.1)
METASTASES TO LUNG	0	0	0	1(0.1)	0	1(<0.1)
METASTASIS	0	0	0	0	1(<0.1)	1(<0.1)
METASTATIC MALIGNANT MELANOMA	0	0	0	0	1(<0.1)	1(<0.1)
NEOPLASM	0	0	0	1(0.1)	0	1(<0.1)
NEOPLASM MALIGNANT	0	0	0	1(0.1)	0	1(<0.1)
NON-SMALL CELL LUNG CANCER	1(0.1)	0	0	0	0	1(<0.1)
ORAL NEOPLASM	0	0	0	0	1(<0.1)	1(<0.1)
PANCREATIC CARCINOMA	0	0	0	0	1(<0.1)	1(<0.1)
PANCREATIC CARCINOMA METASTATIC	0	0	0	1(0.1)	0	1(<0.1)
RETINAL NEOPLASM	1(0.1)	0	0	0	1(<0.1)	1(<0.1)
SMALL CELL CARCINOMA	1(0.1)	0	0	0	0	1(<0.1)
SQUAMOUS CELL CARCINOMA OF SKIN	0	0	1(0.2)	0	0	1(<0.1)

(M) Incidence of AE adjusted for males (F) Incidence of AE adjusted for females
 *:Includes all indications: bipolar depression, bipolar mania, dementia, schizophrenia, Psychosis associated with Parkinson's Disease, MDD, alcoholism.
 MedDRA Version: 9.1

Reviewer Comments. *It is difficult to interpret results of multiple pooled studies using different study designs and treatment regimens of Arip. However, the results fail to show evidence for an unexpected cancer related signal in that the incidence of events are generally expected for the general population or for the given diagnostic subgroup of patients. The dementia subgroup showed the highest incidence but the incidence shown above is not unexpected since the majority of patients with dementia are generally elderly patients. The results also fail to show evidence for an unexpected cluster of events within a given Preferred Term category.*

7.1.12 Special Safety Studies

Module 2.7.4 does not describe any special safety studies. 2 ADT-Arip interaction Phase I studies were conducted and safety results from these trials was included in previous sections of this review.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Abilify has not been systematically evaluated for abuse liability or physical dependence (withdrawal or rebound), as described in approved labeling and in trials of the current NDA submission. Section 5.6 of Module 2.7.4 indicates that a search was conducted in the All-Arip Treated safety dataset for AEs suggestive of abuse (for events coded to the terms of drug dependence and drug withdrawal syndrome). Arip was not the drug that was found to be associated with these events based on a review conducted by the cases that were revealed from this search, according to the sponsor.

7.1.14 Human Reproduction and Pregnancy Data

Potential Arip effects on reproduction and pregnancy in humans was not systematically evaluated. Section 5.4 of Module 2.7.4 includes a summary of a search of the Phase II-IV clinical study database of Arip treated subjects (since the last Arip SUR dated October 2005). Search methods are described. A total of 11 cases of confirmed pregnancies were identified in which these cases are summarized as having one of the following outcomes: spontaneous abortion (2 subjects in which one subject only received Arip for 1 day and the other subject received study drug for 3 weeks when each tested positive for pregnancy), induced abortion (5 subjects), outcome unknown (3 subjects), delivered a normal healthy infant (1).

Reviewer Comment. *The above results do not suggest any new clinically remarkable safety signal that should be described in labeling.*

7.1.15 Assessment of Effect on Growth

The MDD trials were conducted in adults. Therefore, potential for effects of Arip on growth were not examined.

7.1.16 Overdose Experience

The sponsor noted that their review of postmarketing safety reports included a reports of overdose. Refer to Section 7.1.17 for postmarketing safety information in which specific cases of overdose or a summary of any new remarkable findings relevant to overdose were not found in Section 6 of Module 2.7.4.

In Section 5.5 of Module 2.7.4 describes results of a search conducted by the sponsor of their Phase II-IV database for all patients since the last Arip SUR in October 2005. They searched for each of the following types of reports (the number of cases revealed for each search is specified in parenthesis):

- Cases with the reported AE term of overdose (8 cases)
- Cases reported to have had a daily dose of over 60 mg of Arip (14 cases)

These 2 search results were reconciled and BMS reviewed additional information on 6 of the cases. These cases are summarized in Section 5.5 of Module 2.7.4. These case summaries generally briefly describe the psychiatric diagnosis, age and sex of the patient and some information on the dose or estimated dose and if the overdose involved additional drugs and generally indicated that each patient was treated in the emergency room or required a brief period of hospitalization (or was transferred from the emergency room to a local mental health resource center). In some cases the subject was specified as completing the study while in other cases the subject was withdrawn from the study. Signs, symptoms and clinical assessment results could not be found in the case summaries. Any description of a subject developing any type of irreversible sequelae or any description of any new and clinical remarkable safety findings regarding overdose could not be found in the sponsor's case summaries of these 6 patients.

7.1.17 Postmarketing Experience

Arip has not been marketed for treatment of patients with MDD.

As previously described in Section 2.6 of this review Arip was first approved for the market in 2002 for the indication of schizophrenia and subsequently for bipolar I disorder.

Section 6 of Module 2.7.4 provides information on worldwide experience and on postmarketing safety surveillance. A summary of safety observations or potentially remarkable cases could not be found in this section of the submission. The sponsor lists past safety related topics of “Cumulative Review” in past Periodic Safety Update Reports (PSURs) previously submitted under the NDA (up to their specified cut-off date). The sponsor lists past Periodic Adverse Drug Reports (PSURs) submitted under the NDA, as well (as of the specified cut-off date). The sponsor provides a list of safety topics in past PSURs and updated in the CCSI (as specified on page 252 of Module 2.7.4. A summary of findings cannot be found in Section 6 of Module 2.7.4. The sponsor indicates that since the first approval of Arip in July 17, 2002, the benefit to risk ratio of Arip “remains favorable” and that the accumulated postmarketing information “has been reflected in the Company Core Safety Information, the Summary of Product Characteristics and in the indicating US Prescribing Information.” The sponsor states that their review of Arip AE data from spontaneous postmarketing reports and from clinical trials (as provided in their Periodic Adverse Drug Experience Reports) “indicated an overall benefit risk profile similar to and consistent with the previously established clinical trial experience as described in the exiting USPI for Abilify.®”

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Reviewer Comment. *Abilify is approved for multiple psychiatric indications and since there is extensive human experience that has included populations that commonly receive concomitant ADT such as in patients with schizoaffective disorders and other patient populations (either under the IND, in past NDAs or at postmarketing). This experience together with MDD trial results in this NDA is adequate for the purpose of this review.*

7.2.1.1 Study type and design/patient enumeration

See section 4.2 of this review for a table that provides information on study type, design and sample sizes. For more details on the study design of efficacy pivotal MDD studies see Section 6 and for more details on Phase I study design (for the 2 drug-drug interaction studies) see Sections 5.1 and 7.1 of this review.

7.2.1.2 Demographics

Refer to Appendices 10.1 and 10.3 for a description of the demographic features of the study population for the pivotal efficacy Studies -139 and -163

Reviewer Comment: *Demographic features of the above subjects are generally comparable to the MDD population.*

7.2.1.3 Extent of exposure (dose/duration)

The following tables show exposure results (these tables were provided in Module 2.7.4 or were extracted from the sponsor's tables).

Table 1.2.1.1A: Number and Percentage of Patients Who Received Study Therapy by Study Interval: Placebo Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

Study Interval (Days)	Placebo		Aripiprazole	
	N	(%)	N	(%)
1-7	366	(100.0)	371	(100.0)
8-14	356	(97.3)	363	(97.8)
15-21	342	(93.4)	350	(94.3)
22-28	329	(89.9)	341	(91.9)
29-35	327	(89.3)	334	(90.0)
36-42	317	(86.6)	322	(86.8)
> 42	103	(28.1)	121	(32.6)

Table 1.2.1.1B: Number and Percentage of Patients Who Received Study Therapy During Randomization (Phase C) by ADT and Study Interval: Placebo Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

Study Interval (Days)	Escitalopram		Fluoxetine		Paroxetine		Sertraline		Venlafaxine XR	
	Placebo	Aripiprazole	Placebo	Aripiprazole	Placebo	Aripiprazole	Placebo	Aripiprazole	Placebo	Aripiprazole
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
1-7	102 (100.0)	118 (100.0)	54 (100.0)	53 (100.0)	28 (100.0)	31 (100.0)	77 (100.0)	69 (100.0)	105 (100.0)	100 (100.0)
8-14	100 (98.0)	114 (96.6)	51 (94.4)	52 (98.1)	27 (96.4)	30 (96.8)	74 (96.1)	68 (98.6)	104 (99.0)	99 (99.0)
15-21	96 (94.1)	111 (94.1)	51 (94.4)	48 (90.6)	27 (96.4)	29 (93.5)	66 (85.7)	66 (95.7)	102 (97.1)	96 (96.0)
22-28	94 (92.2)	110 (93.2)	49 (90.7)	48 (90.6)	25 (89.3)	27 (87.1)	64 (83.1)	63 (91.3)	97 (92.4)	93 (93.0)
29-35	94 (92.2)	108 (91.5)	48 (88.9)	48 (90.6)	25 (89.3)	27 (87.1)	64 (83.1)	60 (87.0)	96 (91.4)	91 (91.0)
36-42	91 (89.2)	102 (86.4)	46 (85.2)	48 (90.6)	25 (89.3)	27 (87.1)	59 (76.6)	57 (82.6)	96 (91.4)	88 (88.0)
> 42	28 (27.5)	37 (31.4)	16 (29.6)	18 (34.0)	9 (32.1)	11 (35.5)	19 (24.7)	25 (36.2)	31 (29.5)	30 (30.0)

Table 1.2.1.1C: Number and Percentage of Patients Who Received Aripiprazole by Overall Mean Dose Category and Duration of Therapy: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

Total Dur. of Trt (days)	Unavailable	2mg		5mg		10mg		15mg		20mg (a)		Total		
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)			
36-42	0	7	(1.9)	80	(21.6)	92	(24.8)	22	(5.9)	0		201	(54.2)	
>42	0	1	(0.3)	44	(11.9)	62	(16.7)	14	(3.8)	0		121	(32.6)	
Total	1	(0.3)	11	(3.0)	158	(42.6)	162	(43.7)	39	(10.5)	0		371	(100.0)

2 mg = ≤ 3.5 mg; 5 mg = > 3.5 mg - ≤ 7.5 mg; 10 mg = > 7.5 - ≤ 12.5 mg; 15 mg = > 12.5 - ≤ 17.5 mg; 20 mg = > 17.5 mg.
 (a) Maximum dose for patients on fluoxetine or paroxetine was 15 mg.

Mean ADT doses (in each of the placebo and Arip groups) shown in Table 1.2.1.1D of Module 2.7.4 were as follows (in the 2 pivotal efficacy trials, combined):

- Escitalopram: Approximately 19 mg/ treatment group
- Fluoxetine: Approximately 38 mg/ treatment group
- Paroxetine: Approximately 47 mg/ treatment group

- Sertraline: Approximately 141 mg/ treatment group
- Venlafaxine: Approximately 213 mg/ treatment group

The ranges of doses shown in Table 1.2.1.1D are generally consistent with study methods and are adequate.

The following tables (provided or extracted from tables in Section 1.2.2 of Module 2.7.4) summarize longer-term OL exposure in MDD patients who were also receiving adjunctive ADT treatment.

Table 1.2.2.1A: Cumulative Number of Patients Who Received Aripiprazole, by Duration of Exposure: All Aripiprazole Dataset by Indication and Overall, Safety Sample

Patient Exposure Years Duration of Treatment	MDD (a)	
	N	(%)
>= 1 day	1055	(100.0)
>= 21 days	976	(92.5)
>= 42 days	873	(82.7)
>= 90 days	630	(59.7)
>=180 days	426	(40.4)
>=270 days	264	(25.0)
>=360 days	153	(14.5)
>=540 days	2	(0.2)
>=720 days	0	(0.0)

Table 1.2.2.1B: Number and Percentage of Patients Who Received Aripiprazole by Overall Mean Dose Category and Duration of Therapy: All Aripiprazole-Treated Patients in Major Depressive Disorder Studies, Safety Sample

Total Dur. of Trt (days)	Unavailable N (%)	2mg		5mg		10mg		15mg		20mg (a)		Total N (%)
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
1-20	6 (0.6)	5 (0.5)	63 (6.0)	4 (0.4)	1 (0.1)	0		79 (7.5)				
21-41	0	13 (1.2)	50 (4.7)	37 (3.5)	3 (0.3)	0		103 (9.8)				
42-89	0	16 (1.5)	115 (10.9)	97 (9.2)	15 (1.4)	0		243 (23.0)				
90-119	0	6 (0.6)	29 (2.7)	48 (4.5)	9 (0.9)	2 (0.2)		94 (8.9)				
120-149	0	4 (0.4)	30 (2.8)	32 (3.0)	12 (1.1)	3 (0.3)		81 (7.7)				
150-179	0	4 (0.4)	10 (0.9)	8 (0.8)	6 (0.6)	1 (0.1)		29 (2.7)				
180-269	0	10 (0.9)	57 (5.4)	68 (6.4)	20 (1.9)	7 (0.7)		162 (15.4)				
270-359	0	7 (0.7)	31 (2.9)	46 (4.4)	20 (1.9)	7 (0.7)		111 (10.5)				
>=360	0	11 (1.0)	40 (3.8)	69 (6.5)	25 (2.4)	8 (0.8)		153 (14.5)				
Total	6 (0.6)	76 (7.2)	425 (40.3)	409 (38.8)	111 (10.5)	28 (2.7)		1055 (100.0)				

2 mg = <= 3.5 mg; 5 mg = > 3.5 mg - <= 7.5 mg; 10 mg = > 7.5 - <= 12.5 mg; 15 mg = > 12.5 - <= 17.5 mg; 20 mg = > 17.5 mg.

(a) Maximum dose for patients on fluoxetine or paroxetine was 15 mg.

Table 1.1B: Tabular Listing of Ongoing Major Depressive Disorder Studies

Study Number	Number of Study Centers ^a / Location/ Study Dates	Design	Study Objective	Study Drugs	Enrolled or Randomized/ Treated	Gender/ Mean Age (Range)
Ongoing Open-label 52-Week Study						
CN138164	66 US centers 9/04 - present	Phase 3: Open-label study to assess long-term safety and tolerability of adjunctive aripiprazole to a marketed ADT. Patients entered from CN138139 and CN138163, or entered de novo.	Safety and Tolerability	Aripiprazole (2-30mg) ^b + ADT ADTs (% aripiprazole-treated): escitalopram sertraline venlafaxine XR ^f fluoxetine paroxetine ^c mirtazapine bupropion not available ^d	930/930 ^e 28% 17% 24% 15% 10% < 1% 5% 1%	314 Males 616 Femal 45.9 years (19-77)

Note: ADT = antidepressant therapy; AE = adverse event; EPS = extrapyramidal symptom; SAS = Simpson-A Movement Scale; ECG = electrocardiogram; SFI = Massachusetts General Hospital Sexual Functioning Inventory

a Centers that randomized patients.
 b Aripiprazole dose range of 2 to 15 mg used in combination with ADTs of fluoxetine and paroxetine.
 c Paroxetine CR and paroxetine (immediate-release formulation) were both allowed.
 d Actual ADT received was not available in the database for some patients at the time of data cutoff.
 e Patients were enrolled from CN138139 and CN138163 and were not randomized.
 f Venlafaxine XR and venlafaxine (immediate release formulation) were also allowed.

Reviewer Comments. Refer to additional tables in section 1.2 of Module 2.7.4.

Note the following regarding the 2 short-term pivotal efficacy trials (-139 and -163)

- The maximum dose of Arip permitted in the fluoxetine and paroxetine groups was 15 mg daily.
- That one of the pivotal trials only used the Paroxetine CR and not the immediate release (IR) formulation (due to unexpected non-safety related reasons, based on that described by the sponsor as either found in the CSR or in Module 2.7.4).
- Venlafaxine XR, not IR was used.
- Subjects receiving venlafaxine were to take study drug with food, while other subjects in these trials were to take study drug with or without food.

The longer-term trial -164 also only allowed up to 15 mg daily of Arip in the above specified SSRI ADT groups, but the IR formulations of venlafaxine and paroxetine were permitted in addition to allowing the XR and CR formulations, respectively. However, note that sample sizes of subjects receiving venlafaxine and paroxetine (and subjects receiving non-SSRI ADTs) were small. Therefore, few subjects would be expected to have received the IR formulations of these 2 drugs.

In light of the above observations, see Section 8.1 and the last section of this review for details and refer to Section 9 for additional comments and recommendations.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No other studies were found in Module 2.7.4.

7.2.2.2 Postmarketing experience

Refer to Section 7.1.16 for this topic.

7.2.2.3 Literature

Section 8.6 summarizes the results of the search. This section discusses the methods of the search. The Otsuka Pharmaceutical Company (OPC) and Bristol-Myers Squibb (BMS) conducted searches involving 11 databases (for online bibliographic references) and a medical scientific literature database in Japan. The BMS search (in which 11 databases were searched) is noted to have been a basic index search (rather than a full text search) since the databases were not full text databases. These searches were conducted using the various search terms for the drug name, brand names, codes and Chem. Abs. Registry numbers. Additional searches were conducted on other databases and using other or additional search terms as described in the literature.pdf in Item 8 of the submission.

Curriculum vitae were included for individuals who conducted the searches and who reviewed the search results.

Section 8.6 provides the results of this search.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience is adequate and as described in related sections of this review (e.g. refer to Section 7.2.1 of this review), from a clinical perspective and for the purposes of this NDA.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable to this NDA since Abilify is already approved.

7.2.5 Adequacy of Routine Clinical Testing

See previous subsections of Section 7.1 of this review for comments relevant to potential limitations with clinical parameter results.

Overall, routine clinical testing was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See Section 5.1 of this review for special ADT-Arip interaction studies and a summary of results. The overall safety results in Section 7 do not reveal an ADT-Arip interaction effect on safety, from a clinical perspective. However, OCPB input is recommended (review is pending at the time of this writing).

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The studies conducted are adequate for the purposes of this NDA.

7.2.8 Assessment of Quality and Completeness of Data

See Sections 4.3 and 4.4 of this review. Based on the observations described in these previous sections and based on results found in Module 2.7.4 (as described in Section 7.1 of this review). Although minor problems, inconsistencies or other relevant aspects of the data are noted in the previous sections, no major issues were identified relevant to the quality and completeness of the data. However, DSI input is recommended which remains pending at the time of this writing.

7.2.9 Additional Submissions, Including Safety Update

A Safety update report was not submitted. See Section 9 of this review regarding inquiries regarding protocol deviations and information provided by the sponsor upon request.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

See previous sections of this review and the final section of this review for any major or potential major issues.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

It was appropriate to pool the 2 MDD efficacy trials for integrated safety results from this dataset and for subgroup analyses on efficacy results. It was appropriate to provide efficacy results for each of these 2 trials separately (as found in CSRs). See Section 4.3 and section 7.1 for additional reviewer comments discussing limitations relevant to the sponsor's approach to pooling studies.

7.4.1.2 Combining data

See the previous section.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Placebo controlled Phase III MDD trials employed a flexible dose design, such that dose-dependent effects were not systematically evaluated and possible exploratory analyses that might be considered would yield limited and difficult to interpret results.

7.4.2.2 Explorations for time dependency for adverse findings

Refer to Section 7.1.5.6.

7.4.2.3 Explorations for drug-demographic interactions

Refer to Section 7.1.5.6.

7.4.2.4 Explorations for drug-disease interactions

No studies were conducted to examine drug-disease interactions.

7.4.2.5 Explorations for drug-drug interactions

See Section 7.1.5.6 and other sections of this review (Section 5.1 and Sections on deaths, SAEs and ADOs in Phase I drug interaction studies) for ADT-Arip interactions for ADTs employed in the trials conducted for this NDA. No other studies on drug-drug interactions were found in the submission. Refer to Section 9 of this review for any major issues, from a clinical perspective. Input from OCPB is also recommended (review is pending at the time of this writing.)

7.4.3 Causality Determination

It is difficult to determine causality of Arip treatment based on preliminary exploratory analyses of data for revealing potential predictors.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

See Section 6 and appendix 10.1 of this review for the dosing regimen used for the pivotal MDD trials (-139 and -163).

See Section 7.2.1 on adequacy of exposure and dose-levels employed and note reviewer comments in Section 7.2.1.3.

See the last section of this review for additional comments and recommendations relevant to proposed labeling.

8.2 Drug-Drug Interactions

The short-term Phase 3 Studies -139 and -163 used a maximum daily-dose-level of 15 mg for paroxetine and fluoxetine (2D6 inhibitors), while other ADT groups were allowed a daily dose of up to 20 mg. The other ADTs included sertraline, escitalopram and venlafaxine.

Only the CR and XR formulations of the paroxetine and venlafaxine groups, respectively, were employed in the above pivotal short-term trials. It is not clear how many subjects received the immediate release formulations for these two ADTs in the ongoing longer-term MDD Arip-ADT adjunctive treatment Study -164 (refer to section 7.2.1.3 of this review for details). Exposure to other approved ADTs (not used in the short-term trials) was limited to only a small number of subjects in the longer term trial (as described in detail in Section 7.2.1.3 of this review).

Safety results on AEs and possibly some ADOs (as discussed in Section 7 of this review) may suggest an exaggerated (more robust) adverse effect with ADT-Arip combination treatment on AEs expected for either drug along. However, the overall safety profile (the nature of the AEs) was generally expected for ADT and/or Arip treatment. The results on SAEs did not suggest drug-drug interactions on these more serious events.

Section 9 of this review provides an outline of the key safety findings with ADT and Arip combined treatment and provides recommendations.

It is also important to note the extensive past human experience with Abilify in other psychiatric populations that commonly use concomitant ADTs (as previously noted in Section 7.2.1 of this review).

Phase I studies (-462 and -463) were conducted to examine venlafaxine XR-Arip and escitalopram-Arip interaction effects on PK in generally young healthy adults. According to the sponsor no meaningful changes in PK were observed in either of these studies and that no dose adjustment of Arip is indicated when combining treatment with these drugs. Population PK results from the short-term MDD trials, -139 and -163 also failed to reveal any drug-drug interactions on PK, according to the sponsor. OCPB input on these results remains pending at the time of this writing.

See the last section of this review for additional comments and recommendations.

8.3 Special Populations

Since Abilify and ADTs used in the MDD trials are approved drugs the sponsor did not conduct any special population studies. Elderly (over 65 year old) MDD patients were excluded from at least the short-term pivotal MDD trials (it is not clear if any subjects were elderly in the 1 OL longterm study -164, although that subject include subjects from the short-term MDD trials, as well as other subjects). See the next section regarding the pediatric population.

8.4 Pediatrics

Section 5.10 of Module 2.7.4 specifies that data from adolescent schizophrenia trials were submitted as a supplemental NDA (sNDA) on 3/23/07 and from pediatric Bipolar mania trials will be submitted as a sNDA in August 2007.

The sponsor indicates no plans for conducting pediatric MDD trials.

***Reviewer Comments.** It is recommended that the sponsor be advised to submit their rationale for not planning to conduct pediatric MDD trials. A deferral from conducting pediatric trials is reasonable at this time, as more knowledge on safety can be gained from a review of results from pediatric Bipolar trials and pediatric schizophrenia trials in the sponsor's sNDA submissions for these other pediatric indications.*

(b) (4)



8.5 Advisory Committee Meeting

An Advisory committee meeting was not held regarding the NDA submission.

8.6 Literature Review

OPC and BMS searched various databases of the medical and scientific literature using methods described in Section 7.2.2.3 of this review. The search results were reviewed by Shahid Ashfaq, MD, Robert Berman, MD and Vlad Cloric, MD who certified that efficacy and/or safety findings based on their review of the literature did not alter or adversely affect conclusions about efficacy and/or safety in the NDA submission (as specified in Item 8 literature.pdf file of the submission).

A summary of the search results could not be found in the literature.pdf file of submission. However, Dr. Berman's certification includes a reference to Section 1.2 of the Clinical Overview section of the submission for a reference to relevant publications for the indication of (b) (4). This section of the submission briefly summarizes past studies of atypical antipsychotic drugs and studies using Arip as adjunctive treatment with ADT in patients with non-psychotic MDD or patients with treatment resistant MDD. The adjunctive Arip treatment resistant studies were either OL prospective or retrospective studies showing that 63 out of 107 patients achieved a response (based on specified criteria). The results of these past studies provided an empirical basis for developing Arip as an adjunctive treatment to ADT in treatment resistant patients (or partial responders).

Section 1.2 of the Clinical Overview also indicates that AEs observed among the 107 patients receiving OL Arip adjunctive treatment (described above) included restlessness, akathisia, nausea, insomnia, sedation, poor concentration and weight gain.

8.7 Postmarketing Risk Management Plan

A postmarketing risk management plan cannot be found in the submission.

8.8 Other Relevant Materials

No other relevant materials were found in the submission.

9 OVERALL ASSESSMENT

9.1 Conclusions

From a clinical perspective and pending input from other disciplines:

- The two pivotal Phase 3 trials are positive for efficacy and
- Aripiprazole (Arip) is adequately safe for adjunctive treatment of Major Depressive disorder (for adjunctive treatment in patients receiving concomitant antidepressant medications).

9.2 Recommendation on Regulatory Action

An Approvable Action is recommended on this NDA.

Specific issues are raised below can be adequately addressed in labeling (Section 9.4 of this review provides key labeling recommendations). Postmarketing risk management activities are also recommended in Section 9.3 of this review as additional approaches to consider for resolving some of the key issues outlined below.

Input from other disciplines is also recommended (OCPB, Biometrics and DSI).

Before considering a final approval action on this NDA it is recommended that issues and labeling are adequately resolved (as recommended below and in subsections that follow).

The Proposed Indication of (b) (4) Adjunctive Treatment of MDD

Patients in the MDD trials were partial responders to ADT and were receiving concomitant ADT treatment.

Recommendation. It is recommended that the specific text for the approved indication for labeling be “adjunctive treatment of MDD.” This specific text is sufficient rather than having to specify partial responders in “Indications and Usage” for reasons that follow. The claim adjunctive treatment is consistent with a patient population that has not adequately responded to ADT monotherapy. Furthermore, Section 14 of labeling provides more detailed information on the pivotal trial design, specifying that partial responders were examined for efficacy. See additional recommendations relevant to labeling in Section 9.4 of this review. These additional recommendations pertain to the proposed titles and text for Sections 1.3 and 2.3 that specify an efficacy claim of “adjunctive treatment of MDD.”

(b) (4)

(b) (4)



ADT-Arip Interaction effects on Safety and PK

Phase 3 Major Depressive disorder (MDD) trials were not designed to systematically evaluate potential antidepressant (ADT)-Arip interaction effects on safety, in that the placebo controlled trials did not include at least a placebo controlled Arip monotherapy treatment group (ideally the study would also include a placebo-placebo group and would also employ a DB design for both drugs). No serious and unexpected safety signal was revealed by the adjunctive Phase 3 MDD trials and the placebo controlled trials included an ADT monotherapy, although ADT was given under OL conditions. Also the safety profile (the type of AEs) was examined to determine if any unexpected events occurred (that were of a nature that differed from adverse events reported with either drug alone). Additionally, there is extensive postmarketing experience with approved antipsychotic drugs that includes Arip, since off-label combination treatment is common in the psychiatric clinical setting. Yet, Phase 3 trial results on the incidence of adverse (AEs) were suggestive of a possible ADT-Arip interaction effect on some AEs that are known to be associated with each drug alone. Moreover, potential ADT-Arip interactions effects on exaggerating adverse events that are known to be associated with both drugs (e.g. weight gain, sedative effects, among others) would not be surprising.

The following summarizes key safety observations in the short-term pivotal MDD trials (the text below is identical to the synopsis in Section 7.1 of this review). Recommendations follow (that are not copied from Section 7.1). The results on the incidence of adverse events in the pivotal adjunctive MDD trials suggested an exaggerated effect of the combined ADT-Arip treatment over the ADT monotherapy group in these trials for some of the AEs that are known to be associated with each of these drugs given alone (and as suggested by comparing these results to those of the monotherapy Arip trials involving other patient populations, as described in approved labeling). The interpretation of these results is limited by the study design of the MDD trials, since the trials did not include DB monotherapy, placebo controlled groups (to allow for a direct comparison between each monotherapy condition against the combined treatment condition and ideally against a placebo-placebo condition). Yet the following observations are notable when contrasted to results of monotherapy trials for other indications described in approved labeling:

- Results on adverse events reported adjunctive major depressive disorder trials suggested an exaggerated effect of the combined antidepressant-Abilify™ treatment over the antidepressant-placebo group or in comparison to results of monotherapy trials for approved indications:
 - The incidence of adverse dropouts was 6% and 2% in adjunctive aripiprazole and placebo groups, respectively. Adverse dropouts due to akathisia and fatigue were most often reported (1.3% and 1.1%, respectively in the adjunctive aripiprazole group, and 0 placebo subjects with either adverse event). These results are compared to the incidence of ADOs in monotherapy as follows:
 - Schizophrenia monotherapy trials: 7% and 9% in Arip and placebo groups, respectively. Treatment groups were similar in the incidence of each type of ADO.
 - Bipolar monotherapy trials: 11% and 9% in Arip and placebo groups, respectively. Treatment groups were similar in the incidence of each type of ADO.
 - Common adverse events ($\geq 5\%$ incidence in Arip-ADT patients that was at least twice that of placebo-ADT patients) in the adjunctive MDD trials were akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision. Insomnia, fatigue and blurred vision were not among the common adverse events (with an incidence of $\geq 5\%$ and twice that of placebo) in monotherapy trials of Bipolar and schizophrenia patients. Yet other AEs meeting this criterion in the monotherapy trials also generally met this criterion in the adjunctive MDD trials or related AEs met this criterion (see section 9.4 of this review for a specific listing of these common AEs in the Bipolar, Schizophrenia and MDD trials).
 - Akathisia showed the most exaggerated adjunctive treatment effect with 2D6 inhibitors (approximately 30% with paroxetine CR and fluoxetine adjunctive treatment). Yet, according to the sponsor no clinically relevant effects on PK were observed in the pivotal trials.
 - Disturbance of attention was reported in 3% and 1% of adjunctive aripiprazole and placebo subjects, respectively. This AE was not among AEs meeting criteria for inclusion in the summary tables for monotherapy trials in approved labeling

- (refer to Table 3 in approved labeling specifying AEs showing an incidence of at least 1% in Abilify groups and an incidence that was greater than placebo).
- Disturbance of attention was most common with venlafaxine XR adjunctive treatment (6% and 1% in adjunctive aripiprazole and placebo groups, respectively and 0 to 3% of subjects receiving other antidepressants)

Also refer to Section 7.1.5.5 noting preliminary observations when comparing the incidence of AEs between the MDD All-Arip treated group (which represents the short-term and the ongoing longterm adjunctive MDD trials) with other diagnostic groups involving trials that generally did not involve adjunctive ADT treatment. Section 7.1.5.6 of this review also discusses these results but when comparing a Bipolar-depressed group to the MDD group in the All-Arip treated dataset. This Section also provides results on a preliminary analyses of the incidence of AEs by ADT subgroups within the Arip and placebo DB groups in the short term Phase 3 MDD trials.

Recommendation. Unless the sponsor can provide data-based justification that a potential ADT-Arip interaction effect on safety does not exist, then it is recommended that these observations be incorporated in labeling (as discussed in Section 9.4 of this review). Also consider additional approaches for examining this potential interaction effect as part of the sponsor's postmarketing activities (as discussed on Section 9.3 of this review).

It is important to note that the safety profile of SAEs and the incidence of SAEs in the MDD trials did not suggest a serous safety signal associated with ADT-Arip combination treatment. Additionally, there is extensive postmarketing experience with approved antipsychotic drugs that includes Arip since off-label combination treatment is common in psychiatric clinical setting. Consequently, a special section under Warnings and Precautions (regarding potential ADT-Arip combination effects on safety) is not warranted in the opinion of the undersigned reviewer. Instead this potential issue can be adequately addressed elsewhere in labeling (in sections on dosing and in adverse reactions as recommended in Section 9.4 of this review).

While a special section under Warnings and Precautions is not recommended, consider describing the results on AEs of disturbance of attention (as previously outlined) in the subsection on "Potential Cognitive and Motor Impairment" under Warnings/Precautions in labeling.

Input from OCPB is recommended regarding PK and PK-PD interaction effects and as recommended for sections of labeling (see Section 9.4 of this review).

Key Safety Observations in the Ongoing Longterm OL Adjunctive MDD Study -164

Key observations with longer-term adjunctive treatment in MDD patients and the potential for ADT-Arip interaction effects also require consideration. The following outlines key observations with longer term treatment (using identical text from the synopsis of key safety findings in Section 7.1 of this review). These observations provide an additional rationale for recommendations in Section 9.3 of this review on postmarketing surveillance and Phase 4 requests for trials to examine for potential ADT-Arip interactions on safety.

ADOs of Disturbance of Attention

Disturbance of attention was among the above described AEs that had an incidence suggestive of an ADT-Arip interaction effect, particularly with venlafaxine in the short-term pivotal trials. Section 7.1.4.2 (under Other Search Strategies) lists cases of ADOs in the longterm study involving disturbance of attention and other AEs that were found by an attempt by the undersigned reviewer to find cases of serotonin syndrome (under subsection entitled “Reviewer Search for Serotonin Syndrome”).

Dyskinesia and Tardive Dyskinesia

Section 7.1.4.1 of this review also describes 12 cases of dyskinesia and TD in primarily the longterm study (under subsection on EPS). The total reported TD cases was 3 and occurred between 68 to 364 days (inclusive) of OL treatment in the longterm OL study. There are reports in the literature of these type of movement disorders induced by SSRIs and other ADTs (found by a pubmed search conducted by the undersigned reviewer). These reports are primarily of case reports in psychiatric patients and also in neurological patients (e.g. Leo RJ, 1996 and others). Mechanistically such events may be anticipated (via indirect agonistic effects on serotonergic systems projecting onto dopamine pathways in the extrapyramidal system, indirectly increasing dopamine release). Therefore, consideration needs to be given to a potential ADT-Arip interaction effect on these more serious EPS-related events.

Weight Gain

Section 7.1.5.6 of this review includes results based on additional analyses and explorations of AEs where the sponsor showed the incidence of AEs over time intervals in the All-Arip MDD dataset. Time-points beyond 42 days of treatment would correspond to treatment received during the ongoing OL Study -164. Weight increase was the only AE with an incidence of at least 5% at any given time interval beyond 42 days of treatment.

ADOs due to increased weight was reported in 2.7% (28/1055 subjects) in the All-Arip MDD group (of the All-Arip dataset) compared to only 0-0.3% of patients in any given non-MDD category (sample sizes/non-MDD category ranged from 593 to 8215 subjects). These results are summarized in section 7.1.3.2 of this review. Note that only 1 ADO due to increased weight occurred in Arip subjects in the short-term trials. This leaves 27 ADOs due to this event among subjects included in the All-Arip MDD dataset. Consequently, these remaining 27 ADOs would have been in the OL longterm, ongoing Study -164. Thus the incidence of ADOs due this event in this ongoing study is actually greater than 2.7% (the incidence would appear to be approximately 8% by using the sample size for only the OL study in the denominator). While weight gain is observed with Arip treatment (as described in approved labeling), the numerically greater incidence in the MDD group compared to other diagnostic groups could be reflecting an ADT by Arip interaction effect (as several ADTs are also associated with weight gain). Yet, it is difficult to interpret these results given a number of limitations with this dataset (as discussed elsewhere in this review, such as in Section 4.3 and in other sections). Yet, a greater combined effect of ADTs with Arip (for those ADTs that are known to increase weight) would not be a surprising finding.

Section 7.1.8.3.2 of this review shows results on outliers on weight gain (at least a 7% increase defines an outlier) over time intervals of ADT-Arip treatment. The incidence was numerically greater over each progressive time-interval of treatment as follows:

- 35% outliers among subjects receiving 36 weeks or greater of treatment
- 28% outliers during weeks 12-35 of treatment
- 6% outliers at weeks 11 or less of treatment.

Note that approved labeling provides results on the incidence of outliers on weight gain by BMI subgroups among subjects in longterm trials (subjects who were categorized into subgroups on the basis of their baseline BMI). Results for each baseline-BMI subgroup in the longterm adjunctive MDD trial (Study -164) could not be found in Module 2.7.4, as the study was specified in the NDA as ongoing (and a CSR was not provided for this study).

Metabolic Parameters

Given the above observations on weight gain, it is important to note the following results on metabolic parameters that may be potentially related (and indirectly related) to increases in weight gain (refer to Section 7.1.7.3.1 of this review for these results). The median change from baseline to each time-interval in the All-Arip treated MDD dataset generally showed consistently greater numerical changes over time for most “metabolic” parameters such as glucose, HgB1Ac, LDL, HDL, triglyceride levels. Note that All-Arip-treated MDD group results for time-points beyond 6 weeks of treatment reflect those from the longterm safety study C...164. The magnitude of these changes was not clinically remarkable. The largest change occurred with fasting triglycerides at the last assessment time interval (>46 weeks of treatment) in which the median change from baseline values was 12.2 (units not shown). A change of 12.2 may have clinical relevance in a patient who has abnormal or borderline values on their lipid profile. Section 7.1.7.3.2 of this review summarizes results on outliers on these parameters. The longterm safety study was reported as an ongoing OL study and the interpretation of these results is further compromised by the absence of a placebo group with a DB study design.

Recommendations: Section 9.3 of this review provides recommendations on postmarketing surveillance and Phase 4 requests for trials to address potential ADT-Arip interaction effects on safety.

(b) (4)

(b) (4)

(b) (4)

The Proposed Maximum Recommended Daily Dose-Level

The sponsor proposes a maximum recommended dose-level of up to (b) (4) mg daily, specifying 2-15 mg daily (b) (4)

Refer to Section 7.2.1.3 of this review on actual exposure of subjects in the short-term pivotal trials (see table 1.2.1.1C) and in the All-Arip dataset that included exposure during the ongoing longterm OL Study -164 (Table 1.2.2.1B).

Based on the sponsor's exposure tables (as shown in Section 7.2.1.3 of this review):

- No subjects received the 20 mg daily dose level in the pivotal trials -139 and -163.
- 39 subjects received the “overall mean dose category” of 15 mg daily dose-level of Arip in the pivotal short-term trials
 - Only 22 subjects received at least 36 days of the 15 mg daily dose-level).

- 28 subjects received the “overall mean dose category” of 20 mg daily doses during the OL longterm study in the All-Arip MDD dataset (approximately 90 or more days).

Other clinical trials for approved indications for Bipolar and Schizophrenia used daily dose-levels of up to 30 mg. It is also not uncommon for these patient populations in the clinical setting to be receiving concomitant ADTs (in clinical practice). However, Phase III trials for these indications generally do not allow for concomitant psychotropic agents (at least the majority of subjects would not be anticipated to be receiving concomitant antidepressants in pivotal trials). In any case, it is important to avoid being overly restrictive with dosing, as long as the maximum dose-level is considered adequately safe and as long as a lower dose level can also be recommended, as in this case (as proposed by the sponsor).

Recommendation. The proposed labeling is adequate based on past experience with much higher dose-levels of up to 30 mg in clinical trials of other psychiatric populations (for approved indications). However, it is recommended that Section 14.3 of proposed labeling specify the actual exposure at the 15 mg and 20 mg dose-levels.

Gender Effects on Efficacy and Safety

One study was positive for gender by treatment group interaction effects and the other study showed trends for a similar gender by treatment group interaction effect. This review describes some potential gender differences on safety but these observations are only considered as preliminary and the results are difficult to interpret (e.g. due to multiple comparisons, interpreting the clinical relevance, among other limitations with interpreting these results).

Recommendation. The sponsor’s proposed labeling describing gender interaction effects are acceptable. However, Biometric input is pending and is recommended.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

A proposed Risk Management program cannot be found in the submission. Sponsors conduct ongoing postmarketing surveillance for safety signals and maintain a database, as well as submit Periodic Safety Update reports according to regulations.

It is recommended that as part of the sponsor’s pharmacovigilance program that they monitor for potential Arip-ADT interaction effects on safety in MDD patients. Refer to Section 9.2 regarding this potential interaction effect on safety and on potentially relevant safety observations in the ongoing OL longterm study.

Consider obtaining input from the Office of Surveillance and Epidemiology as well.

9.3.2 Required Phase 4 Commitments

Issues raised in Section 9.2 of this review can be adequately addressed in labeling, such that requiring Phase 4 trials are not being recommended. However, recommendations for Phase 4 requests and on postmarketing surveillance are each provided (in Sections 9.3.1, above and 9.3.3 below).

9.3.3 Other Phase 4 Requests

(b) (4)

consider the following

Phase 4 requests:

- A Phase 4 request for conducting efficacy MDD trial(s) that exclude(s) patients with Generalized Anxiety disorders (GAD) and that also possibly exclude(s) patients using substances of abuse. A monotherapy MDD trial (that does not restrict entry criteria to partial responders) would be more feasible for excluding GAD patients and for excluding active substance users (in order to achieve a sufficient sample size that may not be achieved by restricting the trial to only including partial responders). Such a study would allow for examining the potential influence of confounding variables on efficacy and in identifying potential predictors of response.
- A Phase 4 request for conducting ADT-Arip adjunctive MDD trial(s) that include(s) placebo controlled double-blind (DB) monotherapy groups in order to allow for direct comparisons between a DB placebo-ADT control group and DB Arip-placebo group on safety variables (ideally the study would also include a placebo-placebo group). The specifics on the study design of such a study would need further consideration and discussions with the sponsor. Refer to Section 9.2 regarding a potential ADT-Arip interaction effect on safety and the limitations with interpreting these safety results.
- Since the MDD trials did not examine the safety of simultaneously initiating ADT with Arip treatment, consider a Phase 4 request for trials designed to examine the safety of concurrent initiation of both drugs. The initiation of both drugs simultaneously, could arise in the clinical setting, since it is not uncommon for treatment resistant patients or partial responders to discontinue to treatment or for patients to present at a later date acutely depressed (and sometimes suicidal) after ADT treatment was terminated. Consequently, initiating adjunctive treatment (both drugs, simultaneously) would be a clinical consideration and relevant to common clinical practices.

9.4 Labeling Review

Key issues were outlined in Section 9.2 of this review that can be adequately addressed in labeling. The following are recommendations and general guidelines for consideration for addressing these potential issues in labeling. The sponsor provided a side-by-side version of labeling that was used for the purposes of recommendations below (also section numbers specified below correspond to section numbers in proposed labeling). This review does not address reformatting changes in response to the new regulations since that aspect of labeling is

under review under another NDA21436 submission that was submitted prior to this NDA submission (but is under review as the time of this writing).

Recommendations for Sections 1, 2 and 6 of Labeling: *It is recommended that consideration be given to changing proposed headings for Sections 1 and 2 (and subheadings for Section 6) of labeling (and for the highlights) from an (b) (4) to the heading of “adjunctive treatment (b) (4) MDD.” It is also recommended that additional key information be included in these sections (1, 2 and 6, as specified below) to emphasize the following:*

- (b) (4)
- That Arip was added onto ongoing ADT treatment (not simultaneously initiated with ADT)
- (b) (4)

(b) (4)

These revisions are important from at least a safety perspective but are also important for clarifying that the efficacy of Abilify was not (b) (4), for simultaneously initiating both drugs, and that efficacy was only examined among partial responders. Moreover information included in Sections 1 and 2 warrant the prominence for placement into these first 2 sections of labeling. Also refer to Section 9.2 of this review, regarding a potential exaggerated adverse effect with combining Arip treatment with ADT treatment on AEs known to be associated with either of these drugs. These observations provides additional rationale for providing the above specified key information into Sections 1 and 2, as well as the following key information as provided for recommended labeling text, below.

Recommended Text (Sections 1, 2, 6 and 7 and corresponding highlights): *consider the following text as an approach to consider for addressing issues raised above and in Section 9.2 of this review. This text is provided for highlighted sections that correspond to Sections 1, 2, 6 and 7 of labeling and also provides an approach for text to consider for the corresponding full-text sections of labeling. OCPB input is recommended for any statements relevant to drug-drug interactions.*

-----INDICATIONS AND USAGE-----

- Adjunctive Treatment of Major Depressive Disorder: (b) (4) (b) (4)

-----DOSAGE AND ADMINISTRATION-----

- (b) (4) Treatment of Major Depressive Disorder (b): (b) (4)

(b) (4)

-----ADVERSE REACTIONS-----

Commonly observed adverse events (incidence of $\geq 5\%$) (b) (4) at least twice that (b) placebo (b) (4) (6.2) (b) (4)
(b) (4)

(b) (4)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

-----DRUG INTERACTIONS-----

- (b) (4)
- *CYP3A4 inducers* May decrease ABILIFY drug levels; double dose when used concomitantly (2.1, 7.1)
- (b) (4)

(b) (4)

Maximum Recommended Dose Levels in Section 2 of Proposed Labeling

It is acceptable to have a maximum recommended daily dose level of (b) (4) mg (b) (4) (b) (4) in Section 2 of labeling (pending OCPB input), for reasons previously discussed in Section 9.2. **Recommendations:** OCPB input is recommended regarding potential drug-drug interactions on PK and PK-PD that would influence dosing recommendations for Section 2 of labeling.

(b) (4)
(b) (4)

(b) (4)

Drug-Drug Interactions (Section 7 and Highlights)

Note revisions under 7.1 and 7.3 that require OCPB input. Note that some of these proposed changes are included under the subheading of “drugs having no clinically important interactions...” (proposed section 7.3). Yet safety results may suggest clinically relevant interaction effects (at least from a PD standpoint).

Recommendations: *OCPB input is recommended.*

(b) (4)

(b) (4)



Recommendations for the Warning and Precautions Section (Section 5 and Highlights)
Consider inserting observations regarding disturbance of attention in the MDD trials as specified in Section 9.2 of this review.

(b) (4)



The following are additional comments on some key aspects of proposed labeling for Section 14.3:

- The SDS is deemed by the Agency as an acceptable key secondary variable. The SDS showed at least trends for efficacy in one study and treatment groups differences in the other study reached a level significance. The sponsor proposes to indicate that one of the trials was positive for efficacy for this variable, which is consistent with the study results of one study reaching a level of significance (the other trial showed trends for being positive on this variable).
- The sponsor's proposed statements on gender effects on efficacy in this section of labeling are also consistent with results of the trials.

Recommendation: *Biometric input is pending and is recommended on efficacy results and OCPB input is recommended on potential drug-drug interaction effects relevant to dosing for this section. .*

9.5 Comments to Applicant

See the previous section of this review that impact on comments to convey to the sponsor.

10 APPENDICES

10.1 Review of Individual Study Reports

The following provides more details on pivotal efficacy trials, as found in the in-text efficacy-related sections of the clinical study reports (CSRs) on these 2 trials (unless otherwise specified I corresponding sections below). Subsections below are in accordance with the Clinical Review MAPP (which provides an outline of subheadings).

See section 4 of this review for details on NDA content and review strategy regarding CSRs.

Study Phases

Two pivotal Phase 3 trials (CN138139 and CN138163 also referred to as C-139 and C-163, respectively) served the basis of the proposed indication (367 aripiprazole subjects and 356 placebo treated subjects). The studies were placebo controlled, randomized, double-blind (DB), multi-center studies (involving US study sites) and involved generally healthy adult patients with MDD who show an inadequate response to ADT treatment.

The study phases are outlined as follows:

- Screening Phase A: Screening for eligibility in which MDD patients how had less than 50% improvement on past ADT (as perceived by the patient) using criteria specified later.
- Phase B: An 8-week phase of single-blind (SB) placebo coadministered with open-label (OL) treatment of 1 of 5 ADTs (escitalopram, sertraline, venlafaxine extended-release, fluoxetine or paroxetine controlled-release). This phase allowed for a prospective identification of inadequate responders as defined by meeting the following criteria during Phase B:
 - Had <50% improvement on the Hamilton Depression Rating Scale (HAMD17)
 - Had a HAMD7 score of at least 14 units
 - Had a Clinical Global Impression (CGI) score of no better than minimal improvement
- Phase C: A 6-week phase in which inadequate responders were randomized to DB placebo or aripiprazole (flexible dose) while continuing their OL ADT (at the same dose received during Phase B of the study). The flexible daily dose range of aripiprazole treatment was either:
 - 2 to 15 mg daily in subjects receiving ADT of a potent CYP2D6 inhibitor (fluoxetine or paroxetine)
 - 2 to 20 mg daily in subjects receiving other ADTs.

Treatment Methods.

Investigators were to follow dosing schedules as outlined below. Dose adjustments outside of the guidelines (as specified in tables shown below) were not permitted, with some exceptions (as specified in the CSR). A patient that could not tolerate the lowest dose-level for the ADT or the DB treatment (placebo or Arip) was withdrawn from the study.

ADT Treatment during Phase B. The choice of ADT was determined by the study physician and as clinically indicated (as described in Section 3.4 of the CSR of each study). Investigators were to follow dosing recommendations as found in approved labeling for each ADT. The table below outlines the dosing schedule (as found in the CSR):

Table 3.4.4A: Phase B: Daily Dosing Schedule for ADTs and Single-Blind Placebo

Study Week ^a	1	2	3	4	5	6	7	8
Escitalopram (mg)	10	10 or 20	10 or 20	10 or 20	10 or 20	10 or 20	10 or 20	10 or 20
Fluoxetine (mg)	20	20	20 or 40	20 or 40	20 or 40	20 or 40	20 or 40	20 or 40
Paroxetine CR (mg)	25	25 or 37.5	25, 37.5 or 50	37.5 or 50				
Sertraline ^a (mg)	50	50 or 100	100 or 150	100 or 150	100 or 150	100 or 150	100 or 150	100 or 150
Venlafaxine XR ^a (mg)	37.5 - 75 ^b	75 or 150	150 or 225	150 or 225	150 or 225	150 or 225	150 or 225	150 or 225
Placebo (tablets)	1	1	1	1	1	1	1	1

Source: Appendix 1.1

^a The prescribed dose for a study week is made at the previous Study Visit (ie the prescribed dose for study week 1 is made at the Baseline Visit, the prescribed dose for study week 2 is made at the Week 1 Visit, etc.).

^b For the first week, patients were prescribed 37.5 mg of venlafaxine XR for 3 days followed by 75 mg/day.

ADT Treatment during Phase C

Subjects were to continue their ADT treatment at the same daily dose level that they were receiving at the end of the prospective observational phase of the study.

DB Arip or Placebo Treatment (DB Treatment Phase/Phase C):

The following dosing schedule was used for adjunctive Arip or placebo treatment in patients who were eligible to enter Phase C of the study (as provided in the CSR):

Table 3.4.4B: Phase C Double-Blind Dosing Schedule

Study Week ^{a,b}	9	10	11	12	13	14
Aripiprazole Dose (mg/day)	5	2, ^c 5 or 10	2, 5, 10 or 15	2, 5, 10, 15 or 20 ^d	2, 5, 10, 15 or 20 ^d	2, 5, 10, ^d 15 or 20 ^d
Placebo (tablets/day)	1	1 - 2	1 - 3	1 - 4 ^e	1 - 4 ^e	1 - 4 ^e

Source: [Appendix 1.1](#)

^a The prescribed dose for a study week is made at the previous Study Visit (ie, the prescribed dose for study week 9 is made at the Week 8 Visit, the prescribed dose for study week 10 is made at the Week 9 Visit, etc.).

^b ADT doses remained unchanged in Phase C from Phase B (ie, patients remained on the same dose as at the end of Phase B).

^c Dose decreases from 5 mg/day to 2 mg/day would entail continued dosing with one tablet per day; however, the tablet strength would be decreased (ie, 2 mg instead of 5 mg of aripiprazole).

^d The aripiprazole 20 mg dose was not an option for patients taking paroxetine CR and fluoxetine. The maximum number of tablets to be administered was 3.

^e For patients taking paroxetine CR or fluoxetine, the maximum number of placebo tablets were 3 (corresponding to the decreased range of allowable aripiprazole doses).

The Timing of Drug Administration Relative to the Time of Day and Meals

Dosing was to be generally consistent with respect to the time of day (given at approximately the safety time each day) without regarding to meals except for venlafaxine XR treatment. This particular ADT was to be given with food.

Eligibility Criteria

The protocols each include eligibility criteria. The following are some of the key criteria in which subjects must meet each of the following conditions to enter into the study:

- Must be a generally healthy male or female adult (18-65 years old) outpatient
- Must have MDD (DSM-IV-TR criteria) with the current episode lasting for at least 8 weeks
- Must have retrospectively failed 1 to no more than 3 antidepressant treatment (ADT) courses (of an approved antidepressant drug) during their current depressive episode (using prespecified criteria using a treatment response questionnaire).
- Subjects must have a HAMD-17 Total score of ≥ 18 at baseline
- Must meet criteria for retrospectively showing an inadequate response to 1 to no more than 3 ADT courses as defined in a subsection below.
- Must meet entry criteria for Phase C as defined in a subsection below.

Reviewer comments.

“Significant substance use disorder within the past twelve months” was among the exclusionary criteria. Yet a number of subjects tested positive or were using opioid substances, barbiturates and sometimes other or additional substances of abuse. Refer to Table 4.3 in the CFR for each study showing a large number of subjects testing positive on the urine drug screen that were primarily patients taking opiate analgesics and barbiturate containing drugs including patients taking these drugs for migraine headache. For example Table 4.3 shows that 25 or 26 subjects in each treatment group tested positive on urine drug testing for Study -139 (with similar observations for Study -163). Over 20 subjects in each group also failed to be eligibility criteria relevant to the MDD diagnosis in study -139 with generally similar proportions of protocol deviators in this category in Study -163. Also see later, common concomitant drugs that included analgesics. See section 9 of this review for additional comments and recommendations.

Patients with Axis I disorders that were listed in the protocol were excluded, but this list did not include Generalized Anxiety disorder (but included several other anxiety disorders were listed, such as Panic disorder). See section 9 of this review for additional comments and recommendations.

Several Axis II disorders were also listed among exclusionary criteria, that were appropriate for the study.

Criteria for a Previous Inadequate Response to Antidepressant Treatment

The following specifies criteria for a previous inadequate response to ADT as copied from the study report:

Patients who had reported a history for the current depressive episode of an inadequate response to at least 1 and no more than 3 adequate antidepressant treatments. An inadequate response was defined as less than a 50% reduction in depressive symptoms severity, as assessed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ). An adequate trial was defined as an antidepressant treatment for at least 6 weeks duration (at least 3 weeks for combination treatments) at a minimum dose as specified in the ATRQ;

- A patient who reported experiencing a greater than or equal to a 50% reduction in depressive symptoms to a medication that was prescribed in the current episode may also have qualified if the following were met: at the Screening Visit the patient reported a less than 50% reduction in depressive symptoms relative to the patient’s last well period; and, the patient reported having an inadequate response to a subsequent, adequate antidepressant trial of at least 6 weeks duration (as

defined in the ATRQ). This criterion was relevant in cases where patients experienced an initial but non-enduring antidepressant response

- If a patient had had only 1 adequate antidepressant trial in the current episode, he or she must not have been assigned that same antidepressant, including different formulations of the same medication, in the open-label prospective phase of the study (ie, if paroxetine CR was the 1 adequate antidepressant trial, the patient must not have been assigned to paroxetine and if venlafaxine was the 1 adequate antidepressant trial the patient must not have been assigned to venlafaxine XR). In addition, patients whose sole adequate antidepressant trial in the current episode was citalopram may not have been assigned to escitalopram
- Patients must have had at least 1 trial with an antidepressant that lasted at least 6 weeks at an adequate dose (refer to ATRQ) in the current depressive episode

The following is a key exclusionary criterion relevant to past response to ADT:

Patients who reported an inadequate response (less than 50% reduction in depressive symptom severity) to more than 3 adequate trials of antidepressant treatments during the current depressive episode (including monotherapy treatment and distinct combination regimens) at a therapeutic dose (as defined by the ATRQ) and for an adequate duration (minimum duration of 6 weeks for any monotherapy and 3 weeks for any combination regimen)

Additional Entry Criteria for Phase C of the Study

Subjects entering Phase C of the study must meet the following criteria at the end of Phase B of the study:

- Must have a HAMD-17 total score of at least 14 units and a CGI-I Score of ≥ 3
- Must show <50% improvement from baseline on the HAM-D17 Total Score
- Must be 18-65 years old

Table 3.5.1: Flow Chart/ Schedule of Events

	PHASE A Screening Phase 7-28 days		PHASE B Prospective Treatment Phase 8 Weeks						PHASE C Randomization Phase 6 Weeks					
	Pre-Treatment Visit		End of Week:						End of Week:					
	Screen Baseline		1	2	3	4	6	8 ^a	9	10	11	12	13	14 ^b
PROCEDURE														
Informed Consent	X													
Demographic Data	X													
Entrance Criteria	X						X							
Medical History	X	X ^c												
Psychiatric History	X	X ^c												
Antidepressant History (ATRQ)	X													
M.I.N.I.	X													
EFFICACY														
HAM-D 17	X	X					X							X
MADRS		X	X		X	X	X	X	X	X	X	X	X	X
CGI-S	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X	X	X	X	X
IDS - Self-Rated		X	X	X	X	X	X	X	X	X	X	X	X	X
SAFETY														
Physical Exam ^d	X						X							X
Vital Signs ^{e,f}	X	X	X		X		X		X	X	X	X	X	X
12 Lead ECG	X						X							X
Clinical Laboratory Tests (hematology, chemistry, urinalysis, prolactin) ^g	X						X							X
Pregnancy Test (WOCBP) ^h	X	X					X							X
Drug Screen/Blood Alcohol ⁱ	X						X							
PK Sampling ^j					X	X	X				X	X	X	
SFI		X					X							X
SAS		X					X		X	X	X	X	X	X
AIMS		X					X		X	X	X	X	X	X
Barnes Akathisia		X					X		X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X

	Screen	Baseline	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
OTHER																	
Q-LES-Q Short Form		X							X								X
Resource Utilization Form		X							X								X
SDS		X							X								X
Concomitant Therapy		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Therapy			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Baseline Visit Form		X															
End of Phase/Study Form									X								X

- ^a If a patient discontinued prematurely from Phase B, the Week 8 Visit procedures were completed and the Week 8/Early Termination Visit scheduled within 24 hours after the last dose of study medication, whenever possible.
- ^b If a patient discontinued prematurely from Phase C, the Week 14 Visit procedures were completed and the Week 14/Early Termination Visit scheduled within 24 hours after the last dose of study medication, whenever possible.
- ^c Confirmed medical and psychiatric history and updated, if necessary.
- ^d Height measurements included at the Screen Visit Only.
- ^e Vital signs included supine and standing blood pressure and pulse.
- ^f Vital signs scheduled at the same visit as blood samples were completed before blood was drawn.
- ^g Samples for clinical laboratory tests were drawn fasting (for 10 hours), if possible.
- ^h Serum pregnancy test was performed at the Screening Visit. Urine or serum pregnancy test was performed at the Baseline Visit (or within 72 hours prior to the first dose of study medication).
- ⁱ Drug screen for cocaine, other stimulants, heroin and opioids must have been negative and blood alcohol level must have been less than 0.08% (or equivalent) prior to enrollment into Phase B. These tests may have been repeated at any time during the study at the discretion of the investigator.
- ^j Every possible effort was made to collect samples at the same time at each visit. Furthermore, the patient was advised to take study medication at the same time each day throughout the study, but most importantly, prior to each PK sampling.

Demographic Features

Treatment groups of each study were generally or adequately similar on demographic features (age, gender, race, BMI and others). The following summarizes demographic features of each treatment group:

- Mean age: 45 years old (ranged from approximately 19 to 65 years old).
- Gender: 63 to 67% female in Studies C...139 and C...163, respectively.
- “Race:” Approximately 90% “White”, Approximately 7% “Black/African American” and a smaller percentage of subjects in other categories.
- Mean BMI: Approximately 30 kg/m² (range of approximately 16-58 kg/m²)

Baseline Severity of Illness

The baseline mean and median scores on the MADRS were approximately 30 across ADT groups and among all subjects of Phase B for each trial. Mean CGI scores were also approximately 4 for each ADT group and among all subject of Phase B for each Trial. These results were found in Supplementary Table S.3.8 of each CSR.

The table below shows the end-of-Phase B mean values on the MADRS Total score (as provided by the sponsor in Module 2.7.3). Small treatment group differences were observed between the placebo and Arip groups in Study C...163 but efficacy results used the end-of-Phase B score as a cofactor in the ANCOVA model used for analyzing primary efficacy results. Also the sponsor indicates that a sensitivity analyses still demonstrated “robustness” of efficacy results with respect to the end-of-Phase B differences between the groups.

TABLE 4.2.1: MEAN CHANGE FROM END OF PHASE B (WEEK 8) TO END OF PHASE C (WEEK 14, LOCF) IN MADRS TOTAL SCORE (CN138139, CN138163)

Table 4.2.1: Mean Change from End of Phase B (Week 8) to End of Phase C (Week 14, LOCF) in MADRS Total Score (CN138139, CN138163)

Protocol/ Treatment	N	MADRS Total Score ^a			
		Mean End of Phase B	Mean Change at End of Phase C	Treatment Difference (95% CI) Versus Placebo	P-Value ^b
CN138139					
Placebo	172	25.65	-5.77	--	--
Aripiprazole	181	25.88	-8.78	-3.01 (-4.66, -1.37)	< 0.001
CN138163					
Placebo	184	26.55 ^c	-5.65	--	--
Aripiprazole	185	24.59 ^c	-8.49	-2.84 (-4.53, -1.15)	0.001

^a MADRS Total Score is from 0 to 60. A negative change score signifies improvement.

^b ANOVA model, with double-blind treatment and study center as main effects, is used for end of Phase B comparisons. ANCOVA model, with double-blind treatment and study center as main effects, and end of Phase B assessment as covariate, is used for mean change from end of Phase B comparisons. Means, treatment differences between aripiprazole and placebo, 95% CIs for the differences and the p-values for treatment comparisons are based on ANOVA/ANCOVA model.

^c Treatment difference between placebo and aripiprazole statistically significant at end of Phase B, p < 0.001.

Disposition

Results on disposition of subjects are summarized below rather than providing copies of the sponsor’s summary tables.

Reviewer Comments. Upon review of Tables 5.1A and B in the CSRs of each pivotal study the following summarizes the disposition of subjects in Phase B and Phase C of the 2 trials.

Disposition in Phase B: the majority of dropouts during Phase B were due to an adverse event (6% in each study), subject-withdraw of consent (6% in each trial) and lost-to-follow-up (5% in each trial). Approximately 80% of subjects of each trial completed phase B and approximately 58% of these Phase-B-completers were randomized to DB treatment in Phase C. ADT groups in Phase B showed some numerical differences between ADT groups on the incidence of more common reasons for early withdraw in a given study. However, the ADT group differences were not consistent across trials and they were adequately small in magnitude for the main objectives of these trials (the incidence between groups did not differ by more than approximately 5% and generally differed by approximately 2-3%). Only a few subjects withdrew due to other reasons (administratively withdrawn, other known reasons, among other categories) and ADT groups were similar in the incidence in these other categories.

Disposition in Phase C: The majority of randomized subjects completed Phase C of each study (85% and 89% in Studies C...163 and C...139, respectively). As expected a slightly greater incidence of ADOs occurred in the Arip compared to placebo groups of each study (4% and 1%, respectively in Study C...163 and 3% and 2%, respectively in Study C...139). Approximately 1 or 2% of subjects withdrew due to lack of efficacy in each trial. These results and results of other disposition categories did not reveal any clinically remarkable findings that would alter overall conclusions on the efficacy or safety results of these 2 trials.

Concomitant Medications

Reviewer Comments. An in-text summary of these results cannot be found in in-text sections of the CSRs but some results relevant to concomitant medications were found in supplemental tables that were reviewed as described below.

Anticholinergic, opioid, “other analgesic & antipyretic” agents were most commonly used in concomitant medications (incidence of $\geq 5\%$ for any given treatment group) during the double-blind phase of Studies -139 and -163 (based on a review of supplemental Table S.4.8 showing the incidence for medication categories for each treatment group as found in the supplemental tables section of the CSRs). Anticholinergic agent use was numerically greater in the Arip group compared to the placebo group in that they were generally commonly used in the Arip group ($\geq 5\%$) compared to the placebo group (< 1 or 2% , approximately).

Supplemental table S4.9 was also found in the supplemental tables section of the CSRs which showed the incidence of EPS medications during DB treatment (benztropine and propranolol). Both drugs were commonly used in the Arip groups of each study ($\geq 5\%$) compared to the placebo groups (< 1 - 2% , approximately).

The common use of anticholinergic agents and propranolol (as an EPS agent) in Arip groups compared to less common use of these agents in placebo groups is not an unexpected finding, given the drug class.

Efficacy Analyses and Results

Primary Efficacy Analyses Results

Statistical methods involved comparing treatment groups on the mean change from baseline of the DB phase to treatment endpoint (Study Week 14, LOCF dataset) on the MADRS Total Score. The statistical test employed was the analysis of covariance (ANCOVA):

- Covariate: the MADRS Total Score at baseline of the DB phase
- Main effects: treatment and study center

See efficacy results in Section 6 and Appendix 10.3 of this review.

Key Secondary Efficacy Analyses and Results

Similar statistical methods were employed for comparing treatment groups on the SDS except that a hierarchical testing procedure was employed due to multiple group comparisons, as described in the CSR and the protocol.

Other Secondary Efficacy Analyses and Results

The protocols included methods for key secondary analyses (as described in the CSRs) and the CSRs provided the results. Some of these results are shown in Appendix 10.3 and Section 6 provides reviewer comments and conclusions relevant to secondary efficacy results.

10.2 Line-by-Line Labeling Review

See section 9.4 of this review for overall labeling recommendations. A draft of line-by-line labeling recommendations will follow this review (provided as a draft to assist the Team Leader for preparing labeling recommendations for the Division Director, in accordance with standard Division procedures (as understood by the undersigned reviewer).

10.3 Appendix to the Integrated Review of Efficacy (Section 6)

10.3.1: This table is Table 3.3.A of Module 2.7.3 of the NDA
MADRS Total Score: Mean Change from End of Phase B to End of Phase C by Patient Population Subsets:
Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), LOCF Data Set,
Efficacy Sample

	MADRS Total Score (a)						Treatment Comparison (b)		Interaction Test	
	Placebo			Aripiprazole			Aripiprazole - Placebo		P-value	
	N	Mean	SE	N	Mean	SE	Diff	(95% CI)	ANCOVA (c)	Gail-Simon (d)
GENDER										
Male	119	-6.29	0.71	132	-6.93	0.67	-0.64	(-2.56 , 1.27)		
Female	237	-5.43	0.53	234	-9.64	0.53	-4.21	(-5.69 , -2.73)	0.005	NA
AGE GROUP										
<= 50 Years	242	-5.50	0.51	227	-8.36	0.53	-2.86	(-4.31 , -1.40)		
> 50 Years	114	-6.22	0.75	139	-9.14	0.68	-2.91	(-4.92 , -0.90)	0.986	NA
RACE										
White	324	-5.68	0.45	323	-8.70	0.45	-3.02	(-4.26 , -1.78)		
Black	23	-7.21	1.71	28	-9.45	1.55	-2.25	(-6.89 , 2.40)		
Other	9	-4.73	2.27	15	-6.09	1.72	-1.36	(-7.33 , 4.61)	0.927	NA
ETHNICITY										
Hispanic/Latino	30	-6.49	1.29	16	-5.60	1.79	0.89	(-3.55 , 5.32)		
Not Hispanic/Latino	326	-5.66	0.45	350	-8.80	0.43	-3.14	(-4.36 , -1.92)	0.167	NA
END PHASE B MADRS TOTAL SCORE (MEDIAN=26)										
<= 26	189	-4.87	0.55	208	-8.05	0.52	-3.19	(-4.67 , -1.70)		
> 26	167	-6.76	0.67	158	-9.43	0.69	-2.67	(-4.56 , -0.77)	0.711	NA
END OF PHASE B MADRS RESPONSE										
< 25% Improvement (e)	262	-5.97	0.50	238	-9.35	0.53	-3.38	(-4.81 , -1.95)		
>= 25% Improvement (f)	94	-5.39	0.80	128	-7.24	0.68	-1.84	(-3.92 , 0.24)	0.242	NA
NUMBER OF PREVIOUS ADTs IN CURRENT EPISODE										
1	237	-5.63	0.52	249	-8.55	0.51	-2.92	(-4.35 , -1.48)		
2	95	-6.14	0.85	94	-9.31	0.85	-3.17	(-5.53 , -0.80)		
>= 3	23	-5.31	1.51	22	-7.36	1.62	-2.05	(-6.46 , 2.36)	0.949	NA
DURATION OF CURRENT EPISODE (MEDIAN=19.2)										
<= 19.2 Months	171	-5.95	0.60	189	-8.23	0.57	-2.28	(-3.91 , -0.64)		
> 19.2 Months	185	-5.53	0.60	177	-9.13	0.62	-3.60	(-5.29 , -1.90)	0.289	NA
ADT										
Escitalopram	99	-4.86	0.85	115	-8.30	0.79	-3.44	(-5.74 , -1.15)		
Fluoxetine	52	-6.50	1.10	53	-8.46	1.08	-1.96	(-5.04 , 1.12)		
Paroxetine	27	-4.78	1.41	30	-8.90	1.35	-4.12	(-8.06 , -0.18)		
Sertraline	74	-5.90	0.89	68	-9.29	0.93	-3.39	(-5.93 , -0.85)		
Venlafaxine XR	104	-6.28	0.78	100	-8.85	0.80	-2.57	(-4.78 , -0.36)	0.914	NA
ALL SSRIs										
All SSRIs (g, h)	252	-5.51	0.51	266	-8.59	0.49	-3.08	(-4.47 , -1.69)	---	---

(a) MADRS total score is from 0 to 60. A negative change score signifies improvement.
 (b) ANCOVA model, with double-blind treatment and study as main effects and End of Phase B assessment as covariate, is used for mean change from End of Phase B comparisons. Means, standard errors, treatment differences between aripiprazole and placebo, and 95% confidence intervals for the differences are based on ANCOVA model.
 (c) ANCOVA model, with double-blind treatment, study and subgroup as main effects, End of Phase B assessment as covariate, and treatment-by-subgroup as interaction effect.
 (d) Gail-Simon test for qualitative interaction is applicable only in case the interaction p-value for ANCOVA is <= 0.05 and if the estimated treatment differences for the subgroups are in opposite direction. NA= not applicable.
 (e) Nonresponse
 (f) Partial Response
 (g) Does not include venlafaxine XR.
 (h) ANCOVA and Gail-Simon test are not applicable since only 1 subgroup presented.

Table 10.3.2
Mean Change from End of Phase B to End of Phase C in
MADRS Total Score by Gender: Placebo-Controlled Studies
in Major Depressive Disorder (CN138139, CN138163), LOCF
Data Set, Efficacy Sample
 (This table is Table 3.3B from Module 2.7.3 of the NDA)

Protocol/ Treatment	MADRS Total Score					
	Placebo		Aripiprazole		Treatment Difference ^a (95% CI) Versus Placebo	P-Value ^b
N	Mean Change	N	Mean Change ^a			
CN138139						
Male	60	-7.32	70	-6.84	0.48 (-2.13, 3.09)	0.002
Female	112	-5.11	111	-10.11	-5.00 (-7.10, -2.90)	
CN138163						
Male	59	-5.22	62	-7.11	-1.90 (-4.80, 1.01)	0.374
Female	125	-5.73	123	-9.21	-3.48 (-5.58, -1.38)	

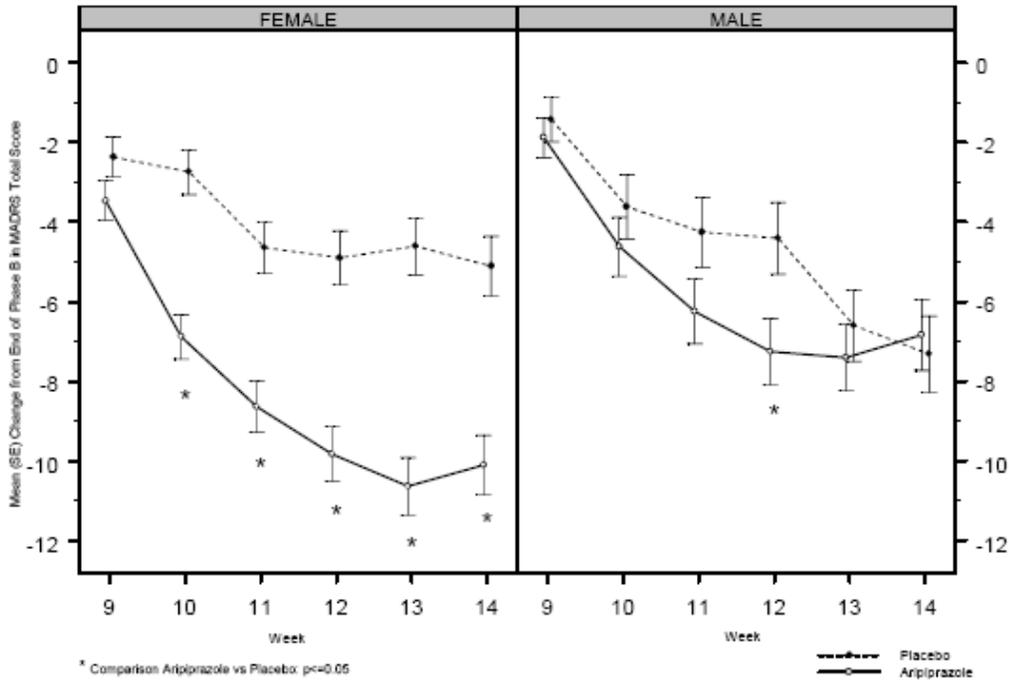
^a Means, treatment differences, and confidence intervals are based on an ANCOVA model with double-blind treatment as main effect and end of Phase B assessment as covariate.

^b P-value of the treatment-by-gender interaction effect. The ANCOVA model used had double-blind treatment and gender as main effects, end of Phase B assessment as covariate, and treatment-by-gender as interaction effect.

Figure 10.3.3

Adjusted Mean Change from End of Phase B to Phase C in MADRS Total Score by Gender, Study CN138139, LOCF Data Set, Efficacy Sample

(The below figures are Figures 3.3A and B in Module 2.7.3 of the NDA)



Continued on next page

Figure 10.3.4

**Adjusted Mean Change from End of Phase B to Phase C in MADRS
Total Score by Gender, Study CN138163, LOCF Data Set, Efficacy
Sample**

(Figure 3.3B in Module 2.7.3)

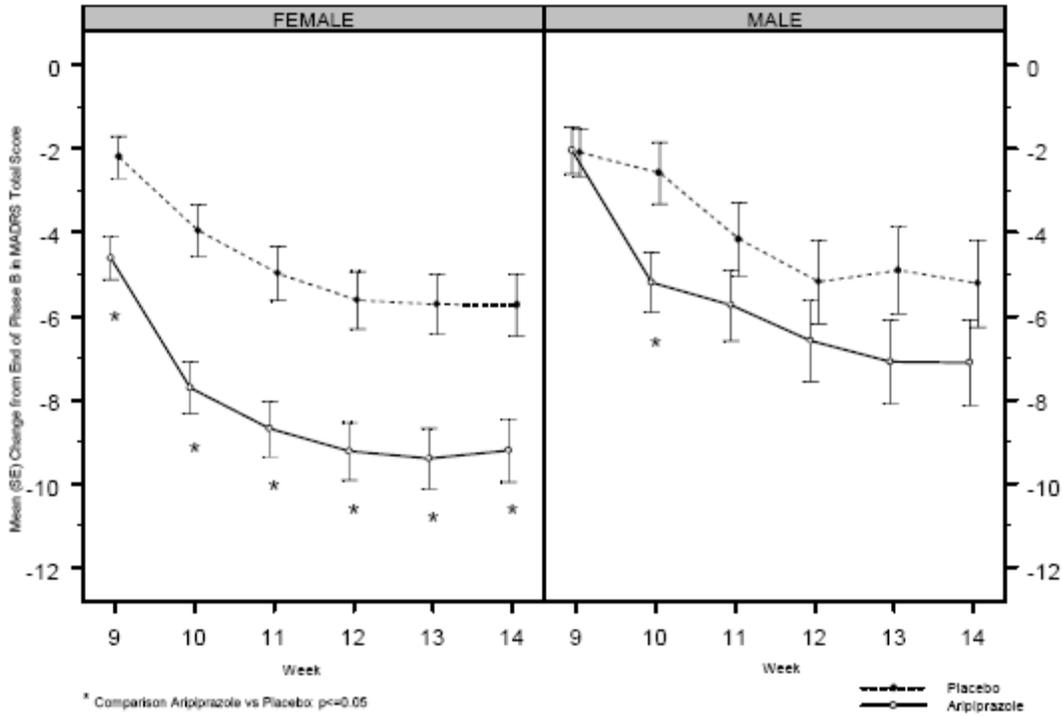


Table 10.3.5

Mean Change from End of Phase B (Week 8) to End of Phase C (Week 14) in HAM-D17 Total Score: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), LOCF Data Set, Efficacy Sample

(This table is Table 3.2.3.2A in Module 2.7.3)

Protocol/ Treatment	N	Mean End of Phase B	HAM-D17 Total Score ^a		P-Value ^b
			Mean Change at End of Phase C	Treatment Difference (95% CI) Versus Placebo	
CN138139					
Placebo	147	19.73	-4.89	--	--
Aripiprazole	152	19.68	-7.17	-2.28 (-3.54, -1.02)	< 0.001
CN138163					
Placebo	170	19.64 ^c	-4.41	--	--
Aripiprazole	181	18.75 ^c	-6.77	-2.35 (-3.60, -1.11)	< 0.001

^a HAM-D17 total score is from 0 to 52. A negative change score signifies improvement.

^b ANOVA model, with double-blind treatment and study center as main effects, is used for end of Phase B comparisons. ANCOVA model, with double-blind treatment and study center as main effects and end of Phase B assessment as covariate, is used for mean change from end of Phase B comparisons. Means, treatment differences between aripiprazole and placebo, 95% CIs for the differences and the p-values for treatment comparisons are based on ANOVA/ANCOVA model.

^c The treatment difference between placebo and aripiprazole was statistically significant at end of Phase B, p = 0.021.

Table 10.3.6

Mean CGI-Improvement Score at Week 14: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), LOCF Data Set, Efficacy Sample
 (this table is Table 3.2.3B of Module 2.7.3)

Protocol/ Treatment	Mean CGI-Improvement Score ^a			
	N	Mean Score	Treatment Difference (95% CI) versus Placebo	P - Value ^b
CN138139				
Placebo	172	2.81	--	--
Aripiprazole	181	2.49	-0.32 (-0.53, -0.11)	0.003
CN138163				
Placebo	184	2.91	--	--
Aripiprazole	185	2.42	-0.49 (-0.70, -0.28)	< 0.001

^a CGI Improvement Scale: 1-very much improved; 2-much improved; 3-minimally improved; 4-no change; 5-minimally worse; 6-much worse; 7-very much worse. Improvement was assessed relative to the end of Phase B.

^b ANCOVA model, with double-blind treatment and study center as main effects, and CGI-Severity at end of Phase B as covariate, is used for mean CGI-Improvement relative to end of Phase B comparisons. Means, treatment differences between aripiprazole and placebo, 95% CIs for the differences and the p-values for treatment comparisons are based on ANCOVA model.

Table 10.3.7

Number and Percentages of Patients with a MADRS Response: End of Phase B through End of Phase C (Week 14), LOCF Data Set, Efficacy Sample
 (this table is Table 3.2.3.2F in Module 2.7.3)

Week	CN138139					CN138163				
	Number with Response ^a /Number Assessed (%)		Treatment Comparison ^b Aripiprazole/Placebo			Number with Response ^a /Number Assessed (%)		Treatment Comparison ^b Aripiprazole/Placebo		
	Placebo	Aripiprazole	RR	(95% CI)	P-value	Placebo	Aripiprazole	RR	(95% CI)	P-value
9	3/164 (1.8)	11/177 (6.2)	3.79	(1.06, 13.56)	0.025	6/174 (3.4)	13/173 (7.5)	2.15	(0.81, 5.72)	0.114
10	14/172 (8.1)	30/181 (16.6)	2.05	(1.13, 3.72)	0.015	18/184 (9.8)	42/185 (22.7)	2.26	(1.35, 3.80)	0.001
11	27/172 (15.7)	46/181 (25.4)	1.65	(1.09, 2.49)	0.016	25/184 (13.6)	49/185 (26.5)	1.87	(1.21, 2.89)	0.004
12	27/172 (15.7)	55/181 (30.4)	1.95	(1.30, 2.92)	<0.001	30/184 (16.3)	52/185 (28.1)	1.68	(1.13, 2.51)	0.009
13	35/172 (20.3)	60/181 (33.1)	1.67	(1.17, 2.38)	0.004	30/184 (16.3)	62/185 (33.5)	2.01	(1.36, 2.96)	< 0.001
14	41/172 (23.8)	61/181 (33.7)	1.45	(1.04, 2.01)	0.027	32/184 (17.4)	60/185 (32.4)	1.86	(1.27, 2.71)	< 0.001

^a Response defined as at least 50% reduction from end of Phase B in MADRS Total Score.

^b CMH General Association Test, controlling for study center.

10.4 Appendix to the Integrated Review of Safety (Section 7)

Table 10.4.1 (Table 2.1.A-2 in Module 2.7.4)

Incidence of Treatment-Emergent AEs by ADT That Occurred in at Least 2 Percent of Patients in the Pooled Aripiprazole Group: Placebo-Controlled Studies in Major Depressive Disorder (CN138139, CN138163), Safety Sample

	Placebo	Aripiprazole
NUMBER OF PATIENTS SCREENED FOR AES	366	371
ESCITALOPRAM	102	118
FLUOXETINE	54	53
PAROXETINE	28	31
SERTRALINE	77	69
VENLAFAXINE XR	105	100
NUMBER OF PATIENTS WITH ≥1 AE	233 (63.7)	307 (82.7)
ESCITALOPRAM	65 (63.7)	103 (87.3)
FLUOXETINE	32 (59.3)	42 (79.2)
PAROXETINE	20 (71.4)	27 (87.1)
SERTRALINE	42 (54.5)	56 (81.2)
VENLAFAXINE XR	74 (70.5)	79 (79.0)
SYSTEM ORGAN CLASS		
PREFERRED TERM	INCIDENCE (%)	INCIDENCE (%)
EYE DISORDERS		
VISION BLURRED		
ESCITALOPRAM	2 (2.0)	5 (4.2)
FLUOXETINE	0	4 (7.5)
PAROXETINE	1 (3.6)	4 (12.9)
SERTRALINE	1 (1.3)	1 (1.4)
VENLAFAXINE XR	1 (1.0)	7 (7.0)
GASTROINTESTINAL DISORDERS		
CONSTIPATION		
ESCITALOPRAM	1 (1.0)	6 (5.1)
PAROXETINE	1 (3.6)	2 (6.5)
SERTRALINE	1 (1.3)	1 (1.4)
VENLAFAXINE XR	4 (3.8)	8 (8.0)
NAUSEA		
ESCITALOPRAM	6 (5.9)	4 (3.4)
FLUOXETINE	2 (3.7)	2 (3.8)
PAROXETINE	2 (7.1)	1 (3.2)
SERTRALINE	3 (3.9)	2 (2.9)
VENLAFAXINE XR	5 (4.8)	6 (6.0)
DIARRHOEA		
ESCITALOPRAM	8 (7.8)	3 (2.5)
FLUOXETINE	2 (3.7)	1 (1.9)
PAROXETINE	1 (3.6)	3 (9.7)
SERTRALINE	1 (1.3)	4 (5.8)
VENLAFAXINE XR	4 (3.8)	1 (1.0)
DRY MOUTH		
ESCITALOPRAM	7 (6.9)	4 (3.4)
FLUOXETINE	1 (1.9)	1 (1.9)
PAROXETINE	2 (7.1)	3 (9.7)
SERTRALINE	3 (3.9)	1 (1.4)
VENLAFAXINE XR	2 (1.9)	2 (2.0)
FLATULENCE		
ESCITALOPRAM	1 (1.0)	2 (1.7)
FLUOXETINE	0	3 (5.7)
PAROXETINE	1 (3.6)	1 (3.2)
SERTRALINE	1 (1.3)	0
VENLAFAXINE XR	3 (2.9)	2 (2.0)

Table 10.4.1 continued.

SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE (%)	INCIDENCE (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
FATIGUE		
ESCITALOPRAM	8 (7.8)	12 (10.2)
FLUOXETINE	2 (3.7)	3 (5.7)
PAROXETINE	1 (3.6)	5 (16.1)
SERTRALINE	1 (1.3)	6 (8.7)
VENLAFAXINE XR	3 (2.9)	5 (5.0)
FEELING JITTERY		
ESCITALOPRAM	0	4 (3.4)
PAROXETINE	1 (3.6)	0
SERTRALINE	0	2 (2.9)
VENLAFAXINE XR	1 (1.0)	5 (5.0)
INFECTIONS AND INFESTATIONS		
UPPER RESPIRATORY TRACT INFECTION		
ESCITALOPRAM	5 (4.9)	6 (5.1)
FLUOXETINE	4 (7.4)	4 (7.5)
PAROXETINE	4 (14.3)	5 (16.1)
SERTRALINE	1 (1.3)	5 (7.2)
VENLAFAXINE XR	2 (1.9)	2 (2.0)
INVESTIGATIONS		
WEIGHT INCREASED		
ESCITALOPRAM	3 (2.9)	4 (3.4)
FLUOXETINE	0	1 (1.9)
PAROXETINE	0	2 (6.5)
SERTRALINE	2 (2.6)	2 (2.9)
VENLAFAXINE XR	4 (3.8)	3 (3.0)
METABOLISM AND NUTRITION DISORDERS		
INCREASED APPETITE		
ESCITALOPRAM	2 (2.0)	3 (2.5)
FLUOXETINE	0	1 (1.9)
PAROXETINE	2 (7.1)	1 (3.2)
SERTRALINE	0	3 (4.3)
VENLAFAXINE XR	2 (1.9)	2 (2.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
ARTHRALGIA		
ESCITALOPRAM	5 (4.9)	7 (5.9)
PAROXETINE	0	1 (3.2)
SERTRALINE	3 (3.9)	2 (2.9)
VENLAFAXINE XR	2 (1.9)	5 (5.0)
MYALGIA		
ESCITALOPRAM	1 (1.0)	3 (2.5)
FLUOXETINE	0	2 (3.8)
PAROXETINE	1 (3.6)	0
SERTRALINE	0	2 (2.9)
VENLAFAXINE XR	2 (1.9)	3 (3.0)
BACK PAIN		
ESCITALOPRAM	1 (1.0)	5 (4.2)
FLUOXETINE	1 (1.9)	0
PAROXETINE	2 (7.1)	0
SERTRALINE	1 (1.3)	1 (1.4)
VENLAFAXINE XR	1 (1.0)	2 (2.0)
NERVOUS SYSTEM DISORDERS		
AKATHISIA		
ESCITALOPRAM	4 (3.9)	25 (21.2)
FLUOXETINE	2 (3.7)	18 (34.0)
PAROXETINE	2 (7.1)	9 (29.0)
SERTRALINE	4 (5.2)	14 (20.3)
VENLAFAXINE XR	4 (3.8)	26 (26.0)
HEADACHE		
ESCITALOPRAM	9 (8.8)	9 (7.6)
FLUOXETINE	3 (5.6)	4 (7.5)
PAROXETINE	4 (14.3)	2 (6.5)
SERTRALINE	9 (11.7)	3 (4.3)
VENLAFAXINE XR	15 (14.3)	11 (11.0)
SOMNOLENCE		
ESCITALOPRAM	4 (3.9)	7 (5.9)
FLUOXETINE	3 (5.6)	2 (3.8)
PAROXETINE	3 (10.7)	1 (3.2)
SERTRALINE	2 (2.6)	3 (4.3)
VENLAFAXINE XR	2 (1.9)	10 (10.0)

Table 10.4.1 continued.

SYSTEM ORGAN CLASS PREFERRED TERM	INCIDENCE (%)	INCIDENCE (%)
TREMOR		
ESCITALOPRAM	1 (1.0)	5 (4.2)
FLUOXETINE	5 (9.3)	1 (1.9)
PAROXETINE	1 (3.6)	0
SERTRALINE	3 (3.9)	5 (7.2)
VENLAFAXINE XR	4 (3.8)	7 (7.0)
SEDATION		
ESCITALOPRAM	4 (3.9)	4 (3.4)
FLUOXETINE	0	2 (3.8)
PAROXETINE	0	2 (6.5)
SERTRALINE	1 (1.3)	3 (4.3)
VENLAFAXINE XR	1 (1.0)	4 (4.0)
DIZZINESS		
ESCITALOPRAM	2 (2.0)	5 (4.2)
FLUOXETINE	1 (1.9)	1 (1.9)
PAROXETINE	0	1 (3.2)
SERTRALINE	1 (1.3)	4 (5.8)
VENLAFAXINE XR	3 (2.9)	3 (3.0)
DISTURBANCE IN ATTENTION		
ESCITALOPRAM	1 (1.0)	4 (3.4)
FLUOXETINE	0	1 (1.9)
SERTRALINE	2 (2.6)	1 (1.4)
VENLAFAXINE XR	1 (1.0)	6 (6.0)
EXTRAPYRAMIDAL DISORDER		
ESCITALOPRAM	0	5 (4.2)
FLUOXETINE	0	2 (3.8)
VENLAFAXINE XR	0	1 (1.0)
PSYCHIATRIC DISORDERS		
RESTLESSNESS		
ESCITALOPRAM	2 (2.0)	14 (11.9)
FLUOXETINE	2 (3.7)	6 (11.3)
PAROXETINE	0	3 (9.7)
SERTRALINE	1 (1.3)	8 (11.6)
VENLAFAXINE XR	2 (1.9)	14 (14.0)
INSOMNIA		
ESCITALOPRAM	2 (2.0)	10 (8.5)
FLUOXETINE	1 (1.9)	5 (9.4)
PAROXETINE	0	2 (6.5)
SERTRALINE	2 (2.6)	7 (10.1)
VENLAFAXINE XR	4 (3.8)	6 (6.0)
ABNORMAL DREAMS		
ESCITALOPRAM	3 (2.9)	2 (1.7)
FLUOXETINE	0	1 (1.9)
PAROXETINE	1 (3.6)	2 (6.5)
SERTRALINE	1 (1.3)	2 (2.9)
VENLAFAXINE XR	4 (3.8)	2 (2.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
HYPERHIDROSIS		
ESCITALOPRAM	1 (1.0)	3 (2.5)
FLUOXETINE	2 (3.7)	1 (1.9)
SERTRALINE	2 (2.6)	3 (4.3)
VENLAFAXINE XR	5 (4.8)	1 (1.0)

The incidence of AEs for a particular System Organ Class is the incidence of all AEs in that System Organ Class.
 MedDRA Version: 9.1

Table 10.4.2 Outlier Criteria for Laboratory Parameters

Laboratory Tests	Criteria
Chemistry^a	
AST (SGOT)	≥ 3 x upper limit of normal (ULN)
ALT (SGPT)	≥ 3 x ULN
Alkaline phosphatase	≥ 3 x ULN
LDH	≥ 3 x ULN
BUN	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Uric acid	
Men	≥ 10.5 mg/dL
Women	≥ 8.5 mg/dL
Bilirubin (total)	≥ 2.0 mg/dL
CPK	≥ 3 x ULN
Prolactin	> ULN
Hematology^a	
Hematocrit	
Men	≤ 37 % and decrease of ≥ 3 percentage points from Baseline
Women	≤ 32 % and decrease of ≥ 3 percentage points from Baseline
Hemoglobin	
Men	≤ 11.5 g/dL
Women	≤ 9.5 g/dL
White blood count	≤ 2800/ mm ³ or ≥ 16,000/ mm ³
Eosinophils	≥ 10%
Neutrophils	≤ 15%
Platelet count	≤ 75,000/ mm ³ or ≥ 700,000/ mm ³
Urinalysis^a	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Casts	Increase of ≥ 2 units

Continued on the next page

Table 10.4.2, continued. Outlier Criteria for Laboratory Parameters

Additional Criteria	
AST/Total Bilirubin ^b	AST ≥ 3 x ULN and Total Bilirubin > 2 mg/dL
ALT/Total Bilirubin ^b	ALT ≥ 3 x ULN and Total Bilirubin > 2 mg/dL
Chloride	≤ 90 mEq/L or ≥ 118 mEq/L
Potassium	≤ 2.5 mEq/L or ≥ 6.5 mEq/L
Sodium	≤ 126 mEq/L or ≥ 156 mEq/L
Calcium	≤ 8.2 mg/dL or ≥ 12 mg/dL
Glucose, fasting	≥ 115 mg/dL
Cholesterol Total	≥ 240 mg/dL
LDL Cholesterol	≥ 160 mg/dL
HDL Cholesterol	≤ 30 mg/dL
Triglycerides	
Men	≥ 160 mg/dL Men
Women	≥ 120 mg/dL Women

^a As defined in “Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates,” FDA Division of Neuropharmacological Drug Products draft (2/27/87).

^b Based on Hy’s Law.¹

Table 10.4.3. Outlier Criteria for Vital Sign Parameters

Vital Sign	Criterion Value	Change from Baseline
Heart rate ^a	120 bpm	≥ 15 bpm increase
	50 bpm	≥ 15 bpm decrease
Systolic blood pressure ^a	180 mmHg	≥ 20 mmHg increase
	90 mmHg	≥ 20 mmHg decrease
Diastolic blood pressure ^a	105 mmHg	≥ 15 mmHg increase
	50 mmHg	≥ 15 mmHg decrease
Orthostatic Hypotension ^b	≥ 20 mmHg decrease in systolic blood pressure and a 25 bpm increase in heart rate from supine to standing	

^a As defined in “Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates,” FDA Division of Neuropharmacological Drug Products draft (2/27/87).

^b Blood pressure measurements were obtained after a patient had been supine for 5 minutes. A repeat measurement was then taken after the patient had been standing for 2 minutes.

Table 10.4.4. Outlier Criteria for ECG Parameters

Variable	Criterion Value ^a	Change Relative to Baseline ^a
Rate		
Tachycardia	≥ 120 bpm	increase of ≥ 15 bpm
Bradycardia	≤ 50 bpm	decrease of ≥ 15 bpm
Rhythm		
Sinus tachycardia ^b	≥ 120 bpm	increase of ≥ 15 bpm
Sinus bradycardia ^c	≤ 50 bpm	decrease of ≥ 15 bpm
Supraventricular premature beat	≥ 2 per 10 seconds	any increase
Ventricular premature beat	≥ 1 per 10 seconds	any increase
Supraventricular tachycardia	all	not present → present
Ventricular tachycardia	all	not present → present
Atrial fibrillation	all	not present → present
Atrial flutter	all	not present → present
Conduction		
1° atrioventricular block	PR ≥ 0.20 second	increase of ≥ 0.05 second
2° atrioventricular block	all	not present → present
3° atrioventricular block	all	not present → present
Left bundle-branch block	all	not present → present
Right bundle-branch block	all	not present → present
Pre-excitation syndrome	all	not present → present
Other intraventricular conduction block ^d	QRS ≥ 0.12 second	increase of ≥ 0.02 second
Infarction		
Acute or subacute	all	not present → present
Old	all	not present → present ≥ 12 weeks post study entry
ST/T Morphological		
Myocardial ischemia	all	not present → present
Symmetrical T-wave inversions	all	not present → present
Increase in QT _c	QT _c > 450	

^a Criteria developed for a previous BMS filing based upon discussions with the FDA Division of Neuropharmacological Drug Products.

^b No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

^c No current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.

^d No current diagnosis of left bundle branch block or right bundle branch block.

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this page is the manifestation of the electronic signature.**

/s/

Karen Brugge
9/27/2007 06:48:41 PM
MEDICAL OFFICER

Gwen Zornberg
10/23/2007 10:29:12 PM
MEDICAL OFFICER

I concur with Dr. Brugge's recommendation for an approvable
action based on the acceptable clinical safety and
efficacy findings analyzed in her review. Specific issues
will be addressed in labeling.