CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215430Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multidisciplinary Review and Evaluation

Application Type	Original 505(b)2 NDA
Application Number(s)	NDA 215430
Priority or Standard	Priority
Submit Date(s)	February 21, 2021
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Division/Office	Division of Psychiatry/Office of Neuroscience
Review Completion Date	August 18, 2022
Established/Proper Name	Bupropion hydrochloride and dextromethorphan hydrobromide tablets
(Proposed) Trade Name	Auvelity
Pharmacologic Class	Antidepressant
Code name	2020100
Applicant	Axsome Therapeutics
Dosage form	Tablets
Applicant proposed Dosing Regimen	• Starting dose: one tablet by mouth daily for 3 days • After 3 days, one tablet by mouth twice daily, separated by at least 8 hours.
Applicant Proposed Indication(s)/Population(s)	Treatment of major depressive disorder (MDD)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	370143000
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Not applicable
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Not applicable
Recommended Dosing Regimen	Not applicable

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OB, Office of Biostatistics
OCP, Office of Clinical Pharmacology
OPQ, Office of Pharmaceutical Quality
OPDP, Office of Prescription Drug Promotion
OSI, Office of Scientific Investigations
OSE, Office of Surveillance and Epidemiology
PLT, Patient Labeling Team
CSS, Controlled Substance Staff
DEPI, Division of Epidemiology
DMEPA, Division of Medication Error Prevention and Analysis
DP, Division of Psychiatry
DPMH, Division of Pediatric and Maternal Health
DRISK, Division of Risk Management

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BID	twice daily
BLA	biologics license application
BP	blood pressure
BUP	bupropion
CSS	Controlled Substance Staff
C-SSRS	Columbia-Suicide Severity Rating Scale
COA (PRO)	clinical outcome assessment (patient-reported outcome)
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum concentration
COVID-19	coronavirus disease-2019
CR	complete response
CRF	case report form
CSR	clinical study report
DM	dextromethorphan
DMF	Drug Master File
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DX	dextrorphan
ECG	electrocardiogram
EFD	embryo-fetal developmental
FDA	Food and Drug Administration
GD	gestational day
HAMD-17	Hamilton Depression Rating Scale
ICH	International Conference on Harmonisation
IID	inactive ingredients database
LD	listed drug
LOCF	last observation carried forward
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MDE	major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effect model for repeated measure

MPPRC	Medical Policy and Program Review Council
MTD	maximum tolerated dose
NDA	new drug application
NMDA	N-methyl-D-aspartate
NOAEL	no observed adverse effect level
OSI	Office of Scientific Investigation
PK	pharmacokinetics
PT	preferred term
PWC-20	Physician Withdrawal Checklist
QIDS-SR-16	Quick Inventory of Depressive Symptomatology – Self-Rated
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SCID-5-CT	Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Clinical Trials Version
SD	standard deviation
SE	standard error
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TRD	treatment-resistant depression
USP	United States Pharmacopeia
VAMS	Visual Analog Mood Scale
VC	variance-component

1. Executive Summary

1.1. Product Introduction

AXS-05 (proposed proprietary name: Auvelity) is a fixed-dose combination drug containing bupropion HCl 105 mg (an aminoketone) and dextromethorphan HBr 45 mg (an uncompetitive N-methyl-D-aspartate receptor antagonist and sigma-1 receptor agonist). The proposed indication for AXS-05 is for the treatment of major depressive disorder (MDD). The proposed dosing regimen for Auvelity tablets is one tablet daily by mouth for 3 days, then one tablet by mouth twice daily, with doses separated by at least 8 hours.

Dextromethorphan is approved as a cough suppressant and available over the counter. It is also approved in combination with quinidine sulfate for pseudobulbar affect (trade name: Nuedexta). Bupropion is approved for the treatment of major depressive disorder (trade names: Wellbutrin, Wellbutrin SR, Wellbutrin XL, Forfivo XL, Aplenzin) and for the treatment of smoking cessation (trade name: Zyban). This 505(b)(2) new drug application (NDA) relies, in part, on the Agency's findings of safety and effectiveness for Nuedexta (NDA 021879) and Wellbutrin SR (NDA 020358).

The Applicant proposes that the combination of bupropion and dextromethorphan may have additive antidepressant effects because each drug interacts with receptor systems believed to be involved in the modulation of mood. The Applicant also proposes that pharmacokinetic complementarity between the two components may enhance the ability of dextromethorphan to exert an antidepressant effect. When given alone, dextromethorphan is metabolized quickly by cytochrome P450 isoenzyme 2D6 (CYP2D6), and systemic exposures are low. However, when given concomitantly with bupropion, a CYP2D6 inhibitor, dextromethorphan exposure is increased.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of the effectiveness of AXS-05 for the treatment of MDD (Section 8.1.5) from one adequate and well-controlled trial plus confirmatory evidence. In addition, the Applicant has demonstrated that each component of the fixed-dose combination drug contributes to the claimed effects (21 CFR 300.50).

The Applicant submitted two trials to support the effectiveness of AXS-05 for the treatment of MDD. Study MDD-301 was an adequate and well-controlled trial in which 327 subjects with MDD were randomized to receive AXS-05 (one tablet twice daily) or placebo twice daily for 6 weeks. Subjects receiving AXS-05 had a statistically superior improvement on the primary efficacy endpoint (change in Montgomery-Åsberg Depression Rating Scale [MADRS] total score from baseline to Week 6) compared to subjects receiving placebo. This trial demonstrated the efficacy of AXS-05 compared to placebo in the treatment of MDD.

Study MDD-201 was a phase 2 study in which 97 subjects with MDD were randomized to receive AXS-05 (one tablet twice daily) or bupropion SR (105 mg twice daily) for 6 weeks. The daily bupropion dose in each arm was lower than the labeled usual adult target dose for Wellbutrin SR. However, because each treatment arm included the same dose of bupropion, this study allowed for the assessment of the independent contribution of dextromethorphan to the therapeutic effect of the combination product. This study was positive on the Applicant's pre-specified primary efficacy endpoint (mean change in MADRS total score from baseline to each time point from Week 1 to Week 6 at which an onsite visit occurred). The statistically significant improvement on the Applicant's pre-specified primary efficacy endpoint, along with the magnitudes of separation between AXS-05 and bupropion on MADRS scores at early time points in the study, provided confirmatory evidence of effectiveness. Although the effectiveness of bupropion was not isolated in this study given its design, the contribution of bupropion is evident, in part, because dextromethorphan could not have had an antidepressant effect on its own at this dose without the inhibition of CYP2D6 by bupropion, given its otherwise rapid metabolism by CYP2D6 as shown by PK data (Figure 12). Additionally, bupropion is an approved antidepressant.

Collectively, the evidence described above is sufficient not only to provide substantial evidence of effectiveness of AXS-05 to treat MDD but also to fulfill the combination rule (21 CFR 300.50).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

AXS-05 (bupropion hydrochloride 105 mg and dextromethorphan hydrobromide 45 mg tablets; proposed trade name: Auvelity) is a fixed-dose combination drug product proposed as a treatment of major depressive disorder (MDD) in adults. The Applicant has submitted data to demonstrate that AXS-05 produces greater reduction in MDD symptoms (measured by the MADRS total score) than bupropion hydrochloride or placebo. The review team recommends approval of this NDA.

MDD is a common, serious, and life-threatening psychiatric syndrome characterized by at least 2 weeks of depressed mood or loss of interest or pleasure, in addition to other depressive symptoms, that causes clinically significant distress or impairment in functioning. MDD impacts individuals' social functioning, educational and occupational functioning, self-care, physical health, and quality of life. In severe episodes, MDD can result in psychiatric hospitalization or suicide. There are dozens of antidepressants approved for the treatment of MDD, and most target serotonergic, noradrenergic, and/or dopaminergic neurotransmission. There are limited data supporting the superiority of one antidepressant over another, but the safety and tolerability differ across drugs and drug classes. Half or more patients do not experience symptomatic remission from MDD from a given antidepressant trial, and most antidepressants require up to 8 to 12 weeks of treatment for patients to experience maximal improvement. There is a need for more effective antidepressants that provide therapeutic benefits more quickly.

The Applicant has submitted two studies to support the effectiveness of AXS-05 for the treatment of MDD. Study MDD-301 was a phase 3 adequate and well-controlled trial in which 327 subjects with MDD were randomized to receive AXS-05 (one tablet twice daily) or placebo twice daily for 6 weeks. Study MDD-301 was positive on its primary efficacy endpoint (change from baseline to Week 6 on the MADRS total score) as well as key secondary endpoints that demonstrated benefit at Week 1 and Week 2. Study MDD-201 was a phase 2 study in which 97 subjects with MDD were randomized to receive AXS-05 (one tablet twice daily) or bupropion SR (105 mg twice daily) for 6 weeks. Study MDD-201 was positive on its pre-specified primary efficacy endpoint (mean change in MADRS total score from baseline to each time point from Week 1 to Week 6 at which an onsite visit occurred). The statistically significant improvement on the pre-specified primary efficacy endpoint, along with the magnitudes of separation between AXS-05 and bupropion on MADRS scores at early time points in the study, provided confirmatory evidence of effectiveness. Although the effectiveness of bupropion was not isolated in this study given its design, the contribution of bupropion is evident, in part, because dextromethorphan could not have had an antidepressant effect on its own at this dose without the inhibition of CYP2D6 by bupropion, given its otherwise rapid metabolism by CYP2D6 (Figure 12). Additionally, bupropion is an approved antidepressant.

The safety profile of AXS-05 was generally well-characterized in the submitted application. AXS-05 appears to be well-tolerated, and the overall safety profile does not appear to be substantially worse than other antidepressants approved for the treatment of MDD. The most common

treatment-emergent adverse reactions were dizziness, nausea, headache, dry mouth, and somnolence. Dextromethorphan, at high doses, is known to produce psychedelic-like and dissociative effects that are associated with abuse potential. However, there was minimal evidence suggesting abuse liability in the AXS-05 development program, and AXS-05 does not appear to present an increased liability for abuse compared to widely available over-the-counter dextromethorphan products. There were several safety uncertainties, including the need for additional data on the effects of AXS-05 on pregnancy, embryofetal development, and postnatal development; the neurotoxic potential of dextromethorphan to the young and developing brain; and the effects of severe renal and hepatic impairment on AXS-05 pharmacokinetics. The initial label will recommend that AXS-05 should not be used by women who are pregnant or breastfeeding. The safety concerns and uncertainties can be adequately addressed by product labeling and additional studies in the postmarketing period that will inform future label updates.

In conclusion, substantial evidence of effectiveness has been demonstrated by the adequate and well-controlled Study MDD-301 and confirmatory evidence as described above. Collectively, the evidence described above is sufficient to fulfill not only to provide substantial evidence of effectiveness of AXS-05 to treat MDD but also to fulfill the combination rule (21 CFR 300.50). The safety of AXS-05 has been adequately characterized to support product approval, and remaining uncertainties will be addressed by postmarketing studies and through product labeling. AXS-05 is anticipated to be a useful addition to the antidepressant armamentarium. The data from the AXS-05 development program suggest that patients may experience benefits as early as 1 week after initiation of treatment, which is favorable when compared to other available oral antidepressants. The dextromethorphan component of AXS-05 has not been previously demonstrated to have antidepressant effects, and its inclusion in AXS-05 introduces a mechanism of action distinct from other antidepressants.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Major Depressive Disorder (MDD) is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as a clinical syndrome characterized by at least 2 weeks of depressed mood or loss of interest or pleasure (in addition to ≥4 additional symptoms listed in Section 2.1) that cause clinically significant distress or impairment in functioning. • MDD impacts individuals' social functioning, educational and occupational functioning, self-care, physical health, and quality of life. MDD is considered a leading cause of disability worldwide.	Given its prevalence, disabling impacts, and impacts on mortality, MDD is considered to be a common, serious, and life-threatening illness.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• An estimated 7 to 10% of adults in the United States have at least one major depressive episode each year, and the lifetime prevalence of MDD is estimated at 12 to 20%. • MDD is more common in younger adults than older adults, with an estimated 12-month prevalence of 11 to 13% in adults <65 years old versus 5% in adults ≥65 years old. • MDD is more common in women than in men, with an estimated 12-month prevalence of 13% in women and 7% in men. • MDD often has a chronic course with recurrent episodes; following recovery from a major depressive episode, an estimated rate of recurrence over two years is >40%. • Severe episodes of MDD can result in hospitalization or suicide; a 38-year prospective study in patients with MDD found a 27-fold increased incidence of suicide as compared to the general population.	
Current Treatment Options	• The goal of MDD treatment is to reduce symptom severity, restore baseline functioning, and minimize the risk of relapse. • Dozens of antidepressants, grouped by classes such as selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, and serotonin and norepinephrine reuptake inhibitors, are currently approved for the treatment of MDD. Most currently approved treatments target serotonergic, noradrenergic, and/or dopaminergic neurotransmission. The safety and tolerability profiles differ across antidepressant classes according to their mechanisms of action. • There is limited evidence supporting the superiority of one antidepressant over another. Few comparative efficacy trials have been conducted, and network meta-analyses have found relatively small differences that were judged to be not clinically relevant. When	Although there are numerous antidepressants approved for the treatment of MDD, the fact that half or more patients do not experience remission from an antidepressant trial indicates the need for more effective antidepressants. Relatedly, the fact that it may require 8 to 12 weeks of antidepressant treatment for patients to experience substantial improvement indicates the need for antidepressants that provide benefits more quickly. The treatment armamentarium would benefit

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	grouped together, meta-analyses of randomized controlled antidepressant trials have found that approximately 43 to 50% of patients receiving antidepressants experience remission from MDD by 6 weeks, as compared to 25 to 37% of patients receiving placebo treatment. Meta-analyses have found that patients starting antidepressants may experience some improvement within 1 or 2 weeks, but many patients require 8 to 12 weeks of treatment to experience substantial improvement or remission. • Antidepressant selection is generally based on factors such as safety, adverse reaction profile, potential for interactions with other drugs or comorbid illnesses, ease of use, and patient preference. • Patients who do not have an adequate response to initial treatment with an antidepressant may benefit from switching to a different antidepressant or augmenting their current treatment with an additional drug. Several atypical antipsychotics are approved for the adjunctive treatment of MDD, and other off-label augmentation agents include lithium, thyroid hormone, or a second antidepressant. • Patients with treatment-resistant depression (generally defined as patients who do not respond satisfactorily after two adequate trials of antidepressants) may be treated with a Food and Drug Administration-approved drug for treatment-resistant depression, such as olanzapine/fluoxetine monotherapy or esketamine in conjunction with an oral antidepressant. • Nonpharmacologic treatments for MDD include psychotherapy, repetitive transcranial magnetic stimulation, and electroconvulsive therapy. Nonpharmacologic treatments are often administered in conjunction with antidepressants. • A key gap in our understanding of MDD treatment is determining	from novel antidepressants to provide additional treatment options, particularly if the novel antidepressant is more effective or provides benefit more quickly than existing drugs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	which treatment(s) will be effective and well-tolerated for a specific patient. This frequently results in the need for trials of several different antidepressants before an acceptable treatment is identified.	
Benefit	• The Applicant submitted two studies to demonstrate the effectiveness of AXS-05 for the treatment of MDD: Studies MDD-201 and MDD-301. • Study MDD-201 was a phase 2 study in which 97 subjects with MDD were randomized to receive AXS-05 (one tablet twice daily) or bupropion SR (105 mg twice daily) for 6 weeks. The prespecified primary efficacy endpoint was the mean change from baseline on the MADRS total score, averaged across each time point in the study at which an onsite visit occurred (Weeks 1 to 6). • The prespecified primary efficacy endpoint in Study MDD-201 has not previously been accepted by the Agency to support regulatory approval of an antidepressant. One potential consideration of an efficacy endpoint that averages changes from baseline across multiple intermediate time points is that a statistically positive result could be driven by treatment differences early in the time course that wane by end of treatment. The Division advised the Applicant at the Pre-NDA meeting that the change from baseline to end of treatment was more typically used to support the approval of antidepressants. • In Study MDD-201, patients receiving AXS-05 had a significantly greater improvement on the Applicant's pre-defined primary efficacy endpoint and analysis than patients who received bupropion (bupropion-subtracted difference: 4.90 (SE: 0.93), $p<0.001$). However, the Applicant's analysis included one subject who never took a dose of bupropion and three subjects who received bupropion but had no	The submitted data meets the standard for substantial evidence of effectiveness, which is provided by one adequate and well-controlled study and confirmatory evidence. Study MDD-301 is a positive, adequate, and well-controlled study that demonstrated the efficacy of AXS-05 versus placebo in the treatment of MDD. Study MDD-201 was positive on its pre-specified primary efficacy endpoint, even when four subjects who should not have been included according to the pre-defined criteria were removed from the mITT analysis set. The statistically significant superiority of AXS-05 to bupropion on the primary endpoint, along with the magnitudes of separation between treatment arms at early time points, demonstrate the contribution of dextromethorphan to AXS-05 as well as provide confirmatory evidence for the effectiveness of AXS-05. Although the effectiveness of bupropion was not isolated in Study MDD-201, the contribution is evident, in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	postbaseline efficacy assessments; these four patients should not have been included in the efficacy analysis set according to the prespecified modified intent-to-treat (mITT) population definition. When these four patients are removed, the bupropion-subtracted treatment difference decreased to 3.78 (SE: 2.14) but remained statistically significant ($p<0.001$). Multiple sensitivity analyses conducted by the biostatistical reviewer yielded the same conclusion of a significant treatment difference on the Applicant's prespecified primary efficacy endpoint. • The Applicant and the Agency also analyzed Study MDD-201 using the efficacy endpoint traditionally accepted to support the approval of antidepressants (change from baseline to end of treatment in MADRS total score without averaging scores at intermediate time points). In this case, AXS-05 was found to be significantly superior to bupropion by the Applicant's analysis, but the treatment difference became non-significant after removing the four patients who should not have been included in the mITT analysis set based on the prespecified mITT population definition. • Study MDD-301 was a phase 3 study in which 327 subjects with MDD were randomized to receive AXS-05 (one tablet twice daily) or placebo twice daily for 6 weeks. The prespecified primary efficacy endpoint was the change from baseline to Week 6 on the MADRS total score. Key secondary endpoints included (1) the change in MADRS total score from baseline to Week 1, (2) the change in MADRS total score from baseline to Week 2, (3) the percentage of subjects achieving MADRS total score of ≤10 ("remission") at Week 2, and the percentage of subjects achieving a ≥50% reduction in MADRS total score ("response") at Week 6.	part, because dextromethorphan could not have had an antidepressant effect on its own at this dose without the inhibition of CYP2D6 by bupropion, given its otherwise rapid metabolism by CYP2D6 (Figure 12). Additionally, bupropion is an approved antidepressant. Collectively, these sources of evidence are sufficient to fulfill the combination rule (21 CFR 300.50). The benefit of AXS-05 is anticipated to be clinically meaningful to patients. The clinical research literature suggests that a 6- to 9-point reduction in MADRS total score is considered to be clinically meaningful to patients with MDD. In Study MDD-301, over 70% of subjects receiving AXS-05 experienced a ≥7-point reduction in MADRS total score by Week 6. Further, the statistically significant differences between AXS-05 and placebo on the MADRS total score at Week 1 and Week 2 suggest that patients may experience improvement more quickly than is typical for most approved antidepressants. One uncertainty regarding benefit is whether the dextromethorphan component of this combination product continues to contribute

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The prespecified primary efficacy endpoint for Study MDD-301 is acceptable and has been used to support the approval of numerous antidepressants. The key secondary endpoints comparing the treatment effects at Weeks 1 and 2 are useful to demonstrate symptomatic benefit at earlier time points than the end of treatment. The key secondary endpoints comparing the percentage of subjects meeting "response" or "remission" definitions are not currently accepted for labeling, because these concepts can be variably defined and understood by clinicians. • In Study MDD-301, patients receiving AXS-05 had a significantly greater improvement on the MADRS total score from baseline to Week 6 than patients receiving placebo (placebo-subtracted difference: 3.87 (SE: 1.26), p=0.002). AXS-05 also showed statistically significant improvement versus placebo at Week 1 (placebo-subtracted difference: 2.23 (SE: 0.83), p=0.007) and at Week 2 (placebo-subtracted difference: 3.44 (SE: 1.03), p<0.001). • There were no noteworthy differences in efficacy findings in Studies MDD-201 or MDD-301 according to gender, race, or age.	to long-term efficacy of AXS-05 for the treatment of MDD. In Study MDD-201, the magnitudes of mean difference between the AXS-05 and bupropion arms decreased from Weeks 3 to 6. The Applicant will conduct a postmarketing study to establish whether dextromethorphan provides a long-term contribution to benefit.
Risk and Risk Management	• The safety database included a total of 1114 subjects exposed to at least one dose of AXS-05 in the three 6-week controlled trials (Studies MDD-201, MDD-301, and 301) and the long-term, open-label safety trial (Study 303). Subjects in Study 301 had treatment-resistant MDD, as opposed to non-treatment-resistant MDD in the other two controlled trials, but their inclusion in the safety database is acceptable given the population similarities. The safety database included 597 subjects exposed to AXS-05 for ≥6 months and 110 subjects exposed for ≥12 months, meeting International Conference on Harmonisation (ICH) E1 exposure guidelines. The extent and	The safety profile is generally well-characterized. AXS-05 appears to be well-tolerated, and the safety profile does not appear to be substantially worse than other antidepressants approved for the treatment of MDD. Dextromethorphan, at high doses, is known to produce psychedelic-like and dissociative effects that are associated with abuse potential. However, there was minimal

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	quality of the safety database are acceptable. • The overall understanding of the safety profile of AXS-05 is also informed by the safety database of the listed drug (LD) bupropion sustained-release (Wellbutrin SR, approved for the treatment of MDD) and the LD dextromethorphan hydrobromide/quinidine sulfate (Nuedexta, approved for the treatment of pseudobulbar affect). • The most common treatment-emergent adverse reactions to AXS-05 experienced by subjects in 6-week controlled trials were dizziness (13.7%), nausea (10.2%), headache (6.6%), dry mouth (5.5%), and somnolence (5.2%). • AXS-05 appeared to be well-tolerated, with only 2.7% of subjects discontinuing participation in the 6-week trials due to treatment-emergent adverse events and 8.4% of subjects discontinuing participation in the 12-month safety study due to treatment-emergent adverse events. • The safety review did not identify any significant safety issue that had not been previously identified and labeled for the LDs. • Patients with moderate renal impairment show greater exposure to dextromethorphan, bupropion, and metabolites of bupropion; therefore, patients with moderate renal impairment should use once-daily rather than twice-daily dosing of AXS-05 and patients with severe renal impairment should not use AXS-05. • Patients who are CYP2D6 poor metabolizers or who use strong CYP2D6 inhibitors show greater exposure to dextromethorphan; therefore, patients who are CYP2D6 poor metabolizers or who use strong CYP2D6 inhibitors should use once-daily rather than twice-daily dosing of AXS-05. • Regarding the abuse potential for AXS-05, neither bupropion nor	evidence suggesting abuse liability in the AXS-05 development program. Overall, AXS-05 does not appear to present an increased liability for abuse compared to widely available over-the-counter dextromethorphan products. There were some safety uncertainties related to effects on pregnancy, embryofetal development, and postnatal development. In addition, the Applicant has not addressed the neurotoxic potential of dextromethorphan to the young and developing brain as described in the Nuedexta label. The label will recommend against the use of AXS-05 in women who are pregnant or breastfeeding until adequate data are collected in the postmarketing setting to support revision. The Applicant should also evaluate the effect of severe renal and hepatic impairment on the pharmacokinetics of AXS-05 in order to provide appropriate dosing recommendations for these populations. Overall, the safety concerns can be adequately addressed by product labeling, and safety uncertainties can be addressed by product labeling and postmarketing studies to support future labeling revisions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	dextromethorphan is scheduled under the Controlled Substances Act. High doses of dextromethorphan are known to produce psychedelic-like and dissociative effects. The Controlled Substances Staff concluded that, relative to highly concentrated and flavored dextromethorphan products available over-the-counter, AXS-05 does not appear to present an increased liability for abuse. The Controlled Substances Staff recommends that AXS-05 should not be controlled under the Controlled Substances Act but that the label should include a Drug Abuse and Dependence section that describes the abuse-related risks of dextromethorphan. • The Applicant conducted an embryofetal development toxicity study in pregnant mice and found no effects on embryofetal development. However, based on embryofetal developmental toxicity findings in rabbits in the labels of both listed drugs, the Nonclinical Pharmacology/Toxicology team recommends that an embryofetal developmental toxicity study be conducted in rabbits. No studies were conducted with AXS-05 to evaluate its effects on fertility or on pre- or postnatal development, and the Applicant is relying on findings described in the listed drug labels. Because the data in the Nuedexta label is confounded by the presence of quinidine, the Nonclinical team also recommends that the Applicant conduct fertility and pre- and postnatal studies in the postmarketing period.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient-reported outcome (PRO)	7.3
		☐	Observer-reported outcome (ObsRO)	
		X	Clinician-reported outcome (ClinRO)	7.3
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data were not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

Major depressive disorder (MDD) is a serious and life-threatening illness that affects the individual's social functioning, educational and occupational functioning, self-care, physical health, and quality of life. MDD is considered a leading cause of disability worldwide[1] and is associated with increased mortality rates.

The 2017 National Survey on Drug Use and Health revealed that an estimated 17.3 million adults in the United States had at least one major depressive episode (MDE) that year. This number represented 7.1% of all adults in the United States. The lifetime prevalence of MDD is estimated at 12 to 20%. MDD is more common in younger adults than older adults, with an estimated 12-month prevalence of 11 to 13% in adults <65 years old versus 5% in adults >65 years old. MDD is more common in women than in men, with an estimated 12-month prevalence of 13% in women and 7% in men. The illness often has a chronic course with recurrent episodes; following recovery from a major depressive episode, the estimated rate of recurrence over 2 years is >40%. Severe episodes can result in hospitalization or suicide. A 38-year prospective study in patients with MDD found a 27-fold increased incidence of suicide as compared to the general population.

According to the DSM-5[2], an MDE is a period of at least 2 weeks characterized by five or more of the following symptoms, with at least one of the symptoms being either (1) depressed mood or (2) loss of interest or pleasure:

1. Depressed mood most of the day, nearly every day.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
3. Significant weight loss when not dieting, or weight gain, or decrease or increase in appetite nearly every day.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day.
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day.
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day.
9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

In addition to the presence of these symptoms, an MDE is characterized by clinically significant distress caused by the symptoms or impairment in social, occupational, or other important areas of functioning. A patient may be diagnosed with MDD after it is determined that the

[1] https://www.who.int/news-room/fact-sheets/detail/depression. Accessed July 26, 2021.
[2] American Psychiatric Association (2013).

patient has had either a single MDE or recurrent MDEs.

2.2. Analysis of Current Treatment Options

Table 1 lists the antidepressant medications currently approved for the treatment of major depressive disorder. Most currently approved treatments target serotonergic, noradrenergic, and/or dopaminergic neurotransmission. The safety and tolerability profiles differ across antidepressant classes according to their mechanisms of action. Nonpharmaceutical treatment modalities include electroconvulsive therapy, transcranial magnetic stimulation, and psychotherapy.

There is limited evidence supporting the superiority of one antidepressant over another. Few comparative efficacy trials have been conducted, and network meta-analyses have found relatively small differences that were judged to be not clinically relevant[3]. When grouped together, meta-analyses of randomized controlled antidepressant trials have found that approximately 43 to 50% of patients receiving antidepressants experience remission from MDD by 6 weeks, as compared to 25 to 37% of patients receiving placebo treatment[4]. Meta-analyses have found that patients starting antidepressants may experience some improvement within 1 or 2 weeks, but many patients require 8 to 12 weeks of treatment to experience substantial improvement or remission[5].

Although many treatment options are available, it is currently not possible to predict which treatment will be effective for a particular patient. Patients who do not experience symptom relief from the first antidepressant prescribed may respond to an antidepressant from another class. Alternatively, switching to a different antidepressant within the same class may benefit some patients, because a patient may experience differences in tolerability even among antidepressants in the same class. For these reasons, there is societal benefit in expanding the range of antidepressant treatment options available to clinicians, particularly if a novel antidepressant is more effective or provides benefit more quickly than existing drugs.

[3] Gartlehner, G, RA Hansen, LC Morgan, K Thaler, L Lux, M Van Noord, U Mager, P Thieda, BN Gaynes, T Wilkins, M Strobelberger, S Lloyd, U Reichenpfader, and KN Lohr, 2011, Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis, Ann Intern Med, 155(11):772-785.

[4] Gibbons, RD, K Hur, CH Brown, JM Davis, and JJ Mann, 2012, Benefits from antidepressants: synthesis of 6-week patient-level outcomes from double-blind placebo-controlled randomized trials of fluoxetine and venlafaxine, Arch Gen Psychiatry, 69(6):572-579.

[5] Trivedi, MH, AJ Rush, SR Wisniewski, AA Nierenberg, D Warden, L Ritz, G Norquist, RH Howland, B Lebowitz, PJ McGrath, K Shores-Wilson, MM Biggs, GK Balasubramani, and M Fava, 2006, Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice, Am J Psychiatry, 163(1):28-40.

Table 1. Currently Approved Antidepressant Medications

Medication Class	Approved Medications
Tricyclic antidepressants	Imipramine, desipramine, amitriptyline, nortriptyline, doxepin, amoxapine, trimipramine, protriptyline, maprotiline
Monoamine oxidase inhibitors	Phenelzine, tranylcypromine, isocarboxazid, maprotiline, selegiline patch
Selective serotonin reuptake inhibitors	Fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram, vilazodone
Serotonin and norepinephrine reuptake inhibitors	Venlafaxine, duloxetine, desvenlafaxine
Other antidepressants	Bupropion, trazodone, nefazodone, mirtazapine

Source: Generated by the Clinical Reviewer.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

AXS-05 has not been marketed in the United States or in any other country.

3.2. Summary of Presubmission/Submission Regulatory Activity

February 9, 2017 Fast Track Designation

- Granted on the basis of innovative pharmacodynamic and pharmacokinetic mechanisms proposed for the combination product.

March 25, 2019 Breakthrough Therapy Designation

- Granted on the basis of the results of Study AXS-05-MDD-201 which, as reported by the Applicant, demonstrated statistically significant improvement in depressive symptoms compared to a widely used approved treatment (bupropion) and an onset of therapeutic effect that appeared to be more rapid than typically seen for approved antidepressants.

April 3, 2019 End-of-Phase 2 Meeting

- ***Food and Drug Administration (FDA) Combination Rule:*** The Agency agreed that dextromethorphan, if given alone at the dosage used in AXS-05, would be metabolized too quickly to allow the direct evaluation of its effects on symptoms of depression. The Agency agreed that the completed study AXS-05-MDD-201 and the ongoing Study AXS-05-301, if successful, would satisfy the fixed combination drug product requirement. Because Study AXS-05-MDD-201 appeared to have demonstrated that dextromethorphan contributes an antidepressant effect beyond the antidepressant effect of bupropion, the Agency agreed that the proposed trial, AXS-05-MDD-301, could be designed to include only a placebo control.

- ***MDD*** (b) (4) ***indication:*** The Agency agreed that the combination of a phase 2 trial in MDD, a phase 3 trial in MDD, and a phase 2/3 trial in treatment-resistant depression (TRD) would support a new drug application (NDA) filing for the indication of treatment of MDD. However, this set of trials would not support (b) (4) (b) (4)

- ***Extrapolation of safety:*** The Agency noted that, although the combination of dextromethorphan and quinidine is approved for chronic use, it is unlikely that data on that combination can be used to extrapolate the long-term safety of the combination of dextromethorphan and bupropion. The dextromethorphan exposure is considerably higher when dextromethorphan is combined with bupropion than when it is combined

with quinidine, so the safety data in the Nuedexta database may underestimate the safety risks of the level of dextromethorphan exposure that will occur with chronic use of AXS-05. The Agency expressed that the most appropriate plan would be to directly assess the safety of AXS-05 by continuing to build the AXS-05 safety database until it reaches the number of patients recommended by the ICH E1 Guideline (at least 1500 subjects with short-term exposure, 300 to 600 subjects with exposure for at least 6 months, and 100 subjects with exposure for at least 1 year).

- ***Long-term safety trial:*** The Applicant asked whether patients who had not participated in a previous AXS-05 trial could enroll directly into the planned open-label trial. The Agency responded that this would be acceptable, as long as the protocol included a minimum 6-week lead-in treatment period for de novo patients and enrolled only AXS-05 responders into the open-label treatment period. The Agency also clarified that both MDD and TRD patients could, and should, be included in the safety database.

- ***Nonclinical, bridging toxicity studies:*** The Applicant was completing a 3-month repeat-dose toxicity study of AXS-05 in mice and intended to initiate an embryo-fetal developmental (EFD) toxicity study of AXS-05 in mice. The Agency asked why mouse and not rabbit would be used for the bridging toxicity studies. The Applicant stated that the mouse appeared to be a better model than the rat, given that it is closer to the human pharmacokinetic (PK) profile. The Agency did not object to this rationale and indicated that the validity of the studies would be a review issue.

- ***Biometrics, Study MDD-201 efficacy analysis:*** The Agency noted that whether the completed study AXS-05-MDD-201 is considered positive will be a matter of review. The primary efficacy analysis is based on last observation carried forward (LOCF) mixed-effect model for repeated measure (MMRM) method. Unless the dropout rates are negligible, inferences based on the LOCF imputation approach are more likely to be biased as they would likely overestimate or underestimate treatment effects.

- ***Clinical Pharmacology, 505(b)(2) bridging:*** The Agency noted that, for submission of a 505(b)(2) application that relies on findings of safety and/or effectiveness for one or more LDs, the Applicant must establish a bridge (e.g., via comparative bioavailability data) between the proposed product and each LD. The Agency also noted that some properties are unique to the combination product (e.g., drug interaction potential, PK in specific populations), and that information cannot be borrowed from the LDs. Therefore, the development program would need to include studies of drug-drug interactions, PK in specific populations (e.g., CYP2D6 poor metabolizers, hepatic impairment, renal impairment), and a thorough study of potential for QT interval prolongation (thorough QT interval study). The Applicant agreed to submit protocols for the recommended studies.

- ***Control Substance Staff, abuse potential:*** As AXS-05 is formulated with two central nervous system-active drugs that activate receptors linked to abuse-related effects and drugs that are abused, the Agency recommended that the Applicant characterize the abuse potential of the combination product. The Agency recommended conducting a clinical assessment of physical dependence and withdrawal at the conclusion of a planned clinical study. The Agency further recommended that the Applicant monitor and report all central nervous system or abuse-related adverse events (AEs) from the clinical studies and provide detailed narratives for these AEs. The Agency asked the Applicant to provide the list of terms that prompted these reports, including abuse-related AE terms. The Agency mentioned the high dextromethorphan plasma levels produced in humans following administration of AXS-05 and the possibility of the Applicant needing to conduct a human abuse potential study. The Agency recommended that the Applicant justify with supportive data whether a human abuse potential study would or would not be needed as part of their abuse potential assessment of AXS-05.

June 11, 2020 Pre-NDA Meeting

- ***Key secondary endpoints:*** The Agency previously agreed that the change in the Montgomery-Åsberg Depression Rating Scale (MADRS) scores at Week 1 and Week 2 were acceptable key secondary endpoints. The Applicant asked whether the replication of each of the key secondary endpoints in at least two of the three controlled trials would be sufficient to support description of the key secondary endpoints in product labeling. The Agency stated that details of product labeling would be a matter of the final review of data from each of the three studies.

- ***Nonclinical, bridging toxicity studies:*** The Applicant noted that the 3-month bridging general toxicity and EFD toxicity studies have been completed. The Applicant also noted that the existing nonclinical data on bupropion, dextromethorphan, and the combination of dextromethorphan and quinidine, from the current product inserts for Wellbutrin, Wellbutrin SR, and Nuedexta, will be included in the NDA. The Agency requested that the Applicant provide a justification for why the mouse is the most relevant species and how the data from the mouse studies will provide a bridge to the nonclinical data in the different sections of the label of the LD. The Applicant agreed to submit the justification to the investigational new drug application for review before filing the NDA.

- ***Biometrics, Study MDD-201 efficacy analysis:*** The Agency noted that Study AXS-05-MDD-201 was originally submitted as a phase 2 study to evaluate the safety and tolerability of AXS-05. The primary efficacy endpoint (mean change from baseline in MADRS total score, averaged across all visits), which did not appear in the study protocol but was added to the Statistical Analysis Plan later, has not previously been used to support regulatory approval of an antidepressant. More typically, the Agency would use the mean change from baseline to end of treatment in MADRS total score (without averaging across visits). The primary analysis, LOCF analysis of covariance, is also difficult to justify unless the

dropout rate is negligible. For the planned NDA submission, the Agency requested that the Applicant include justifications for the suitability of the primary analysis as well as sensitivity analyses to assess the impact of the improbable missing data assumptions under the primary analysis. The Agency asserted that the acceptability of Study AXS-05-MDD-201 to support approval of AXS-05 would be a matter of review.

- ***Clinical Pharmacology, CYP2D6 and CYP2B6:*** The Agency did not agree with the Applicant's plan to evaluate the PK of AXS-05 in CYP2D6 poor metabolizers through a cross-study comparison. The Agency stated that the study must include a group of CYP2D6 extensive metabolizers as a control. The Applicant agreed to include both CYP2D6 extensive metabolizers and poor metabolizers in the proposed study. The Agency also noted that the effect of CYP2B6 inducers/inhibitors on exposure of dextromethorphan must be evaluated to provide specific dosing instructions.

- ***Clinical Pharmacology, 505(b)(2) bridging:*** The Agency asserted that a 505(b)(2) application must include establishment of an appropriate scientific bridge to each LD on which the application would intend to rely. PK information on the interaction potential between dextromethorphan and bupropion would need to be submitted in the NDA package. After confirmation from the Applicant that in vitro cytochrome P450 inhibition/induction data for dextromethorphan was the only piece of information they planned to rely on from Nuedexta for the 505(b)(2) application, the Agency recommended, and the Applicant agreed to, generation of their own in vitro data regarding CYP induction/inhibition potential at relevant dextromethorphan concentration levels. Therefore, reliance on Nuedexta for this 505(b)(2) application did not seem necessary from a clinical pharmacology perspective.

- ***Control Substances Staff, abuse potential:*** The Agency agreed that a comprehensive evaluation of abuse-related adverse events produced by AXS-05 in all clinical studies, in comparison to its components and placebo, would provide an adequate assessment of the abuse potential of AXS-05.

February 22, 2021 **Receipt date for NDA**

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

The Office of Scientific Investigations inspected the Applicant, Axsome Therapeutics, Inc., and the clinical investigator sites of Dr. Linda Harper (Site #201, Study MDD-201), Dr. Howard Hassman (Site #823, Study MDD-301), Dr. John Joyce (Site #807, Study MDD-301; Site #401,

Study MDD-201), and Dr. Lora McGill (Site #808, Study MDD-301). Sites were selected based on enrollment, strong contribution to efficacy results, complaints, and inspection history. Based on the results of these inspections, the conduct of the two studies was adequate, and the clinical data generated from the inspected sites appear to be reliable and able to support this application.

The Applicant was inspected in accordance with the Sponsor/Monitor/Contract Research Organization data validation compliance program, CP 7348.810. No areas of concern were found.

The Office of Scientific Investigation (OSI) also conducted inspections related to two complaints, detailed below.

Complaint #9790

Dr. Hassman was selected for inspection due to an anonymous complaint alleging that the Hassman Research Institute asked their employees to do unethical things, such as switching subjects' blood and urine samples to make them eligible for a clinical trial. In addition, the complainant alleged that this issue was not related to a specific trial but occurred across the institute.

Inspection Results

The field investigator called the complainant, but the phone number provided in the complaint was no longer in service. In addition, the field investigator was not able to interview any of the laboratory technicians who participated in the inspected studies because they had left the institute. Therefore, the complaint could not be investigated further. OSI recommended that the Agency conduct sensitivity analysis with regard to the efficacy data from Dr. Hassman's site because of the allegation that could not be investigated.

Reviewer's Comment: Refer to the efficacy results for Study MDD-301 (Section 8.1.2.2) for the sensitivity analysis for Dr. Hassman's site (Site #823).

Complaint #9454

The inspection investigated a complaint regarding the Applicant's adverse event reporting for Study 301. OSI received this complaint in February 2020 regarding Axsome Therapeutics' conduct of the study. The complainant alleged (b) (4)

(b) (4)

Inspection Results

The inspection did not find any evidence as was alleged. The Applicant did reclassify one serious adverse event to a nonserious adverse event for one subject (#) for Study MDD-201. Specifically, this subject presented to an emergency room at about 4 pm because she had experienced tunnel vision, visual hallucinations, hearing voices, and racing thoughts earlier that day. The psychiatric consult found the subject to be lucid, coherent, oriented, and alert, with no psychotic symptoms, and cleared her for discharge at about 6 pm the same day. Because the subject's husband was out of town, the subject was admitted to hospital at 6:17 pm for overnight observation. The subject was discharged the next day at about 11:30 am.

4.2. Product Quality

Refer to the Integrated Quality Assessment review for full details about the product quality review.

On October 22, 2021, the Office of Product Quality (OPQ) communicated a Discipline Review Letter, describing the following deficiencies and the information needed to resolve the deficiencies:

Drug Product

Deficiency:

- The Office of Product Quality noted that the proposed analytical methods for quantification of related substances in the drug product has a limit of quantification (LOQ) of %. The Office of Product Quality was concerned that these analytical methods might not be adequately sensitive to capture the stability trend of the impurities/degradants in the drug product.

Information needed to resolve deficiency:

- To further improve the overall analytical method sensitivity, the Applicant was advised to revise and/or re-validate the current analytical methods with a LOQ of % or below.

Biopharmaceutics Deficiencies

Deficiency:

- The NDA provided a single dissolution method for both bupropion and dextromethorphan components of the proposed drug product, which was deemed not optimal for each active pharmaceutical ingredient.

Information needed to resolve deficiency:

- The Agency instructed the Applicant to develop and validate an optimal dissolution method for each component of AXS-05 ER Tablets, fixed-dose combination product (i.e., extended-release bupropion HCl and immediate-release dextromethorphan HBr). The Applicant was advised to submit their final dissolution acceptance criteria proposal for AXS-05 ER Tablets, based on the data generated from the unexpired clinical and registration batches and the first six commercial batches, using the new dissolution method.

On December 29, 2021, the Applicant submitted an amendment addressing the drug product and biopharmaceutics deficiencies:

Drug Product: The Applicant revalidated the analytical method CTMLP 3898 to lower the LOQ to (b) (4)% for known and unknown bupropion hydrochloride related compounds. The LOQ for unknown dextromethorphan hydrobromide related compounds is also (b) (4)% for the proposed commercial strength. The analytical method CTMLP 4006 was also revalidated by the Applicant to lower the LOQ to (b) (4)% for known bupropion hydrochloride related compounds. OPQ concluded that the revised LOQ value of (b) (4)% for degradation products in the proposed commercial drug product are acceptable.

Biopharmaceutics: The Applicant submitted two separate dissolution methods for each component of the proposed drug product (CTMLP 5319 for dissolution release of dextromethorphan, and CTMLP 5320 for dissolution release of bupropion hydrochloride). OPQ concluded that the proposed dissolution method and acceptance criteria for the batch release and stability testing of dextromethorphan and bupropion from the fixed-dose combination tablet are accepted on an interim basis.

In the context of adequate resolution of the two deficiencies described above, OPQ recommends approval of this application.

4.3. Clinical Microbiology

Not relevant to this submission.

4.4. Devices and Companion Diagnostic Issues

Not relevant to this submission.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This application submitted by Axsome Therapeutics for AXS-05 is an oral, fixed-dose combination of dextromethorphan (DM) and bupropion (BUP) developed via the 505(b)(2) regulatory pathway for the treatment of MDD. AXS-05 is available in a single strength, as a tablet containing 45 mg dextromethorphan hydrobromide monohydrate and 105 mg of bupropion hydrochloride. The maximum recommended human dose (MRHD) of AXS-05 in adults is one tablet twice a day for a total daily dose of 90 mg dextromethorphan HBr and 210 mg bupropion HCl. The Applicant is relying on nonclinical data from four sources to support this NDA: (1) the Agency's previous findings of safety for Nuedexta; (2) the Agency's previous findings of safety for Wellbutrin SR; (3) published literature on bupropion and dextromethorphan; and (4) studies conducted by the Applicant with AXS-05 and/or one of its components.

In humans, when dextromethorphan is given as a single agent, systemic exposure is low because the drug is quickly eliminated due to extensive metabolism through CYP2D6. The bupropion component of AXS-05 inhibits CYP2D6, thereby increasing exposure to dextromethorphan and enhancing its pharmacologic effects. The mechanism by which AXS-05 exerts its antidepressant effect is presumed to be related to the glutamatergic and monoaminergic mechanisms of action of its components.

No primary pharmacodynamic studies have been conducted with AXS-05. However, both active moieties in AXS-05, dextromethorphan and bupropion, are well-characterized agents and their pharmacology has been extensively described in the literature and in the product labels for the LDs, Wellbutrin SR and Nuedexta. Dextromethorphan is described in the current (January 2021) FDA listing of Established Pharmacologic Class (EPC) as an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, and sigma-1 receptor agonist, which modulates glutamate signaling in the CNS. Dextromethorphan is extensively metabolized through CYP2D6 to dextrorphan, which is then rapidly glucuronidated. Bupropion, which is described in the FDA EPC list as "aminoketone," is a relatively weak inhibitor of the neuronal reuptake of norepinephrine and dopamine and does not inhibit the reuptake of serotonin. Bupropion is also a CYP2D6 inhibitor; however, this effect is not currently reflected in the EPC list. Bupropion is metabolized to three active metabolites: hydroxybupropion, threohydroxybupropion, and erythrohydroxybupropion.

No secondary pharmacodynamic studies have been conducted with AXS-05. The safety of the components of AXS-05 with respect to potential unintended pharmacodynamic effects is supported by published literature and FDA's previous findings of the LDs, Wellbutrin SR and Nuedexta.

No safety pharmacology studies have been conducted with AXS-05. However, the safety of AXS-05 with respect to potential effects on organ system function is supported by data from repeat-

dose toxicity studies conducted with AXS-05 in mice and rats and by the FDA's previous findings for the LDs, Wellbutrin and Nuedexta. The clinical findings in the repeat-dose toxicity studies up to 13 weeks in mice were primarily convulsions or related to convulsions (e.g., tremors, closed eyelids, reduced activity, slow respiration rate), seen in both the AXS-05 and bupropion treatment groups; therefore, these effects were attributed to the bupropion component of AXS-05. In published reports, bupropion and its metabolites have been reported to cause convulsions in mice; seizures are also a known clinical risk based on the Wellbutrin SR product label. Increased mortality rate in male mice was also observed with AXS-05 compared to each component alone.

Pharmacokinetic and toxicokinetic studies in mice and rats were conducted with AXS-05. In both species, T_{max} was between 0.5 to 3.3 hours for dextromethorphan and 0.5 to 1.7 hours for bupropion. Following single and repeated doses of AXS-05, exposure to dextromethorphan and bupropion increased more than dose proportionally. In mice, exposure to dextromethorphan and bupropion was generally higher in males than females. In rats, although exposure to dextromethorphan was similar in both sexes, exposure to bupropion was lower (>2-fold) in males than females. Following repeated dosing with AXS-05, exposure to the dextromethorphan metabolite dextrorphan and its conjugated form (dextrorphan-o-glucuronide) decreased. The T_{max} for dextrorphan was between 0.55 and 3.3 hours in mice and rats and did not change with repeated dosing with AXS-05. However, for dextrorphan-o-glucuronide, although T_{max} was similar to dextrorphan in mice, it was between 16.3 and 24 hours in rats following single dose. With repeat dosing, T_{max} in male rats decreased to 1.7 hours. Following repeat dosing with AXS-05, exposure to bupropion metabolites decreased in both mice and rats; however, there were significant species differences. Exposure to bupropion and hydroxybupropion (the primary pharmacologically active metabolite) decreased by ≥95% in rats but only ≤50% in mice. This difference is one reason that mice, rather than rats, were chosen by the Applicant as the test system for toxicology studies with AXS-05. No other metabolism, distribution, and excretion studies were conducted with AXS-05 in animals.

The general toxicity of AXS-05 was evaluated in a 13-week, repeat-dose, bridging toxicity study in mice. Animals were treated with AXS-05 at 26/57, 34/75, or 68/150 mg/kg DM/BUP; bupropion alone at 150 mg/kg; or dextromethorphan alone at 68 mg/kg for 13 weeks. The dose-limiting toxicity was convulsions and/or related clinical signs such as spasms, muscle tremors, reduced activity, closed eyelids, and slow respiration rate. These findings were seen in both the AXS-05 (68/150 mg/kg) and bupropion alone (150 mg/kg) treatment groups and, therefore, were attributed to the bupropion component of AXS-05. Similar findings were reported in published studies with bupropion and its metabolites and in the Wellbutrin SR package insert, which describes seizure as a known clinical risk. Other findings related to AXS-05 in mice also were attributed to its bupropion component and included hepatocellular hypertrophy with greater liver weight, necrosis of renal proximal tubule epithelium, and trends toward higher serum concentrations of urea nitrogen, triglycerides, and phosphorus in males and higher cholesterol concentration in females. Marked, locally extensive coagulative necrosis of the heart was present in one high dose male given AXS-05 and one male given bupropion alone. The NOAEL in the 13-week general toxicity study was considered to be the mid-dose

level (34/75 mg/kg/day). Based on the results of the 13-week bridging toxicity study, there was no toxicologic interaction between the two active ingredients in AXS-05. However, an increased mortality rate in males was observed with AXS-05 compared to the bupropion alone. All other findings related to administration of AXS-05 were also seen with the administration of bupropion alone at an equivalent dose level and were considered to be due to the bupropion component of AXS-05.

No genotoxicity studies have been conducted with AXS-05. The Applicant is relying on previous findings of safety with respect to genotoxicity for Wellbutrin SR and Nuedexta and the published literature. AXS-05 is considered not to pose genotoxic hazard to patients based on the FDA's previous findings of safety with respect to genotoxicity for Wellbutrin SR and Nuedexta.

The Applicant did not conduct carcinogenicity studies in two species for their product. The Applicant had proposed to use data from the dextromethorphan alone arm of the Nuedexta label. Reference to the carcinogenicity data in Nuedexta does not adequately characterize the carcinogenic potential of dextromethorphan, let alone in combination with bupropion. Specifically, the referenced single-dose PK data in rats provided by the Applicant do not characterize concentration at steady state, and the referenced study only tests one dose of dextromethorphan alone and it is not clear that this dose adequately meets high dose selection criteria recommended in ICH S1C(R2). In addition, the carcinogenic potential of the combination of dextromethorphan and bupropion has not been assessed especially in light of the findings reported in the referenced bupropion labeling of liver findings and the potential PK interaction between the two active drug substances. Therefore, a study testing the combination of the two drugs that includes a high dose arm for each single agent, as was done for Nuedexta, will allow for the characterization of the carcinogenic potential of the combination of dextromethorphan and bupropion

With respect to effects on pregnancy and embryofetal development, AXS-05 was evaluated in an embryofetal developmental (EFD) toxicity study in pregnant mice (BUP/DM: 57/26, 75/34, 150/68, 150/0, 0/68). In this EFD study, based on the deaths seen at the mid-dose level (BUP/DM: 75/34 mg/kg/day), the maternal NOAEL and MTD were considered to be 57/26 mg/kg/day of BUP/DM. Based on the absence of effects on embryofetal development at any dose level, the fetal NOAEL was considered to be 150/68 mg/kg/day of BUP/DM. Based on these results, daily oral administration of AXS-05 during the period of organogenesis at up to the MTD did not affect embryofetal development in pregnant mice. However, based on the embryofetal developmental toxicity findings in rabbits as described in the labels of both Wellbutrin and Nuedexta, an evaluation of the additive effect of the combination of those two products should have been assessed in rabbits. An EFD study with AXS-05 in pregnant rabbits will allow for the evaluation of the combination product's effect on embryofetal development.

No studies were conducted with AXS-05 to evaluate its effects on fertility or on pre- and postnatal development. The Applicant is relying on fertility and pre- and postnatal findings described in Wellbutrin and Nuedexta labels. Even though the Applicant may rely on fertility and pre- and post-natal data on bupropion (as stated in Wellbutrin SR label), fertility and pre-

and post-natal data on Nuedexta is confounded by the presence of quinidine. Therefore, a fertility study and a pre- and post-natal study with AXS-05 will allow for the evaluation of the combination product's effect on the fertility and pre- and postnatal development.

Dextromethorphan and its primary metabolite dextrorphan are NMDA receptor antagonists. Several compounds in this class are known to cause neuronal vacuolation and neurodegeneration in the retrosplenial/posterior cingulate cortices in the brain of adult rats, a finding referred to as "Olney lesions." In addition, this class of drugs is believed to produce apoptosis in the developing young brain (7-day of age or younger in rats, which corresponds to the developing human brain in the third trimester of gestation through the first several months of life and may extend to approximately three years of age). No studies examining the potential of AXS-05 to cause apoptosis were submitted by the Applicant; this relates to their product because of the neurotoxic findings in the developing brain described in the Nuedexta label. The Applicant based their argument that such a study is not needed on the results of a published report (Carliss RD et al., 2007; NeuroToxicology 28: 813-818). However, this study did not use the appropriate age of animals to reflect effects on the young developing brain (i.e., 7 day-old rats). Therefore, this study does not address the potential concern for the effect of dextromethorphan on the young developing brain. Further evaluation for this effect should be conducted with this product.

Recommendation

The Applicant has not provided sufficient scientific rationale for leveraging the Nuedexta data in Sections 8.1, 8.2, and 13.1 of the product label that are confounded by the coadministration of quinidine with dextromethorphan.

Reference to the carcinogenicity data in Nuedexta does not adequately characterize the carcinogenic potential of dextromethorphan, let alone in combination with bupropion. Specifically, the referenced single-dose PK data in rats provided by the Applicant do not characterize concentration at steady state, and the referenced study only tests one dose of dextromethorphan alone and it is not clear that this dose adequately meets high dose selection criteria recommended in ICH S1C(R2). To address this deficiency, the Applicant should submit appropriate justification that the referenced studies adequately characterize the carcinogenic potential of dextromethorphan in accordance with ICH S1C(R2) recommendation with respect to dose selection. Alternatively, the Applicant should conduct carcinogenicity studies in two species to address the carcinogenic potential of dextromethorphan. Given the findings reported in the referenced bupropion labeling of liver findings and the potential PK interaction between the two active drug substances, the Applicant should consider designing the study to test the combination of the two drugs and including a high dose arm for each single agent, as was done for Nuedexta. Although the referenced nonclinical data allow for labeling of risk in Section 13, it is not ideal; therefore, the Agency will issue a PMR to conduct carcinogenicity studies to address the lack of information on the combined effect/s of dextromethorphan and bupropion in product labeling.

Further studies (Segment I and III) involving the active components of AXS-05 are necessary in order for the product label to be adequately informative to both prescribers and patients. Furthermore, even though AXS-05 was evaluated in an embryofetal development study in pregnant mice, both Wellbutrin and Nuedexta labels indicate developmental toxicity, including fetal malformations and embryo lethality, in pregnant rabbits during organogenesis. Although the referenced nonclinical data allow for labeling of risk in Sections 8.1 and 13, it is not ideal; therefore, the Agency will issue a PMR to conduct EFD study in rabbits, a fertility and pre- and postnatal study studies to address the lack of information on the combined effect/s of dextromethorphan and bupropion in product labeling.

The neurotoxic effect of dextromethorphan on the developing young brain should also be evaluated based on the findings in developing brain described in the Nuedexta label. Given the known and expected toxicities of the referenced products, the AXS-05 label will state that AXS-05 is not recommended for use in pregnant or lactating women. The benefit of the drug was deemed appropriate for approval at this time and, although not ideal, the existing referenced non-clinical data will permit labeling of risk for Sections 8 and 13 of the product label. However, to address the combined effect/s of dextromethorphan and bupropion in the product labeling and to assist clinicians in proper decision making, the Agency will issue several non-clinical post-marketing requirements (see list in Section 13 Post Marketing Requirements and Commitment). As such from a non-clinical perspective, the submission is considered approvable.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant is submitting the current application via the 505(b)(2) regulatory pathway, with Wellbutrin SR (NDA 020358) and Nuedexta (NDA 021879) as the LDs.

5.3. Pharmacology

No primary pharmacology studies have been conducted with AXS-05. The Applicant stated that the components of AXS-05, dextromethorphan and bupropion, are well-characterized agents and their pharmacology has been extensively described in the literature (a review of the published data was provided in the pharmacology written summary).

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
AXS-05: A pharmacokinetic study following oral administration to male and female mice (Study No. 036027; Applicant Reference No. AXS005-TM001)	The absorption and PK profiles of DM and BUP were assessed in mice and rats following single and repeated (3-day) oral doses of AXS-05 or one of its active ingredients alone (Tables 1 to 3). In both species, T_{max} was between 0.5 to 3.3 hours for DM and 0.5 to 1.7 hours for BUP. Exposure to DM and BUP increased more than dose proportionally following single and repeated doses of AXS-05. In mice, exposure of DM and BUP was generally higher in males than in females. In rats, exposure to DM was similar in both sexes, but exposure to BUP was lower (>2-fold) in males than females.

Type of Study	Major Findings
AXS-05: A pharmacokinetic study following oral administration to male and female rats (Study No. 035555, Applicant Reference No. AXS005-TR003)	Exposure to DM metabolites, dextrorphan (DX) and dextrorphan-O-glucuronide, decreased after repeated daily dosing with AXS-05. For DX, T_{max} was between 0.5 and 3.3 hours in mice and rats and did not change with repeated dosing with AXS-05. For dextrorphan-O-glucuronide, T_{max} was similar to DX in mice; however, it was between 16.3 and 24 hours in rats after single doses. With repeated doses, T_{max} in male rats decreased to 1.7 hours. In both mice and rats, exposure to BUP and its pharmacologically active metabolite hydroxybupropion decreased with repeated dosing with AXS-05, but there was a significant difference between species. More specifically, with repeated daily administration of AXS-05, bupropion and hydroxybupropion concentrations decreased by ≥95% in rats but by ≤50% in mice. Based on these data, the Applicant chose mice as the test species for the general toxicology studies with AXS-05.

Table 1. Mean DM, DX, BUP, and Hydroxybupropion Plasma PK Parameters on Day 1 and Day 3 in Mice Given ASX-05 (75/34 mg/kg), BUP/DM or DM Alone

Analyte	Day	Sex	Treatment[a]	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)	C_{max} (ng/mL)
Dextromethorphan	1	F	AXS-05 (DM/BUP)	581.82	883.31	226.19
			DM	263.89	NC	170.55
		M	AXS-05 (DM/BUP)	690.16	NC	192.62
			DM	269.47	NC	159.83
	3	F	AXS-05 (DM/BUP)	365.88	NC	115.52
			DM	502.93	527.51	198.20
		M	AXS-05 (DM/BUP)	472.58	673.79	227.76
			DM	360.30	NC	185.30
Dextrorphan	1	F	AXS-05 (DM/BUP)	276.30	356.23	144.12
			DM	164.89	NC	121.50
		M	AXS-05 (DM/BUP)	238.72	NC	80.93
			DM	226.90	251.33	127.66
	3	F	AXS-05 (DM/BUP)	151.33	288.56	46.02
			DM	210.06	234.15	94.55
		M	AXS-05 (DM/BUP)	124.91	190.19	52.14
			DM	186.11	210.96	77.07
Bupropion	1	F	AXS-05 (DM/BUP)	885.78	NC	785.76
		M		1500.59	NC	1056.20
	3	F		164.27	NC	164.27
		M		132.18	NC	264.36
Hydroxybupropion	1	F	AXS-05 (DM/BUP)	8526.31	9868.37	2281.62
		M		12144.87	26852.91	2276.98
	3	F		5218.92	6421.75	1486.67
		M		6304.95	8550.54	1731.74

Source: Applicant, Study AXS005-TM001, Pharmacokinetic Report, Tables 4-1, 4-2.
[a] AXS-05 (DM/BUP) dose was 75 mg/kg BUP and 34 mg/kg DM. DM alone dose was 34 mg/kg.
Abbreviations: AUC_{0-inf}, area under the curve; AUC_{0-t}, area under the curve to last measurable concentration; BUP, bupropion; C_{max}, maximum concentration; DM, dextromethorphan; DX, dextrorphan; F, female; M, male; NC, not calculated; PK, pharmacokinetic

Type of Study	Major Findings
	Table 2. Systemic Exposure to Parent Drugs and Metabolites in Male Rats After One and Three Doses of AXS-05 at 150/67.5 (BUP/DM) mg/kg/Day

	C_{max} (ng/mL)		AUC_{0-24} (h*ng/mL)	
Analyte	**1st Dose**	**3rd Dose**	**1st Dose**	**3rd Dose**
Dextromethorphan				
Parent drug	537	200	3298	2512
Dextrorphan metabolite	149	46	651	439
Dextrorphan-O-glucuronide metabolite	2034	3498	28,137	56,944
Total drug-related material			32,086	59,895
Bupropion				
Parent drug	2757	67	8353	33
Hydroxybupropion metabolite	328	117	1936	501
Erythrohydroxybupropion metabolite	78	7	397	38
Threohydroxybupropion metabolite	166	20	1084	111
Total drug-related material			11,770	683

Source: Study AXS005-TR003, Pharmacokinetic Report, Tables 4-1, 4-2, 4-3, 4-4, 4-5, 4-6, 4-7.
Abbreviations: AUC_{0-24}, area under the curve to 24 hours; BUP, bupropion; C_{max}, maximum concentration; DM, dextromethorphan

Table 3. Systemic Exposure to Parent Drugs and Metabolites in Female Rats After One and Three Doses of AXS-05 at 150/67.5 (BUP/DM) mg/kg/Day

	C_{max} (ng/mL)		AUC_{0-24} (h*ng/mL)	
Analyte	**1st Dose**	**3rd Dose**	**1st Dose**	**3rd Dose**
Dextromethorphan				
Parent drug	511	315	2965	2342
Dextrorphan metabolite	137	45	715	567
Dextrorphan-O-glucuronide metabolite	2668	2769	39,156	58,805
Total drug-related material			42836	61,714
Bupropion				
Parent drug	4053	588	25,034	2998
Hydroxybupropion metabolite	242	153	4552	1009
Erythrohydroxybupropion metabolite	5	0	29	0
Threohydroxybupropion metabolite	17	4	244	23
Total drug-related material			29,859	4030

Source: Applicant, Study AXS005-TR003, Toxicokinetic Report, Tables 4-1, 4-2, 4-3, 4-4, 4-5, 4-6, 4-7.

Abbreviations: AUC_{0-24}, area under the curve to 24 hours; BUP, bupropion; C_{max}, maximum concentration; DM, dextromethorphan

Distribution	No studies were conducted with AXS-05 to evaluate the distribution of dextromethorphan and bupropion after administration of AXS-05. Based on literature references provided by the Applicant the brain-to-plasma ratios are 8 to 16 for dextromethorphan and 4 to 5 for unconjugated dextrorphan in rats. The binding of dextromethorphan to plasma proteins in rat was 71.6% (consistent with the protein bound fraction in humans of 60-70%). Bupropion is 84% bound to human plasma proteins at concentrations up to 200 mcg/mL, with similar extent of protein binding for hydroxybupropion, and about half the extent for threohydroxybupropion.

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Metabolism</td><td>No studies were conducted with AXS-05 to evaluate the metabolism of dextromethorphan and bupropion after administration of AXS-05. The metabolism of dextromethorphan and bupropion have been described in the literature and in the product labels of the listed drugs. Based on literature references provided by the Applicant, formation of dextrorphan, the primary metabolite of dextromethorphan, in liver microsomes from five different mouse strains after incubation with dextromethorphan is similar to that in human liver microsomes, indicating that dextromethorphan metabolism is similar in mice and humans. Published works also show that although qualitatively, animals (mouse, rat, dog) produce the same bupropion metabolites present in humans, quantitatively, bupropion metabolites in mice are similar to humans.</td></tr>
<tr><td>Excretion</td><td>No studies were conducted with AXS-05 to evaluate the excretion of dextromethorphan and bupropion after administration of AXS-05. Based on literature references provided by the Applicant, dextromethorphan and bupropion are excreted primarily in urine in rats and humans.</td></tr>
<tr><td>TK data from general toxicology studies
<u>Mouse</u>
13-week oral (gavage) toxicity of AXS-05 (BUP HCl and DM HBr) study in mice with a 4-week recovery (Study No. 036629-1; Applicant Reference No. AXS-005-TM003).
• NOAEL: BUP HCl at 75 mg/kg and DM HBr at 34 mg/kg.</td><td><u>Mouse</u>
Table 4. Mean Bupropion Plasma TK Parameters on Day 1 and Day 90 in Mice Given AXS-05 or Bupropion Alone
<table>
<tr><th rowspan="2">Analyte</th><th rowspan="2">Day</th><th rowspan="2">Sex</th><th colspan="2">Treatment (mg/kg)</th><th>AUC_{0-t} (h*ng/mL)</th><th>AUC_{0-inf} (h*ng/mL)</th><th>C_{max} (ng/mL)</th></tr>
<tr><th>BUP</th><th>DM</th></tr>
<tr><td rowspan="12">Bupropion</td><td rowspan="8">1</td><td rowspan="4">F</td><td>57</td><td>26</td><td>1120</td><td>1170</td><td>1220</td></tr>
<tr><td>75</td><td>34</td><td>1790</td><td>1830</td><td>1720</td></tr>
<tr><td>150</td><td>68</td><td>4990</td><td>5030</td><td>3190</td></tr>
<tr><td>150</td><td>0</td><td>6260</td><td>6290</td><td>3630</td></tr>
<tr><td rowspan="4">M</td><td>57</td><td>26</td><td>3110</td><td>3260</td><td>2520</td></tr>
<tr><td>75</td><td>34</td><td>3980</td><td>4040</td><td>3250</td></tr>
<tr><td>150</td><td>68</td><td>10500</td><td>10800</td><td>6000</td></tr>
<tr><td>150</td><td>0</td><td>11000</td><td>11100</td><td>4760</td></tr>
<tr><td rowspan="4">90</td><td rowspan="4">F</td><td>57</td><td>26</td><td>77.2</td><td>81.8</td><td>98.1</td></tr>
<tr><td>75</td><td>34</td><td>91.3</td><td>-</td><td>173</td></tr>
<tr><td>150</td><td>68</td><td>164</td><td>171</td><td>250</td></tr>
<tr><td>150</td><td>0</td><td>238</td><td>241</td><td>375</td></tr>
<tr><td rowspan="4">M</td><td>57</td><td>26</td><td>112</td><td>-</td><td>194</td></tr>
<tr><td>75</td><td>34</td><td>325</td><td>331</td><td>563</td></tr>
<tr><td>150</td><td>68</td><td>292</td><td>-</td><td>261</td></tr>
<tr><td>150</td><td>0</td><td>403</td><td>448</td><td>404</td></tr>
</table>
-, Value could not be calculated.

Source: Reviewer, Adapted from Study AXS-TM003, Toxicokinetic Report. Table 10.141.

Abbreviations: AUC0-∞; area under the curve; AUC_{0-t}, area under the curve to last measurable concentration; BUP, bupropion; Cmax, maximum concentration; DM, dextromethorphan; F, female; M, male</td></tr>
</table>

Type of Study	Major Findings

BUP: Ranged from 0.5 to 1 hour on Days 1 and 90, regardless of sex.
DM: Ranged from 0.5 to 1 hour on Days 1 and 90, regardless of sex.

$T_{1/2}$

BUP: Ranged from 0.74 to 1.42 hours on Day 1 and 0.28 to 0.53 hours on Day 90, independent of sex, day, and dose.
DM: Ranged from 1.02 to 8.79 hours independent of sex and dose.

Accumulation

BUP: Decrease in exposure between Day 1 and Day 90 in both sexes (Table 4); accumulation ratios ranged from 0.0277 to 0.173 for Day 90 versus Day 1, indicating no accumulation of BUP.
DM: Decrease in exposure between Day 1 and Day 90 in both sexes (Table 6). The accumulation ratios ranged from 1.02 to 1.53 for Day 90 versus Day 1.

Dose proportionality

With AXS-05 (BUP and DM combined), exposure to BUP generally increased with dose in both sexes. Exposure to DM increased in a greater than dose-proportional manner in both sexes.
DM and metabolite dextrorphan (DX) in mice given AXS-05 or dextromethorphan alone: With AXS-05, exposure to DM following the 1st and 90th doses generally increased with dose level in both sexes. At a DM dose level of 68 mg/kg, exposure to DM was similar between AXS-05 and DM alone after the 1st dose but lower with AXS-05 than with DM alone after the 90th dose (Table 7).

Table 5. Mean Hydroxybupropion Plasma TK Parameters on Day 1 and Day 90 in Mice Given AXS-05 or Bupropion Alone

Analyte	Day	Sex	Treatment (mg/kg)		AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	C_{max} (ng/mL)
			BUP	DM			
Hydroxybupropion	1	F	57	26	5990	6210	1730
			75	34	6380	6790	1860
			150	68	13400	21000	3020
			150	0	14900	24600	3080
		M	57	26	8570	10600	1760
			75	34	11800	-	1810
			150	68	36800	36900	3080
			150	0	19300	72900	2780
	90	F	57	26	3770	4260	1490
			75	34	4820	5410	1660
			150	68	7710	10100	1900
			150	0	8330	10300	2540
		M	57	26	5790	7080	1790
			75	34	6090	6600	2200
			150	68	9040	16700	2260
			150	0	11600	13400	2790

-, Value could not be calculated

Source: Reviewer, Adapted from Study AXS-TM003, Toxicokinetic Report. Table 10.142.

Abbreviations: $AUC_{0-\infty}$; area under the curve; AUC_{0-t}, area under the curve to last measurable concentration; BUP, bupropion; C_{max}, maximum concentration; DM, dextromethorphan; F, female; M, male

Type of Study	Major Findings

Exposure to DM and the metabolite DX decreased substantially with repeated dosing with AXS-05 at all dose levels but not with DM alone.
Exposure to dextrorphan-O-glucuronide did not change appreciably with repeated dosing with AXS-05 at any dose level or with DM alone.
Exposure to BUP and its metabolites erythrohydroxybupropion and threohydroxybupropion decreased substantially with repeated dosing at all AXS-05 dose levels and with BUP alone.
Exposure to the metabolite hydroxybupropion decreased slightly with repeated dosing at all BUP dose levels and with BUP alone (Table 6).

Table 6. Mean Dextromethorphan Plasma TK Parameters on Day 1 and Day 90 in Mice Given AXS-05 or Dextromethorphan Alone

Analyte	Day	Sex	Treatment (mg/kg)		AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	C_{max} (ng/mL)
			BUP	DM			
Dextromethorphan	1	F	57	26	473	484	222
			75	34	550	610	386
			150	68	1760	3060	758
			0	68	1710	1720	817
		M	57	26	676	755	343
			75	34	1090	2340	463
			150	68	4160	4190	1250
			0	68	3060	3090	1380
	90	F	57	26	236	253	94.3
			75	34	401	575	165
			150	68	730	1210	222
			0	68	2490	2630	978
		M	57	26	437	519	200
			75	34	562	605	388
			150	68	889	-	327
			0	68	3210	3340	1410

-, Value could not be calculated

Source: Reviewer, Adapted from Study AXS-TM003, Toxicokinetic Report. Table 10.145.

Abbreviations: $AUC_{0-\infty}$; area under the curve; AUC_{0-t}, area under the curve to last measurable concentration; BUP, bupropion; C_{max}, maximum concentration; DM, dextromethorphan; F, female; M, male

Type of Study	Major Findings

Table 7. Mean Dextrorphan Plasma TK Parameters on Day 1 and Day 90 in Mice Given AXS-05 or Dextromethorphan Alone

Analyte	Day	Sex	Treatment (mg/kg)		AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	C_{max} (ng/mL)
			BUP	DM			
Dextrorphan	1	F	57	26	336	340	211
			75	34	361	388	273
			150	68	833	1210	499
			0	68	1160	1160	754
		M	57	26	236	250	133
			75	34	349	502	195
			150	68	865	968	425
			0	68	1130	1140	776
	90	F	57	26	128	134	62.7
			75	34	151	205	83.9
			150	68	205	288	82.8
			0	68	867	926	530
		M	57	26	106	123	51.2
			75	34	84.3	160	64.7
			150	68	164	-	55.0
			0	68	863	877	331

-, Value could not be calculated
Source: Reviewer, Adapted from Study AXS-TM003, Toxicokinetic Report. Table 10.146.
Abbreviations: $AUC_{0-\infty}$; area under the curve; AUC_{0-t}, area under the curve to last measurable concentration; BUP, bupropion; C_{max}, maximum concentration; DM, dextromethorphan; F, female; M, male

Table 8. Systemic Exposure to Parent Drugs and Metabolites in Male Mice After the First and Last Doses of AXS-05 at the 13-Week NOAEL (75/34 BUP/DM mg/kg)

	C_{max} (ng/mL)		AUC_{0-24} (h*ng/mL)	
Analyte	**1st Dose**	**90th Dose**	**1st Dose**	**90th Dose**
Dextromethorphan				
Parent drug	463	388	1090	562
Dextrorphan metabolite	195	65	349	84
Dextrorphan-O-glucuronide metabolite	4220	5270	30,400	24,000
Total drug-related material			31,839	24,646
Bupropion				
Parent drug	3250	563	3980	325
Hydroxybupropion metabolite	1810	2200	11,800	6090
Erythrohydroxybupropion metabolite	125	31	819	80
Threohydroxybupropion metabolite	564	147	3620	427
Total drug-related material			20,219	6922

Source: Applicant; Study AXS005-TM003, Toxicokinetic Report, Tables 10.141, 10.142, 10.143, 10.144, 10.145, 10.146, 10.147.
Abbreviations: AUC_{0-24}, area under the curve to 24 hours; BUP, bupropion; C_{max}, maximum concentration; DM, dextromethorphan

Type of Study	Major Findings

Table 9. Systemic Exposure to Parent Drugs and Metabolites in Female Mice After the First and Last Doses of AXS-05 at the 13-Week NOAEL (75/34 BUP/DM mg/kg)

	C_{max} (ng/mL)		AUC_{0-24} (h*ng/mL)	
Analyte	**1st Dose**	**90th Dose**	**1st Dose**	**90th Dose**
Dextromethorphan				
Parent drug	386	165	550	401
Dextrorphan metabolite	273	84	361	151
Dextrorphan-O-glucuronide metabolite	5360	6370	20,900	24,700
Total drug-related material			21,811	25,252
Bupropion				
Parent drug	1720	173	1790	91
Hydroxybupropion metabolite	1860	1660	6380	4820
Erythrohydroxybupropion metabolite	83	10	305	23
Threohydroxybupropion metabolite	375	46	1290	106
Total drug-related material			9765	5040

Source: Applicant; Study AXS005-TM003, Toxicokinetic Report, Tables 10.141, 10.142, 10.143, 10.144, 10.145, 10.146, 10.147.

Abbreviations: AUC_{0-24}, area under the curve to 24 hours; BUP, bupropion; C_{max}, maximum concentration; DM, dextromethorphan

TK data from reproductive toxicology studies

CD-1 Mouse: AXS-05: Study for effects on embryo-fetal development following oral gavage administration to pregnant female CD-1 mice (Study No. 2553-14860; Applicant Reference No. AXS-005-TM005)

Maternal NOAEL (BUP/DM): 57/26 mg/kg.

Fetal NOAEL (BUP/DM): 150/68 mg/kg

CD-1 Mouse

Dose proportionality:

BUP: Exposure to BUP increased with dose level. The exposure was greater than proportional to dose after the first dose; however, exposure was approximately proportional to dose after the last dose. Exposure to BUP decreased substantially (by 92% to 96%) with repeated daily dosing at all dose levels (Table 10).

DM: The exposure (in term of AUC) to DM increased with dose. Exposure was greater than proportional to dose following the first dose; however, after the last dose, exposure was proportional to dose (Table 10).

AUC:

Table 10. Summary of Toxicokinetics Parameters

GD	Analyte	Treatment AXS-05	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	$T_{½}$ (h)
6	Bupropion	57 mg-26 mg	620	649	799	0.500	0.389
		75 mg-34 mg	1360	1370	1480	0.500	0.593
		150 mg-68 mg	2880	2950	2810	0.500	0.726
	Dextromethorphan	57 mg-26 mg	372	376	211	0.500	1.27
		75 mg-34 mg	601	647	202	0.500	2.18
		150 mg-68 mg	1610	2250	738	0.500	4.15
15	Bupropion	57 mg-26 mg	47.5	NC	79.2	0.500	NC
		75 mg-34 mg	58.8	NC	88.1	0.500	NC
		150 mg-68 mg	161	191	154	0.500	0.658
	Dextromethorphan	57 mg-26 mg	515	553	141	0.500	2.21
		75 mg-34 mg	530	645	161	1.00	3.13
		150 mg-68 mg	1590	1620	269	1.00	4.43

Source: Applicant, Study Report, AXS-005-TM005, page 21.

Abbreviations: $AUC_{0-\infty}$; area under the curve; AUC_{0-t}, area under the curve to last measurable concentration; C_{max}, maximum concentration; h, hours; NC, not calculated; $T_{½}$, half-life; T_{max}, time to maximum concentration

5.5. Toxicology

5.5.1. General Toxicology

The potential toxicity of AXS-05 (dextromethorphan-bupropion) has been evaluated in rat and mouse following single (rat) and repeated administration.

AXS-05: 14-Day Oral Dose Toxicity Study in Mice/Study № 036561 (Applicant Reference No. AXS-005-TM002)

- Treatment-related mortality at the high dose of 300/136 mg/kg/d BUP/DM in males (100%; 6/6) and females (67%; 4/6).
- At the high dose of 300/136 mg/kg/d BUP/DM, there were treatment-related adverse clinical findings such as ataxia, convulsions, muscle tremors, reduced activity, cold to touch, labored and/or slow respiration, prostrate, and partially closed eyelids in males and females.
- At the mid dose of 150/68 mg/kg/d BUP/DM, treatment-related (although sporadic) clinical signs of ataxia (five of the six males), convulsions/tremors (two of each sex), and hyperactivity and rapid respiratory rate in one male.
- The NOAEL for the 14-day repeat dosing of AXS-04 for both males and females is the low dose of 75/34 mg/kg/d BUP/DM.

Conducting laboratory and location: (b) (4)
GLP compliance: No

Methods

Dose and frequency of dosing:	0 (vehicle control), BUP/DM: 75/34 (low dose), 150/68 (mid dose), 300/136 (high dose) mg/kg/day Once daily for 14 days
Route of administration:	Oral gavage
Formulation/vehicle:	Solution/deionized water
Species/strain:	Mice/Crl:CD-1
Number/sex/group:	6/sex/group
Age:	11.3 weeks
Satellite groups/ unique design:	None/no unique study design
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: Changes from the Control

Parameter	Major Findings
Mortality	6/6 high-dose males were euthanized moribund or were found dead on Day 1 (4/6 euthanized moribund and 2/6 found dead). 4/6 high dose females were euthanized moribund on Day 1 (3 were euthanized on Day 1 and 1 was euthanized on Day 3).

<table>
<tr><th>Parameter</th><th>Major Findings</th></tr>
<tr><td>Clinical signs</td><td>
High dose males exhibited the following treatment-related clinical signs: ataxia (3/6), convulsions (6/6), prostrate body position (3/6), reduced activity (5/6), labored breathing (3/6), cold to touch (2/6), slow respiration (4/6), and partially closed eyelids (1/6).
High dose females exhibited the following treatment-related clinical signs: ataxia (6/6), convulsions (5/6), muscle tremors (2/6), lethargy (1/6), prostrate body position (2/6), cold to touch (2/6), reduced activity (3/6), labored breathing (3/6), slow respiration (3/6), and partially closed eyelids (1/6). Two females that lived to their scheduled termination exhibited only ataxia and muscle tremors/convulsions on Day 1 (both females) and Day 7 (one female).
Treatment-related adverse findings (ataxia, convulsions, tremors) at the mid dose of 150/68 mg/kg were as shown in Table 11.
Table 11. Treatment-Related Clinical Observations in Mid Dose Group Animals
<table>
<tr><th colspan="3">Males</th><th colspan="3">Females</th></tr>
<tr><th>Animal #</th><th>Observation</th><th>Study Day</th><th>Animal #</th><th>Observation</th><th>Study Day</th></tr>
<tr><td>313702</td><td>Ataxia</td><td>1</td><td rowspan="3">313730</td><td>Ataxia</td><td>13</td></tr>
<tr><td rowspan="4">313703</td><td>Ataxia</td><td>13</td><td>Convulsions</td><td>13</td></tr>
<tr><td>Convulsions</td><td>2, 3, 5, 12, 13</td><td>Hyperactive</td><td>13</td></tr>
<tr><td>Hyperactive</td><td>12</td><td rowspan="2">313734</td><td>Ataxia</td><td>5</td></tr>
<tr><td>Rapid Respiratory Rate</td><td>2, 12, 13</td><td>Convulsions</td><td>5</td></tr>
<tr><td rowspan="2">313704</td><td>Ataxia</td><td>1</td><td></td><td></td><td></td></tr>
<tr><td>Tremors</td><td>1</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">313705</td><td>Ataxia</td><td>5</td><td></td><td></td><td></td></tr>
<tr><td>Convulsions</td><td>5</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">313706</td><td>Ataxia</td><td>1, 4</td><td></td><td></td><td></td></tr>
<tr><td>Tremors</td><td>1, 4</td><td></td><td></td><td></td></tr>
</table>
Source: Study report, page 20.

Note: In low-dose males, there were no clinical signs after the first dose. In mid-dose males, after the first dose, the only clinical signs were ataxia (three males) and tremors (two males). In high-dose males, after the first dose, all six males had convulsions, all but one had reduced activity, and several had ataxias, slowed and/or labored respiration, and prostrate body position. Two high-dose males died and four high dose males were euthanized for humane reasons on Day 1.
In low-dose females and mid-dose females, there were no clinical signs after the first dose. In high-dose females, after the first dose, all six females exhibited ataxia, all but one had convulsions, and several had reduced activity, slowed and/or labored respiration, prostrate body position, and tremors. Three high-dose females were euthanized for humane reasons on Day 1, and another high-dose female was euthanized for humane reasons on Day 3.
Based on these results, the single-dose NOAEL in mice was 75/34 mg/kg in males and 150/68 mg/kg in females.
There were no treatment-related clinical findings at the low dose.
</td></tr>
<tr><td>Body weights</td><td>There were no treatment-related effects on body weight in males or females.</td></tr>
<tr><td>Hematology</td><td>There were no treatment-related changes in erythroid or leukocyte parameters at any dose. For moribund animals at the high dose, minor changes in erythroid and leukocyte parameters observed in one or two animals were considered agonal and an indirect effect of the test article secondary to treatment-related mortality.</td></tr>
<tr><td>Clinical chemistry</td><td>There were no treatment-related changes in serum chemistry parameters at any dose. For moribund animals at the high dose, minor changes in various serum chemistry parameters were considered agonal and an indirect effect of the test article secondary to treatment-related mortality.</td></tr>
</table>

Parameter	Major Findings
Gross pathology	There were no treatment-related findings.
Organ weights	Not evaluated
Histopathology	Not conducted

Abbreviation: NOAEL, no observed adverse effect level

AXS-05: 13-Week Oral Toxicity Study in Mice with a 4-Week Dose-Free Recovery Period/Study No. 036629-1 (Applicant Reference No. AXS-005-TM003)

- CD-1 mice (n=16/sex/group) were treated with AXS-05 [BUP/DM: 57/26 (low dose), 75/34 (mid dose), 150/68 (high dose), 150/0 (BUP), 0/68 (DM) mg/kg/day] via oral gavage, once daily for 13 weeks, with a 4-week recovery period.
- Convulsions and mortality were observed in mice given AXS-05 at the high dose level and BUP alone; the mortality rate was increased in males. The convulsions and mortality were attributed to the bupropion component of AXS-05, as both also were seen with bupropion alone. However, the mortality rate in males treated with AXS-05 was higher than that with bupropion alone.
- Diffuse hypertrophy (reversible) of centrilobular hepatocytes of both sexes given AXS-05 were observed at the mid and high dose levels or bupropion alone.
- The NOAEL for AXS-05 was the mid dose (BUP/DM: 75/34 mg/kg/day).

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (vehicle control), BUP/DM: 57/26 (low dose), 75/34 (mid dose), 150/68 (high dose), 150/0 (BUP), 0/68 (DM) mg/kg/day Once daily
Route of administration:	Oral gavage
Formulation/vehicle:	Solution/deionized water
Species/strain:	Mice/Crl:CD-1
Number/sex/group:	16/sex/group (10/sex for low dose); 6/sex/group for recovery (0/sex for low dose)
Age:	10.9-11.4 weeks
Satellite groups/ unique design:	Yes (42/sex/group; 6/sex control)/no unique design
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: Changes from Control

Parameter	Major Findings
Mortality	Twenty males and seven females were found dead or euthanized moribund between Day 4 and Day 88 of the study. Among toxicity mice (Groups 1-6), 12 died or were euthanized early for humane reasons; causes of morbidity or mortality are listed in Table 12.

Table 12. Causes of Mortality/Morbidity

Mortality and/or Moribundity				
		Animal Number	Study Day	Possible Cause of Mortality and/or Moribundity
2M	M	316260	65	Marked, locally extensive hepatocellular necrosis with mixed cell inflammation
4M	FD	316284	51	Undetermined
4M	FD	316288	54	Marked, diffuse centrilobular hepatocellular necrosis
4M	FD	316293	4	Undetermined
4M	M	316294	84	Undetermined
4M	M	316295	77	Undetermined
5M	M	316300	65	Moderate, acute, multifocal coagulative necrosis of the myocardium
5M	M	316309	5	Ulcerative dermatitis
5M	M	316310	5	Undetermined
3F	FD	316855	29	Undetermined
4F	FD	316869	23	Undetermined
6F	FD	316891	18	Undetermined

M – Moribund; FD – Found Dead
Source: Study report, page 35.

The cause of morbidity/mortality was undetermined for 8/12 of the toxicity mice found dead or euthanized moribund. In the other four (all males), morbidity/mortality was attributed to hepatocellular necrosis (one each given AXS-05 at the low and high dose levels; i.e., Group 2 #316260 and Group 4 #316288), moderate, acute, multifocal coagulative necrosis of the myocardium (Group 5 #316300), or ulcerative dermatitis (Group 5 #316309).
As shown in Table 13, overall, the morbidity/mortality rate was greater in males dosed with BUP at 150 mg/kg/day, either alone or as AXS-05, than in control males, and the rate was greater with AXS-05 (21%) than with BUP alone (9%).

Table 13. Incidence of Early Death or Euthanasia

	Vehicle	AXS-05			BUP	DM
BUP (mg/kg/d) =	**0**	**57**	**75**	**150**	**150**	**0**
DM (mg/kg/d) =	**0**	**26**	**34**	**68**	**0**	**68**
Males						
Toxicity mice	0/16	1/10	0/16	5/16	3/16	0/16
TK mice	0/6	1/42	0/42	7/42	2/42	1/42
All mice						
Absolute	0/22	2/52	0/58	12/58	5/58	1/58
Relative	0%	4%	0%	**21%**	**9%**	2%
Females						
Toxicity mice	0/16	0/10	1/16	1/16	0/16	1/16
TK mice	0/6	0/42	0/42	0/42	1/42	3/42
All mice						
Absolute	0/22	0/52	1/58	1/58	1/58	4/58
Relative	0%	0%	2%	2%	2%	7%

Source: Study report, Appendix G.
Abbreviations: BUP, bupropion; DM, dextromethorphan; TK, toxicokinetic

<table>
<tr><th>Parameter</th><th>Major Findings</th></tr>
<tr><td>Clinical signs</td><td>
Treatment-related clinical findings were mainly seen in mice dosed with BUP at 150 mg/kg/d, either alone or as AXS-05; the findings were primarily convulsions or findings related to convulsions. The incidence of convulsions was similar with BUP alone and with AXS-05; however, the incidence was greater in males than in females (Tables 14 and 15).
Table 14. Number of Animals With Incidence of Convulsions
<table>
<tr><th></th><th>Vehicle</th><th colspan="3">AXS-05</th><th>BUP</th><th>DM</th></tr>
<tr><th>BUP HCl (mg/kg/d) =</th><th>0</th><th>57</th><th>75</th><th>150</th><th>150</th><th>0</th></tr>
<tr><th>DM HBr (mg/kg/d) =</th><th>0</th><th>26</th><th>34</th><th>68</th><th>0</th><th>68</th></tr>
<tr><td>Males</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Toxicity mice</td><td>0/16</td><td>0/10</td><td>0/16</td><td>4/16</td><td>6/16</td><td>0/16</td></tr>
<tr><td>TK mice</td><td>0/6</td><td>0/42</td><td>0/42</td><td>9/42</td><td>6/42</td><td>0/42</td></tr>
<tr><td>All mice</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Absolute</td><td>0/22</td><td>0/52</td><td>0/58</td><td>13/58</td><td>12/58</td><td>0/58</td></tr>
<tr><td>Relative</td><td>0%</td><td>0%</td><td>0%</td><td>22%</td><td>21%</td><td>0%</td></tr>
<tr><td>Females</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Toxicity mice</td><td>0/16</td><td>0/10</td><td>0/16</td><td>1/16</td><td>4/16</td><td>0/16</td></tr>
<tr><td>TK mice</td><td>0/6</td><td>0/42</td><td>0/42</td><td>2/42</td><td>1/42</td><td>0/42</td></tr>
<tr><td>All mice</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Absolute</td><td>0/22</td><td>0/52</td><td>0/58</td><td>3/58</td><td>5/58</td><td>0/58</td></tr>
<tr><td>Relative</td><td>0%</td><td>0%</td><td>0%</td><td>5%</td><td>9%</td><td>0%</td></tr>
</table>
Source: Study report, page 37.
Abbreviations: BUP, bupropion; DM, dextromethorphan; TK, toxicokinetic

Table 15. Incidence and Frequency of Noteworthy Clinical Signs
<table>
<tr><th>Test Article</th><th colspan="6">AXS-05 (BUP HCl/DM HBr)</th><th colspan="2">BUP HCl</th><th colspan="2">DM HBr</th></tr>
<tr><th>Dose (mg/kg)</th><th colspan="2">57/26</th><th colspan="2">75/34</th><th colspan="2">150/68</th><th colspan="2">150</th><th colspan="2">68</th></tr>
<tr><th>Dose Group</th><th colspan="2">Low</th><th colspan="2">Mid</th><th colspan="2">High</th><th colspan="2">BUP (150)</th><th colspan="2">DM (68)</th></tr>
<tr><th>Group</th><th colspan="2">2</th><th colspan="2">3</th><th colspan="2">4</th><th colspan="2">5</th><th colspan="2">6</th></tr>
<tr><th>Gender</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><th>N</th><th>10</th><th>10</th><th>16</th><th>16</th><th>16</th><th>16</th><th>16</th><th>16</th><th>16</th><th>16</th></tr>
<tr><td>Muscle tremors</td><td></td><td></td><td></td><td></td><td></td><td></td><td>1/1</td><td></td><td></td><td></td></tr>
<tr><td>Convulsions</td><td></td><td></td><td></td><td></td><td>4/7</td><td>1/1</td><td>6/13</td><td>4/5</td><td></td><td></td></tr>
<tr><td>Eye lid closure</td><td></td><td></td><td></td><td></td><td></td><td></td><td>2/2</td><td></td><td></td><td></td></tr>
<tr><td>Hunched Posture</td><td>1/1</td><td></td><td></td><td></td><td></td><td></td><td>2/4</td><td></td><td></td><td></td></tr>
<tr><td>Reduced Activity</td><td>1/1</td><td></td><td></td><td></td><td></td><td></td><td>2/2</td><td></td><td></td><td></td></tr>
<tr><td>Slow respiration rate</td><td></td><td></td><td></td><td></td><td></td><td></td><td>2/2</td><td></td><td></td><td></td></tr>
<tr><td>Spasm</td><td></td><td></td><td></td><td></td><td>2/2</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Note: Data were expressed as Number of animals / Number of days with the observation.
Empty box means no animals were recorded with specific observations.
Source: Study report, page 37.
Abbreviations: BUP, bupropion; DM, dextromethorphan; N, number

There were no treatment-related clinical findings at the low dose of AXS-05 (57/26), the mid dose of AXS-05 (57/26), or DM (68).
</td></tr>
<tr><td>Body weights</td><td>There were no treatment-related changes in mean body weight/body weight gains in males and females dosed with AXS-05 or BUP alone or DM alone.</td></tr>
<tr><td>Ophthalmoscopy</td><td>There were no treatment-related findings.</td></tr>
<tr><td>Hematology</td><td>There were no treatment-related differences in erythroid, leukocyte, and coagulation parameters.</td></tr>
</table>

Parameter	Major Findings
Clinical chemistry	Although there were no clear treatment-related changes in serum chemistry parameters, at the high dose of BUP (150 mg/kg/d), either alone or as AXS-05, there was a trend towards higher BUN, triglycerides, and phosphorous concentrations in males and higher cholesterol concentrations in females (Tables 16 and 17; related to BUP [bold blue] and evidence of recovery [bold green]).

Table 16. Summary of BUN, Triglyceride, and Phosphorous Data for Males

	Veh	AXS-05			BUP	DM
BUP (mg/kg/d) =	**0**	**57**	**75**	**150**	**150**	**0**
DM (mg/kg/d) =	**0**	**26**	**34**	**68**	**0**	**68**
BUN						
Mean (mg/dL)						
End of dosing	22	33	26	37	46	26
End of recovery	23	---	24	20	36	27
Vs. control mean						
End of dosing	---	+50%	+18%	**+68%**	**+109%**	+18%
End of recovery	---	---	+4%	**-13%**	**+57%**	+17%
Mice > highest control						
End of dosing	[33]	1/5	0/4	**2/3**	**2/3**	0/5
End of recovery	[23]	---	1/3	**0/1**	**1/2**	2/3
Triglycerides						
Mean (mg/dL)						
End of dosing	118	154	158	201	211	150
End of recovery	166	---	158	177	139	129
Vs. control mean						
End of dosing	---	+31%	+34%	**+70%**	**+79%**	+27%
End of recovery	---	---	-5%	**+7%**	**-16%**	-22%
Mice > highest control						
End of dosing	[137]	3/5	3/4	**2/3**	**3/3**	3/5
End of recovery	[181]	---	1/3	**0/1**	**0/2**	0/3
Phosphorus						
Mean (mg/dL)						
End of dosing	10.1	11.0	10.6	11.0	**12.4***	11.0
End of recovery	10.3	---	11.2	9.3	10.8	11.7
Vs. control mean						
End of dosing	---	+9%	+5%	+9%	**+23%**	+9%
End of recovery	---	---	+9%	-10%	**+5%**	+14%
Mice > highest control						
End of dosing	[11.3]	1/5	0/4	1/3	**2/3**	2/5
End of recovery	[11.7]	---	1/3	0/1	**1/2**	1/3

*Statistically significant using Dunnett 2-sided test at p<0.05
Source: Study report, Appendix G.
Abbreviations: BUN, blood urea nitrogen; BUP, bupropion; DM, dextromethorphan; Veh, vehicle

Table 17. Summary of Cholesterol Data for Females

	Veh	AXS-05			BUP	DM
BUP (mg/kg/d) =	**0**	**57**	**75**	**150**	**150**	**0**
DM (mg/kg/d) =	**0**	**26**	**34**	**68**	**0**	**68**
Cholesterol						
Mean (mg/dL)						
End of dosing	94	111	120	**150***	**191***	102
End of recovery	114	---	153	129	113	83
Vs. control mean						
End of dosing	---	+18%	+28%	**+60%**	**+103%**	+9%
End of recovery	---	---	+34%	**+13%**	**-1%**	-27%
Mice > highest control						
End of dosing	[116]	1/5	3/5	**4/5**	**5/5**	1/4
End of recovery	[148]	---	1/2	**1/2**	**0/3**	0/3

*Statistically significant using Dunnett 2-sided test at p<0.05
Source: Study report, Appendix G.
Abbreviations: BUP, bupropion; DM, dextromethorphan; Veh, vehicle

Gross pathology	There were no noteworthy treatment-related macroscopic findings at the main necropsy or at the end of the 4-week recovery. In animals that were found dead or moribund, there were no consistent, dose-dependent macroscopic observations that could be attributed to treatment with AXS-05 or its components.

Parameter	Major Findings
Organ weights	There were no treatment-related effects on terminal body weights. The only treatment-related difference in organ weight were minimal increases in mean liver weights in females dosed BUP at all doses, either alone or as AXS-05, and in males dosed BUP at ≥75 mg/kg/d, alone or as AXS-05. The effect on liver weight was greater in females than males (Tables 18 and 19; bold blue). The increase in mean liver weight correlated with hepatocellular hypertrophy seen microscopically. Differences in liver weight resolved by the end of the recovery period (bold green).

Table 18. Summary of Mean Liver Weight Data for Males

	Veh	AXS-05			BUP	DM
BUP (mg/kg/d) =	**0**	**57**	**75**	**150**	**150**	**0**
DM (mg/kg/d) =	**0**	**26**	**34**	**68**	**0**	**68**
Mean						
End of dosing						
Absolute (g)	1.79	1.86	1.88	1.89	1.90	1.84
Vs. body weight (g/kg)	50.9	52.2	55.3	54.8	53.1	50.4
Vs. brain weight (g/g)	3.63	3.70	3.89	3.65	3.90	3.76
End of recovery						
Absolute (g)	1.96	---	1.75	1.94	1.98	2.02
Vs. body weight (g/kg)	52.6	---	49.3	52.0	51.7	52.7
Vs. brain weight (g/g)	3.83	---	3.54	3.76	3.76	3.93
Vs. control mean						
End of dosing						
Absolute	---	+4%	+5%	**+6%**	**+6%**	+3%
Vs. body weight	---	+3%	**+9%**	**+8%**	+4%	-1%
Vs. brain weight	---	+2%	**+7%**	+1%	**+7%**	+4%
End of recovery						
Absolute	---	---	-11%	**-1%**	**+1%**	+3%
Vs. body weight	---	---	**-6%**	**-1%**	-2%	+0%
Vs. brain weight	---	---	**-8%**	-2%	**-2%**	+3%

Source: Study report, Appendix G.
Abbreviations: BUP, bupropion; DM, dextromethorphan; Veh, vehicle

Table 19. Summary of Mean Liver Weight Data for Females

	Veh	AXS-05			BUP	DM
BUP (mg/kg/d) =	**0**	**57**	**75**	**150**	**150**	**0**
DM (mg/kg/d) =	**0**	**26**	**34**	**68**	**0**	**68**
Mean						
End of dosing						
Absolute (g)	1.31	1.47	1.52	1.45	1.63	1.29
Vs. body weight (g/kg)	46.4	51.2	54.1	51.1	**54.7***	47.1
Vs. brain weight (g/g)	2.58	2.95	3.08	2.95	3.16	2.57
End of recovery						
Absolute (g)	1.56	---	1.56	1.50	1.35	1.57
Vs. body weight (g/kg)	49.3	---	48.9	47.5	46.5	54.6
Vs. brain weight (g/g)	3.11	---	2.99	2.83	2.62	3.23
Vs. control mean						
End of dosing						
Absolute	---	**+12%**	**+16%**	**+11%**	**+24%**	-2%
Vs. body weight	---	**+10%**	**+17%***	**+10%**	**+18%**	+2%
Vs. brain weight	---	**+14%**	**+19%**	**+14%**	**+22%**	-0%
End of recovery						
Absolute	---	---	**±0%**	**-4%**	**-13%**	+1%
Vs. body weight	---	---	**-1%**	**-4%**	**-6%**	+11%
Vs. brain weight	---	---	**-4%**	**-9%**	**-16%**	+4%

*Statistically significant using Dunnett 2-sided test at p<0.01
Source: Study report, Appendix G.
Abbreviations: BUP, bupropion; DM, dextromethorphan; Veh, vehicle

Parameter	Major Findings
Histopathology Adequate battery: Yes However, it was not clear from the protocol or the study design whether the brain was evaluated based on the current standards (i.e., seven sections). Based on new information sent by the Applicant (as indicated in the cover letter; Sequence No. 0023, dated 8-2-2021) the brain was further sectioned to produce a total of seven sections.	Liver: Treatment-related diffuse hypertrophy of centrilobular hepatocytes in males and females dosed with BUP at the mid- and high-dose levels, alone, or as AXS-05; because this was also seen in mice given BUP alone, the finding was considered to be due to the BUP component of AXS-05. In mice that were euthanized at the end of dosing, the severity of the finding was graded as minimal or mild (Tables 20 and 21). However, in three mice given BUP at the high dose as AXS-05 that died or were euthanized early, the finding was graded as moderate (one female) or marked (two males). Hypertrophy was reversible because it was not seen in animals at the end of the recovery period. Kidney: Treatment-related multifocal, bilateral necrosis of the epithelium lining the renal proximal tubules (mild) was seen in one male given AXS-05 at the high dose and four males given BUP alone (Table 22). Because this finding was seen as minimal to moderate in four males given BUP alone, it was considered to be due to BUP. Although renal tubule necrosis was reversible and was absent in recovery mice, the finding is considered adverse. In mice given BUP alone, there was minimal to marked, multifocal, bilateral degeneration/regeneration of the epithelium lining the proximal tubules in the kidneys of both males and females (Tables 22 and 23); except for the two males treated with DM alone, this finding was reversible at the end of the recovery period. Heart: At the high dose of AXS-05, there was treatment-related marked, locally extensive, coagulative necrosis in the heart of one male. In the right ventricle, there was necrosis, which was accompanied by marked, locally extensive fibrosis and marked, diffuse, fibrous inflammation in the lungs. Both findings are considered adverse. A similar finding was seen in one male given BUP alone that was euthanized on Day 65; therefore, the above findings were considered to be due to BUP. **Table 20. Summary of Histopathology Findings in the Liver (Males)**

	Males					
	Veh	AXS-05			BUP	DM
BUP (mg/kg/d) =	0	57	75	150	150	0
DM (mg/kg/d) =	0	26	34	68	0	68
Group No. =	1	2	3	4	5	6
Liver – hepatocellular hypertrophy, centrilobular						
Early death/euthanasia						
1 (minimal)	NE	0/1	NE	0/5	0/3	NE
2 (mild)	NE	0/1	NE	2/5	1/3	NE
3 (moderate)	NE	0/1	NE	0/5	0/3	NE
4 (marked)	NE	0/1	NE	2/5	0/3	NE
End of dosing period						
1 (minimal)	0/10	0/9	8/10	0/8	0/9	0/10
2 (mild)	0/10	0/9	0/10	8/8	9/9	0/10
Combined						
1 (minimal)	0/10	0/10	8/10	0/13	0/12	0/10
2 (mild)	0/10	0/10	0/10	10/13	10/12	0/10
3 (moderate)	0/10	0/10	0/10	0/13	0/12	0/10
4 (marked)	0/10	0/10	0/10	2/13	0/12	0/10
Total	0/10	0/10	8/10	12/13	10/12	0/10

NE – Not Examined

Source: Study report, Appendix G.
Abbreviations: BUP, bupropion; DM, dextromethorphan; NE, not evaluated; Veh, vehicle

Parameter	Major Findings
Histopathology, continued	**Table 21. Summary of Histopathology Findings in the Liver (Females)**

	Females					
	Veh	AXS-05			BUP	DM
BUP (mg/kg/d) =	0	57	75	150	150	0
DM (mg/kg/d) =	0	26	34	68	0	68
Group No. =	1	2	3	4	5	6
Liver – hepatocellular hypertrophy, centrilobular						
Early death/euthanasia						
1 (minimal)	NE	NE	0/1	0/1	NE	0/1
2 (mild)	NE	NE	1/1	0/1	NE	0/1
3 (moderate)	NE	NE	0/1	1/1	NE	0/1
4 (marked)	NE	NE	0/1	0/1	NE	0/1
End of dosing period						
1 (minimal)	0/10	0/10	10/10	0/10	0/10	0/9
2 (mild)	0/10	0/10	0/10	10/10	10/10	0/9
Combined						
1 (minimal)	0/10	0/10	**10/11**	0/11	0/10	0/10
2 (mild)	0/10	0/10	**1/11**	**10/11**	**10/10**	0/10
3 (moderate)	0/10	0/10	0/11	**1/11**	0/10	0/10
4 (marked)	0/10	0/10	0/11	0/11	0/10	0/10
Total	0/10	0/10	**11/11**	**11/11**	**10/10**	0/10

NE – Not Examined
Source: Study report, Appendix G.
Abbreviations: BUP, bupropion; DM, dextromethorphan; NE, not evaluated; Veh, vehicle

Table 22. Summary of Histopathology Findings in the Kidneys (Males)

	Males					
	Veh	AXS-05			BUP	DM
BUP (mg/kg/d) =	0	57	75	150	150	0
DM (mg/kg/d) =	0	26	34	68	0	68
Group No. =	1	2	3	4	5	6
Kidneys – degeneration/regeneration, epithelial; proximal tubule						
Early death/euthanasia						
1 (minimal)	NE	0/1	NE	0/5	0/3	NE
2 (mild)	NE	0/1	NE	0/5	1/3	NE
End of dosing period						
1 (minimal)	0/10	0/9	0/10	0/8	3/9	0/10
2 (mild)	0/10	0/9	0/10	0/8	0/9	0/10
3 (moderate)	0/10	0/9	0/10	0/8	1/9	0/10
4 (marked)	0/10	0/9	0/10	0/8	1/9	0/10
Combined						
1 (minimal)	0/10	0/10	0/10	0/13	**3/12**	0/10
2 (mild)	0/10	0/10	0/10	0/13	**1/12**	0/10
3 (moderate)	0/10	0/10	0/10	0/13	**1/12**	0/10
4 (marked)	0/10	0/10	0/10	0/13	**1/12**	0/10
Total	0/10	0/10	0/10	0/13	**6/12**	0/10
Kidneys – necrosis; epithelial; proximal tubule						
Early death/euthanasia						
1 (minimal)	NE	0/1	NE	0/5	1/3	NE
2 (mild)	NE	0/1	NE	1/5	0/3	NE
End of dosing period						
1 (minimal)	0/10	0/9	0/10	0/8	1/9	0/10
2 (mild)	0/10	0/9	0/10	0/8	1/9	0/10
3 (moderate)	0/10	0/9	0/10	0/8	1/9	0/10
Combined						
1 (minimal)	0/10	0/10	0/10	0/13	**2/12**	0/10
2 (mild)	0/10	0/10	0/10	**1/13**	**1/12**	0/10
3 (moderate)	0/10	0/10	0/10	0/13	**1/12**	0/10
Total	0/10	0/10	0/10	**1/13**	**4/12**	0/10

NE – Not Examined
Source: Study report, Appendix G.
Abbreviations: BUP, bupropion; DM, dextromethorphan; NE, not evaluated; Veh, vehicle

Parameter	Major Findings
Histopathology, continued	**Table 23. Summary of Histopathology Findings in the Kidneys (Females)**

	Females					
	Veh	AXS-05			BUP	DM
BUP (mg/kg/d) =	0	57	75	150	150	0
DM (mg/kg/d) =	0	26	34	68	0	68
Group No. =	1	2	3	4	5	6
Kidneys – degeneration/regeneration, epithelial; proximal tubule						
Early death/euthanasia						
1 (minimal)	NE	NE	0/1	0/1	NE	0/1
2 (mild)	NE	NE	0/1	0/1	NE	0/1
End of dosing period						
1 (minimal)	0/10	0/10	0/10	0/10	5/10	0/9
2 (mild)	0/10	0/10	0/10	0/10	4/10	0/9
3 (moderate)	0/10	0/10	0/10	0/10	0/10	0/9
4 (marked)	0/10	0/10	0/10	0/10	0/10	0/9
Combined						
1 (minimal)	0/10	0/10	0/11	0/11	5/10	0/10
2 (mild)	0/10	0/10	0/11	0/11	4/10	0/10
3 (moderate)	0/10	0/10	0/11	0/11	0/10	0/10
4 (marked)	0/10	0/10	0/11	0/11	0/10	0/10
Total	0/10	0/10	0/11	0/11	9/10	0/10
Kidneys – necrosis; epithelial; proximal tubule						
Early death/euthanasia						
1 (minimal)	NE	NE	0/1	0/1	NE	0/1
2 (mild)	NE	NE	0/1	0/1	NE	0/1
End of dosing period						
1 (minimal)	0/10	0/10	0/10	0/10	0/10	0/9
2 (mild)	0/10	0/10	0/10	0/10	0/10	0/9
3 (moderate)	0/10	0/10	0/10	0/10	0/10	0/9
Combined						
1 (minimal)	0/10	0/10	0/11	0/11	0/10	0/10
2 (mild)	0/10	0/10	0/11	0/11	0/10	0/10
3 (moderate)	0/10	0/10	0/11	0/11	0/10	0/10
Total	0/10	0/10	0/11	0/11	0/10	0/10

NE – Not Examined
Source: Study report, Appendix G.
Abbreviations: BUP, bupropion; DM, dextromethorphan; NE, not evaluated; Veh, vehicle

Abbreviations: BUN, blood urea nitrogen; BUP, bupropion; DM, dextromethorphan

General Toxicology; Additional Studies

Single-Dose Toxicity Study in Rats (Study No. 035561; Applicant Reference No. AXS005-TR001)

A single-dose toxicity study in Crl:CD rats was conducted in two phases; the objectives of this study were to establish the single-dose MTD of AXS-05 (phase 1) and to assess toxicity and toxicokinetics following once daily oral administration of AXS-05 for 3 consecutive days at or below the established MTD (phase 2). In the phase 1 part of the study, groups of three or six rats/sex (Table 2) were given AXS-05 (BUP/DM), observed for 3 days for clinical signs of toxicity or effects on body weight, and then euthanized and discarded without examination. Based on the results of phase 1, dose levels (BUP/DM) of 100/45, 200/90, and 300/135 mg/kg/day were administered by oral gavage once daily for 3 consecutive days in phase 2.

Table 2. Group Assignment and Dose Levels in Crl:CD Rats

Dose Group	No. of Animals (M/F)	Test Item	Dose Level BUP/DM (mg/kg)	Dose Conc. BUP/DM (mg/mL)	Dose Volume (mL/kg)	No. of Days Dosed
Phase 1 MTD						
1	3/3	AXS-05	150/67.5	15/6.75	10	1
2	3/3	AXS-05	300/135	30/13.5	10	1
3	3/3	AXS-05	600/270	60/27	10	1
4	3/3	AXS-05	M=1200/540 F=445/200	M=120/54 F=44.5/20	10	1
9	6/6	AXS-05	M= 200/90 F= 100/45	M=20/9 F= 10/4.5	10	1
10	6/6	AXS-05	M=400/180 F= 200/90	M= 40/18 F= 20/9	10	1
11	6/6	AXS-05	M= 800/360 F= 400/180	M= 80/36 F= 40/18	10	1
Phase 2 – Three-Day Repeat Dose						
Dose Group	No. of Animals (M/F)	Test Item	Dose Level BUP/DM (mg/kg/day)	Dose Level BUP/DM (mg/mL)	Dose Volume (mL/kg)	No. of Days Dosed
5	6/6	Vehicle	0	0	10	3
6	6/6	AXS-05	100/45	10/4.5	10	3
7	6/6	AXS-05	200/90	20/9.0	10	3
8	6/6	AXS-05	300/135	30/13.5	10	3

Source: Applicant's Study Report; AXS005-TR001, page 6.
Abbreviations: BUP, bupropion; DM, dextromethorphan; F, female; M, male; No., number

Initial doses showed a sex difference in toxicity (females more sensitive than males); therefore, the phase 1 study explored dose levels from 150/67.5 mg/kg to 1200/540 mg/kg in males and from 100/45 mg/kg to 600/270 mg/kg in females. Males tolerated single doses of AXS-05 at up to 300/135 mg/kg, but deaths occurred at ≥400/180 mg/kg. Females tolerated AXS-05 at up to 150/67.5 mg/kg, but deaths occurred at 200/90 mg/kg. There were no treatment-related abnormal findings at necropsy in any rat that died.

Treatment-related clinical findings were more frequent and seen at lower dose levels in females than males. Following a single dose of AXS-05 at 100/45 mg/kg, females exhibited head bobbing, uncoordinated activity, hyperactivity, hunched posture, and partially closed eyes (males were not given AXS-05 at this dose level). Following a single dose of AXS-05 at 150/67.5 mg/kg, one female had muscle spasms on the day of dosing; however, there were no signs in males. Following single doses of AXS-05 at ≥200/90 mg/kg, clinical signs were seen in both sexes; they included labored breathing, hair loss, stained fur, reduced feces, hunched posture, hyperactivity, salivation, and cage biting. In addition, although less common, there were muscle tremors, uncoordinated movement, muscle convulsions, and prostrate body position. Some of the less common findings were considered agonal observations related to subsequent deaths. Table 3 shows mortality data from both phases combined (in ascending order of dose level and with all animals dosed at each dose level combined). Repeat dosing of up to 3 days in duration did not result in an increase in mortality compared to single doses. Animals undergoing unscheduled mortality died within 24 hours following their initial dose.

Table 3. Mortality in Both Phases Combined

Number of Animals (M/F)	Dose Level BUP/DM (mg/kg)	Male Mortality	Female Mortality
6/12	100/45	0%	0%
3/3	150/67.5	0%	0%
12/12	200/90	0%	25%
9/9	300/135	11%	33%
6/6	400/180	67%	100%
0/3	445/200	-	100%
3/3	600/270	0%	67%
6/0	800/360	83%	-
3/0	1200/540	67%	-

Source: Applicant's Study Report, AXS005-TR001, page 28.
Abbreviations: BUP, bupropion; DM, dextromethorphan; F, female; M, male

In this study, the male NOAEL was 200/90 (BUP/DM) mg/kg/day, as male rats were found to tolerate doses of 200/90 mg/kg/day and below with no mortality, no or few abnormal observations, and no weight loss, even with 3 days of repeat dosing. A female NOAEL was not determined, as female rats dosed at the low dose level of 100/45 (BUP/DM) mg/kg/day for 3 days did not have mortality but had multiple abnormal clinical observations after both a single dose and 3-day repeat dosing and showed body weight loss (-2.8 to -6%; Table 4) after 3 days of dosing.

Table 4. Group Mean Percentage Weight Gain From Day 1 to Day 3

Dose Level▶ Sex▼	100/45	200/90	300/135
Male	+2.1	+1.0	< 1.0 Difference
Female	-3.2	-2.8	-6.0

Source: Applicant's Study Report, AXS005-TR001, page 27.
Dose levels in mg/kg/day bupropion/dextromethorphan

5.5.2. Genetic Toxicology

No studies examining the genotoxic potential of AXS-05 have been submitted by the Applicant. Full genetic toxicology battery was conducted with Wellbutrin SR and Nuedexta, the LDs, and the results are expressed in their respective product labels.

5.5.3. Carcinogenicity

For the two-year carcinogenicity study in rats and 26-week carcinogenicity study in Tg.rasH2 transgenic mice, the Applicant had proposed to use data from the dextromethorphan alone arm of the Nuedexta label. Reference to the carcinogenicity data in Nuedexta does not adequately characterize the carcinogenic potential of dextromethorphan, let alone in combination with bupropion. Specifically, the referenced single-dose PK data in rats provided

by the Applicant do not characterize concentration at steady state, and the referenced study[6] only tests one dose of dextromethorphan alone and it is not clear that this dose adequately meets high dose selection criteria recommended in ICH S1C(R2). To address this deficiency, the Applicant should submit appropriate justification that the referenced studies adequately characterize the carcinogenic potential of dextromethorphan in accordance with ICH S1C(R2) recommendation with respect to dose selection. Alternatively, the Applicant should conduct carcinogenicity studies in two species to address the carcinogenic potential of dextromethorphan. Given the findings reported in the referenced bupropion labeling of liver findings and the potential PK interaction between the two active drug substances, the Applicant should consider designing the study to test the combination of the two drugs and including a high dose arm for each single agent, as was done for Nuedexta.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

No studies examining the potential of AXS-05 to cause reproductive toxicity were submitted by the Applicant. The bupropion component of AXS-05 has been evaluated in a fertility study in rats (results expressed in the LD, Wellbutrin SR, label); bupropion did not affect fertility in rats at doses up to 300 mg/kg/day. Likewise, the dextromethorphan component of AXS-05 has been evaluated in male and female rats (coadministered with quinidine); coadministration of dextromethorphan at up to 50 mg/kg/day and quinidine at 100 mg/kg/day did not affect fertility in rats (results expressed in LD, Nuedexta, label).

Embryo-Fetal Development

AXS-05: Study for Effects on Embryo-Fetal Development Following Oral Gavage Administration to Pregnant Female CD-1 Mice/Study No. 2553-14860; Applicant Reference No. AXS-005-TM005

Key Study Findings

- CD-1 mice (n=25/group) were treated with AXS-05 at BUP/DM dose levels of 57/26 (low dose), 75/34 (mid dose), or 150/68 (high dose) mg/kg during the period of organogenesis (gestational day [GD] 6 to 15).
- Treatment-related maternal mortality and clinical signs were observed at the mid and high doses. No treatment-related effects on embryo-fetal development were observed.
- The NOAEL for maternal toxicity was 57/26 mg/kg/day AXS-05, and the embryo-fetal developmental NOAEL was 150/68 mg/kg/day AXS-05.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

[6] Marier, JF, LE Pope, GJ Yakatan, JE Berg, M Stiles, and P Vachon, 2004, Influence of concomitant quinidine administration on dextromethorphan disposition in rats. J. vet. Pharmacol. Therap., 27: 111-114.

Methods

Dose and frequency of dosing:	0 (vehicle control), BUP/DM: 57/26 (low dose), 75/34 (mid dose), 150/68 (high dose), 150/0 (BUP), 0/68 (DM) mg/kg/day; once daily
Route of administration:	Oral gavage
Formulation/vehicle:	Solution/deionized water
Species/strain:	CD-1 Mouse
Number/sex/group:	25/group
Satellite groups:	TK groups: 36/group (6 control group)
Study design:	Dosing from GD 6 to 15. The dose levels were selected based on the results of a dose range-finding study in which pregnant CD-1 mice were given AXS-05 at BUP/DM dose levels (mg/kg) of 57/26, 75/34, 112.5/34, or 150/68 via oral gavage from GD 6 to 15. Mice tolerated AXS-05 at the low and mid dose levels without adverse effects. At the high dose level, convulsions occurred in one female on GD 15.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameter	Major Findings
Mortality	One main study female (No. 30365) and one TK female (No. 30418) from the mid-dose group and one TK female (No. 30475) from the high-dose group were found dead on GD 8. Although there were no treatment-related clinical signs in these females prior to death (as well as the fact that there was no evidence of dosing error), these deaths were considered treatment-related, based on the results of the previous dose range-finding study in which mice showed mortality at the same dose levels.
Clinical signs	Treatment-related clinical signs of hyperactivity occurred on GD 13-18 and vocalization during handling occurred on GD 13-15 in one low-dose female (No. 30315). One high-dose female (No. 30431) exhibited treatment-related clinical signs of ataxia, minimal convulsions, and was slightly languid on GD 10.
Body weights	There were no treatment-related effects on body weights, body weight changes, or body weight changes adjusted to gravid uterine weight.
Necropsy findings Cesarean section data	There were no treatment-related gross pathology findings. The mean numbers of corpora lutea, implantations, early or late resorptions, dead fetuses, total deaths, and live fetuses were comparable across groups.
Necropsy findings Offspring	There were no treatment-related effects on fetal body weights. There were no treatment-related external, visceral, or skeletal malformations or variations.

Abbreviations: GD, gestational day; No., number; TK, toxicokinetic

Prenatal and Postnatal Development

No studies have been conducted with AXS-05 to evaluate effects on lactation or postnatal development of offspring. The bupropion component of AXS-05 was evaluated in a pre- and post-natal development study in pregnant rats; when bupropion was administered to pregnant rats at doses of up to 150 mg/kg/day from embryonic implantation through lactation, there were no effects on pup growth or development. The results are stated in the label for the LD, Wellbutrin SR.

When the dextromethorphan component of AXS-05 was orally administered (coadministered with quinidine) to female rats during pregnancy and lactation in two separate studies, pup survival and pup weight were decreased at all doses, and developmental delay was observed in offspring at ≥15/100 dextromethorphan/quinidine doses. A NOAEL for adverse developmental effect was not identified. The results are stated in the label for the LD, Nuedexta.

Deficiencies identified in the bridging reproductive toxicity and carcinogenicity studies

After reviewing the data submitted in this application, we concluded that, although the existing referenced non-clinical data from the two listed drugs permit labeling for risk assessment for this product, these data were not ideal. The data were confounded by the presence of another drug that is not part of the current product (i.e., quinidine) and also did not address the combined effect of bupropion and dextromethorphan. However, in view of the clinical benefit for this product, further studies can be conducted post marketing to address the non-clinical sections of the proposed product label as summarized below:

1- The Applicant did not submit an adequate embryofetal study in a second species. Even though the Applicant conducted an embryofetal study in mice, this study did not resolve the concerns about the embryofetal developmental toxicity potential of AXS-05 based on the toxicities observed in rabbits (including malformations and embryo lethality), as described in the product labels of both of Wellbutrin SR and Nuedexta. Therefore, the Agency will issue a PMR to evaluate the combined effect of those two products in rabbits in order to have a better-informed label regarding the embryofetal toxicity of AXS-05.

2- The Applicant has not provided an adequate assessment of the effect of their product on fertility and early embryonic development or on pre- and post-natal development. The Applicant's reliance on fertility and pre- and postnatal data described in Nuedexta label is inadequate due to the confounding effect of quinidine; therefore, the effect of dextromethorphan cannot be determined. In addition, the combined effect of dextromethorphan and bupropion on the endpoints from these studies were not addressed. Therefore, to address this deficiency, the Agency will issue a PMR to conduct a fertility and early embryonic development study and a pre- and post-natal development study with AXS-05. It is recommended that these studies include a high dose for each individual drug to assist in study interpretation.

3- The Applicant did not provide sufficient justification that the referenced carcinogenicity data in the Nuedexta label adequately characterize the carcinogenic potential of dextromethorphan alone, or in combination with bupropion. Specifically, the referenced single-dose PK data do not characterize concentration at steady state, and the referenced study only tests one dose of dextromethorphan alone and it is not clear that this dose adequately meets high dose selection criteria recommended in ICH S1C(R2). To address this deficiency, an appropriate justification that the referenced studies adequately characterize the carcinogenic potential of dextromethorphan in accordance with ICH S1C(R2) recommendation with respect to dose selection should be provided. Alternatively, a carcinogenicity studies in two species to address the carcinogenic potential of dextromethorphan should be conducted. Given the findings reported in the referenced bupropion labeling of liver findings and the potential PK interaction between the two active drug substances, the Applicant should consider designing the study to test the combination of the two drugs and including a high dose arm for each single agent, as was done for Nuedexta. Although the referenced nonclinical data allow for labeling of risk in Section 13, it is not ideal; therefore, the Agency will issue a PMR to conduct carcinogenicity studies to address the lack of information on the combined effect/s of dextromethorphan and bupropion in product labeling.

4- The Applicant did not adequately address the neurotoxic potential of dextromethorphan to the young and developing brain. The publication cited as justification for lack of neurotoxic potential of dextromethorphan does not address this concern, because the developmental age of the animals used in the referenced study does not correspond to the human developmental age in question (i.e., third trimester of gestation to possibly the first few years postnatally). Therefore, the Agency will issue a PMR to conduct a study to address the neurotoxic potential of dextromethorphan using the appropriate animal age group.

5.5.5. Other Toxicology Studies

No studies were conducted specifically to evaluate the local effects of AXS-05 on the gastrointestinal (GI) tract. However, local tolerance was evaluated as part of a 13-week, repeat-dose toxicity study in Crl:CD-1 mice. At necropsy, visible pathologic findings were recorded, and samples of esophagus, stomach, small intestine, and large intestine were collected and fixed. Samples from mice given vehicle, AXS-05 at the high dose level, bupropion alone, or dextromethorphan alone were subsequently examined by light microscopy for histopathologic findings. There were no clinical signs to suggest an effect on GI function and no pathologic findings to suggest an effect on GI tract at any dose level.

Dextromethorphan and its primary metabolite dextrorphan are NMDA receptor antagonists. Several compounds in this class are known to cause neuronal vacuolation and neurodegeneration in the retrosplenial/posterior cingulate cortices in the brain of adult rats, a finding referred to as “Olney lesions.” In addition, this class of drugs is believed to produce apoptosis in the developing young brain (7-day of age or younger in rats, which corresponds to

the developing human brain in the third trimester of gestation through the first several months of life and may extend to approximately three years of age).

No studies examining the potential of AXS-05 to cause apoptosis were submitted by the Applicant, as this relates to their product because of the neurotoxic findings in the developing brain described in the Nuedexta label. Based on a published report[7], the Applicant has concluded that there was no evidence of neuronal vacuolation (Olney lesions), neurodegeneration, or other neuropathologic changes following single or repeated oral administration of dextromethorphan to rats (400 mg/kg/day in males; 120 mg/kg/day in females) for up to 30 days. This study examined brains microscopically 4 to 6 hours postdose for evidence of neuronal vacuolation, and ~24 or 48 hours postdose for neurodegeneration. As a positive control the study used MK-801, which produced characteristic lesions. However, this study did not use animals of the appropriate age to reflect the effects on young developing brain (i.e., 7-day old rats). Therefore, this study does not address the potential concern for the effect of dextromethorphan on the young developing brain.

Issues with impurities and excipients

Based on earlier communication with the chemistry team, the specification of bupropion impurity (b) (4) was exceeding the ICH qualification threshold of (b) (4) %. However, based on an information request (IR) that was sent to the Applicant on 04/05/2022, the Applicant agreed to revise the specification for this drug product impurity to (b) (4) % (eCTD #0029; dated 04/06/2022), to meet the ICH qualification threshold (see CMC review, assessment #1 addendum 2; dated 4-28-2022). Furthermore, according to the chemistry reviewer, levels of impurity (b) (4) have remained within (b) (4) % throughout the 6 months of long-term and 6 months of accelerated stability period and supports the proposed shelf-life of six months. Therefore, the issue with this impurity is resolved and no further qualification is needed.

The levels of the excipient cysteine HCl ((b) (4) mg/day) were identified by the chemistry team to exceed the levels in the Inactive Ingredient Database (IID). In response to an IR (dated 04/07/2022), the Applicant provided justification to support the level of this excipient in the proposed formulation (dated 04/11/2022). The Applicant established the safety of the level of cysteine based on:

- Cysteine is an amino acid which is a normal component of food proteins; based on National Health and Nutrition Examination Survey (NHANES) data, the average daily cysteine intake from food and supplements in the U.S. is up to 2,200 mg, which is (b) (4) times higher than the daily amount in AXS-05.
- Cysteine hydrochloride is FDA approved and marketed under the trade name ELCYS, for parenteral nutritional supplementation at daily doses up to 1571 mg that are approximately (b) (4) times higher than the daily amount in AXS-05.
- Cysteine, like other dietary amino acids, is classified by the FDA as a dietary supplement, and the NIH Dietary Supplement Label Database lists daily doses of marketed cysteine

[7] Carliss, R, A Radovsky, CP Chengelis, T O'Neill, and DL Shuey, 2007, Oral administration of dextromethorphan does not produce neuronal vacuolation in the rat brain, Neurotoxicology, 28:813-818.

hydrochloride tablets that are approximately (b) (4) times higher than the daily amount in AXS-05.

Therefore, based on our assessment of the data provided by the Applicant, we conclude that the Applicant has addressed the safety concern regarding the level of cysteine HCl in AXS-05. Given that the total daily intake of cysteine HCl is deemed adequate from a nonclinical perspective, there is no outstanding safety concern regarding the use of cysteine HCl in the proposed formulation and therefore, the levels proposed for this excipient in this product are deemed safe.

6. Clinical Pharmacology

6.1. Executive Summary

AXS-05 is an oral, bilayer tablet that consists of a fixed-dose combination of 45 mg dextromethorphan hydrobromide and 105 mg bupropion hydrochloride (AXS-05). This 505(b)(2) application partially relies on the literature for in vitro protein binding and metabolism studies for dextromethorphan. This Application also relies on the Agency's previous findings of in vitro protein binding, metabolism, in vitro drug interaction and human mass balance information for bupropion from the LD, Wellbutrin SR, which is an approved drug product for the treatment of MDD. Given the maximum recommended dose of bupropion from AXS-05 is 105 mg BID, which is lower than that recommended for Wellbutrin SR (200 mg BID), and coadministration of dextromethorphan did not affect the pharmacokinetics (PK) of bupropion, a cross-study PK comparison was performed to establish a scientific bridge between AXS-05 and the LD, Wellbutrin SR (Refer to Section 6.3.1).

The clinical pharmacology program for AXS-05 consists of single ascending dose and multiple ascending dose PK studies, studies in specific populations (subjects with moderate renal impairment and subjects with moderate hepatic impairment, patients with CYP2D6 poor metabolizer status), a food effect study, a thorough QT interval study, and drug interaction studies (with strong CYP2D6 inhibitor, strong CYP2B6 inducer, and weak CYP2B6 inhibitor).

The Office of Clinical Pharmacology reviewed the clinical pharmacology studies submitted in this application and finds that the PK of AXS-05 has been adequately characterized to inform product labeling. A scientific bridge between AXS-05 and the LD, Wellbutrin SR is acceptable. Therefore, AXS-05 can rely on select clinical pharmacology data (i.e., in vitro protein binding, metabolism, in vitro drug interactions, and human mass balance) for bupropion from the LD. The proposed dosing regimen of AXS-05 (45 mg dextromethorphan hydrobromide-105 mg bupropion hydrochloride once daily for the initial 3 days, followed by twice daily thereafter) is acceptable for the treatment of MDD. For patients with moderate renal impairment, patients with CYP2D6 poor metabolizers and patients on concomitant use of strong CYP2D6 inhibitors, the recommended dosage is once daily in the morning. Avoid use of AXS-05 in patients on strong CYP2B6 inducers.

Two post-marketing requirement (PMR) studies (1. Evaluate the effect of severe renal impairment on the PK of AXS-05; 2. Evaluate the effect of severe hepatic impairment on the PK of AXS-05) are required to provide appropriate dosing recommendations of AXS-05 in patients with severe renal impairment and patients with severe hepatic impairment, and adequately inform product labeling. Refer to Section 13 for additional information.

6.2. Summary of Clinical Pharmacology Assessment

- Because dextromethorphan is extensively metabolized by CYP2D6, bupropion (a strong CYP2D6 inhibitor) was added to this combination to increase the exposure to dextromethorphan. The combination of 60 mg dextromethorphan+150 mg bupropion administered twice daily (BID) showed substantially higher systemic exposures (maximum plasma concentration [C_{max}]: 42-fold and area under the plasma concentration-time curve [AUC_{0-12h}]: 60-fold) to dextromethorphan compared to dextromethorphan (60 mg BID) when administered alone.
- Following oral administration of AXS-05 (45 mg dextromethorphan hydrobromide-105 mg bupropion hydrochloride) over 10 days (once daily for the initial 3 days followed by twice daily), C_{max}, and AUC_{0-12h} for dextromethorphan were increased approximately 20-fold and 32-fold, respectively, compared to a single dose of AXS-05.
- Compared to fasted conditions, a high-fat, high-calorie diet delayed the time to reach C_{max} (T_{max}) of AXS-05 from 3 to 4 hours for dextromethorphan and bupro+pion. However, food did not appreciably affect the systemic exposures (C_{max} and AUC) to dextromethorphan and bupropion. Therefore, AXS-05 can be administered with or without food.
- At the proposed therapeutic dose (45 mg dextromethorphan hydrobromide-105 mg bupropion hydrochloride, once daily for the initial 3 days followed by twice daily), AXS-05 does not prolong the QT interval to any clinically relevant extent.
- A cross-study PK comparison was performed to establish a scientific bridge between AXS-05 and the LD, Wellbutrin SR. The dose-normalized exposures to bupropion and its major metabolites, hydroxybupropion, threohydroxybupropion and erythrohydroxybupropion at steady state ($C_{max,ss}$ and AUC_{ss}) are comparable between AXS-05 (45 mg dextromethorphan hydrobromide-105 mg bupropion hydrochloride) and 45 mg dextromethorphan and 100 mg Wellbutrin SR in combination. This suggests that AXS-05 can rely on selected clinical pharmacology data for bupropion from Wellbutrin SR.
- Patients with moderate renal impairment showed an increase in steady state systemic exposures (C_{max} and AUC_{0-12h}) to dextromethorphan by approximately 2-fold, bupropion by 1.7-fold, hydroxybupropion by 1.3-fold, threohydroxybupropion by 2.5-fold, and erythrohydroxybupropion by 1.8-fold compared to subjects with normal renal function. Therefore, once daily dosing of AXS-05 is recommended in patients with moderate renal impairment.

- Patients with moderate hepatic impairment showed no appreciable change in systemic exposures to dextromethorphan, hydroxybupropion, and erythrohydroxybupropion, and a 1.7-fold increase in exposure to bupropion and 1.4-fold increase in exposure to threohydroxybupropion compared to subjects with normal hepatic function. Therefore, no dose adjustment of AXS-05 is necessary for patients with moderate hepatic impairment.
- Patients who are CYP2D6 poor metabolizers showed an approximately 3-fold increase in systemic exposure (C_{max} and AUC_{0-12h}) to dextromethorphan and no change in exposure to bupropion and its metabolites compared to CYP2D6 extensive metabolizers. Therefore, once-daily dosing of AXS-05 is recommended in patients who are CYP2D6 poor metabolizers.
- Patients with concomitant use of a strong CYP2D6 inhibitor, paroxetine, showed an approximately 2.5-fold increase in systemic exposure (C_{max} and AUC_{0-12h}) to dextromethorphan and no appreciable change in exposures to bupropion and its active metabolites compared to AXS-05 treatment alone. Therefore, once-daily dosing is recommended when AXS-05 is coadministered with strong CYP2D6 inhibitors.
- Concomitant use of a weak CYP2B6 inhibitor, clopidogrel, did not appreciably change the exposures to dextromethorphan, bupropion, and its metabolites. No dose adjustment of AXS-05 is warranted when AXS-05 is coadministered with weak CYP2B6 inhibitors.
- Coadministration of AXS-05 with a strong CYP2B6 inducer (carbamazepine) showed a decrease in systemic exposures (C_{max} and AUC_{0-12h}) to dextromethorphan by 2.4-fold, bupropion by 4-fold, hydroxybupropion by 1.5-fold, threohydroxybupropion by 3.2-fold and erythrohydroxybupropion by 2.6-fold. The decreases in exposures to dextromethorphan, bupropion and its metabolites are expected to decrease the efficacy of AXS-05 for the treatment of major depressive disorders. Therefore, avoiding coadministration of AXS-05 with strong CYP2B6 inducers is recommended, and alternate treatments should be considered if needed.

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

Dextromethorphan is an uncompetitive antagonist of the N-methyl-D-aspartate receptor, an ionotropic glutamate receptor, and a sigma-1 receptor agonist. Dextromethorphan is extensively metabolized by CYP2D6. Bupropion is a relatively weak inhibitor of the neuronal reuptake of norepinephrine and dopamine and does not inhibit monoamine oxidase or the reuptake of serotonin. Bupropion increases plasma levels of dextromethorphan by inhibiting CYP2D6. The exact mechanism of the antidepressant effect of dextromethorphan and bupropion is not known.

Pharmacokinetics

Dextromethorphan when coadministered with bupropion showed greater than dose-proportional changes in AUC and C_{max} for varying doses of dextromethorphan (30 to 60 mg) and

less than dose-proportional changes for varying doses of bupropion (75 to 150 mg). Following oral administration of AXS-05 (once daily for the initial 3 days followed by twice daily administration), steady state plasma concentrations of dextromethorphan and bupropion are achieved in approximately 8 days. The accumulation ratios for dextromethorphan at steady state are 20 and 32, respectively, based on C_{max} and AUC_{0-12}. The accumulation ratios for bupropion at steady state are 1.1 and 1.5, respectively, based on C_{max} and AUC_{0-12}.

Absorption

The median T_{max} of dextromethorphan and bupropion is approximately 3 hours and 2 hours, respectively. The C_{max} of the hydroxybupropion metabolite occurred approximately 3 hours postdose and was approximately 14-fold the peak level of bupropion; its AUC_{0-12} was about 19-fold that of bupropion. The C_{max} of the erythrohydroxybupropion and threohydroxybupropion metabolites occurred approximately 4 hours postdose and were approximately equal to and 5-fold that of bupropion, respectively. The AUC_{0-12} values were 1.2- and 7-fold that of bupropion, respectively.

AXS-05 can be administered without regard to food.

Distribution

The plasma protein binding of dextromethorphan is approximately 60 to 70% and that of bupropion is 84%.

Metabolism

Dextromethorphan is primarily metabolized by CYP2D6 to dextrorphan. Dextrorphan is glucuronidated to form dextrorphan-O-glucuronide. Bupropion is extensively metabolized to three active metabolites: hydroxybupropion, which is formed via hydroxylation of the tert-butyl group of bupropion, and the amino-alcohol isomers, threohydroxybupropion and erythrohydroxybupropion, which are formed via reduction of the carbonyl group. In vitro findings suggest that CYP2B6 is the principal isoenzyme involved in the formation of hydroxybupropion, and cytochrome P450 enzymes are not involved in the formation of threohydroxybupropion. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite.

Excretion

In CYP2D6 extensive metabolizers, approximately 37 to 52% of the orally administered dose of dextromethorphan is recovered in the urine. Less than 2% of the administered dose is excreted as unchanged parent drug in the urine. In CYP2D6 poor metabolizers, approximately 45% to 83% of the administered dose is recovered in the urine. Approximately 26% of the administered dose is excreted as unchanged parent drug in the urine.

Following oral administration of 200 mg of ^{14}C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. Only 0.5% of the oral dose was excreted as unchanged bupropion.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended oral dose of AXS-05 (45 mg dextromethorphan hydrobromide-105 mg bupropion hydrochloride) is once daily for the initial 3 days followed by twice daily given at least 8 hours apart.

Therapeutic Individualization

Patients with Moderate Renal Impairment

Following oral administration of AXS-05 over 8 days, subjects with moderate renal impairment showed an increase in systemic exposures (C_{max} and AUC_{0-12h}) to dextromethorphan by approximately 2-fold, bupropion by 1.7-fold, hydroxybupropion by 1.3-fold, threohydroxybupropion by 2.5-fold and erythrohydroxybupropion by 1.8-fold, compared to subjects with normal renal function. Therefore, once daily oral administration is recommended in patients with moderate renal impairment.

Patients on Concomitant Strong CYP2D6 Inhibitors

Concomitant use of AXS-05 with the strong CYP2D6 inhibitor paroxetine showed an approximately 2.5-fold increase in systemic exposures (C_{max}: 2.4-fold and AUC_{0-12h}: 2.7-fold) to dextromethorphan and no appreciable change in exposures to bupropion and its active metabolites compared to AXS-05 treatment alone. Therefore, once daily oral administration of AXS-05 is recommended in patients when AXS-05 is coadministered with strong CYP2D6 inhibitors.

Patients on Concomitant Strong CYP2B6 Inducers

Concomitant use of AXS-05 with the strong CYP2B6 inducers carbamazepine showed a decrease in systemic exposures (C_{max} and AUC_{0-12h}) to dextromethorphan by approximately 2-fold, bupropion by 4-fold, hydroxybupropion by 1.5-fold, threohydroxybupropion by 3.2-fold, and erythrohydroxybupropion by 2.6-fold compared to AXS-05 treatment alone. Avoiding the use of AXS-05 with strong CYP2B6 inducers is recommended.

Patients Who are CYP2D6 Poor Metabolizers

AXS-05 showed an approximately 3-fold increase in systemic exposures (C_{max} 3-fold and AUC_{0-12h} 3.4-fold) to dextromethorphan and no appreciable change in exposures to bupropion and its metabolites in a small number of CYP2D6 poor metabolizers (N=3) compared to CYP2D6 extensive metabolizers (N=11). In an open-label study, the mean steady state plasma concentrations of dextromethorphan were generally higher (~2.6-fold) in 12 poor metabolizers treated with AXS-05 compared to extensive metabolizers (N=389). Therefore, once daily oral administration of AXS-05 is recommended in patients who are CYP2D6 poor metabolizers.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. Clinical Pharmacology Questions

Is the Proposed Dosing Regimen Appropriate for the General Patient Population for which the Indication is Being Sought?

Yes. The proposed dosing regimen of AXS-05 (45 mg dextromethorphan hydrobromide-105 mg bupropion hydrochloride, once daily for the initial 3 days followed by twice daily) is acceptable for the treatment of major depressive disorder in adults.

This dosing regimen of AXS-05 (to-be marketed formulation) was evaluated in two phase 2/3 trials (AXS-05-MDD-201 and AXS-05-MDD-301) and an open-label, long-term safety study (AXS-05-303). Refer to Section 8 for additional information on the efficacy and safety of AXS-05 for the treatment of MDD.

Is the Pharmacokinetic Bridge for Bupropion Between AXS-05 and the Listed Drug, Wellbutrin SR Acceptable?

The proposed drug product, AXS-05, relies on select clinical pharmacology data (i.e., human mass balance and in vitro drug interactions) for bupropion from the LD, bupropion hydrochloride sustained-release tablets (Wellbutrin SR). The Applicant performed a cross-study PK comparison to establish a scientific bridge between AXS-05 and the LD, Wellbutrin SR.

Given that the Applicant evaluated the safety and efficacy of AXS-05 for the treatment of MDD in pivotal clinical studies (i.e., AXS-05-MDD-201 and AXS-05-MDD-301), the maximum recommended dose of bupropion from AXS-05 is 105 mg BID, which is lower than that recommended for Wellbutrin SR (200 mg BID), and coadministration of dextromethorphan did not affect the PK of bupropion (Study AXS-05-101), a cross-study PK comparison for bupropion between AXS-05 (Study AXS-05-103) and Wellbutrin SR (Study AXS-05-102) is acceptable.

The cross-study PK comparison results indicate that the exposures to bupropion and its major metabolites—hydroxybupropion, threohydroxybupropion, and erythrohydroxybupropion—at steady state ($C_{max,ss}$ and AUC_{ss}) following administration of AXS-05 (45 mg dextromethorphan hydrobromide-105 mg bupropion hydrochloride; Study AXS-05-103) are comparable to the dose-normalized exposures to bupropion and its metabolites following administration of 45 mg dextromethorphan and 100 mg Wellbutrin SR in combination (Study AXS-05-102, Table 5). Therefore, the proposed drug product, AXS-05 can rely on the selected clinical pharmacology data from the LD, Wellbutrin SR.

Table 5. Cross-Study PK Comparison of Bupropion, Hydroxybupropion, Threohydroxybupropion, and Erythrohydroxybupropion Between AXS-05 and the Listed Drug, Wellbutrin SR

	Study AXS-05-103	Study AXS-05-102	
	AXS-05: 105 mg BUP + 45 mg DEX	100 mg BUP (Wellbutrin SR) + 45 mg DEX	105 mg BUP (Wellbutrin SR) + 45 mg DEX, Dose Normalized
PK Parameter	**N=15**	**N=8**	**N=8**
Bupropion			

	Study AXS-05-103	Study AXS-05-102	
	AXS-05: 105 mg BUP + 45 mg DEX	100 mg BUP (Wellbutrin SR) + 45 mg DEX	105 mg BUP (Wellbutrin SR) + 45 mg DEX, Dose Normalized
PK Parameter	**N=15**	**N=8**	**N=8**
$AUC_{0\text{-}12,\ ss}$ (ng/mL*h)	600 (212)	630 (199)	662 (199)
$C_{max,\ ss}$ (ng/mL)	76 (28)	79 (28)	83 (28)
Hydroxybupropion			
$AUC_{0\text{-}12,\ ss}$ (ng/mL*h)	11585 (3398)	12352 (2108)	12970 (2108)
$C_{max,\ ss}$ (ng/mL)	1097 (313)	1173 (159)	1232 (159)
Threohydroxybupropion			
$AUC_{0\text{-}12,\ ss}$ (ng/mL*h)	4532 (1679)	3643 (1172)	3825 (1172)
$C_{max,\ ss}$ (ng/mL)	416 (148)	342 (101)	359 (101)
Erythrohydroxybupropion			
$AUC_{0\text{-}12,\ ss}$ (ng/mL*h)	1003 (267)	850 (222)	893 (222)
$C_{max,\ ss}$ (ng/mL)	91 (24)	79 (18)	83 (18)

Source: Reviewer's analysis.
Values are means (standard deviation)
Abbreviations: $AUC_{0\text{-}12,ss}$, steady state area under the curve from 0 to 12 hours; BUP, bupropion; $C_{max,ss}$, maximum concentration at steady state; DEX, dextromethorphan; PK, pharmacokinetic

Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

Yes. Following oral administration of AXS-05 over 8 days (Days 1 to 3, once daily; Days 4 to 7, BID; Day 8, once daily), subjects with moderate renal impairment (based on the Modification of Diet in Renal Disease (MDRD) equation, estimated glomerular filtration rate: 30 to <60 mL/min/1.73 m^2) showed increase in steady state systemic exposures (C_{max} and $AUC_{0\text{-}12h}$) to dextromethorphan by approximately 2-fold, bupropion by 1.7-fold, hydroxybupropion by 1.3-fold, threohydroxybupropion by 2.5-fold, and erythrohydroxybupropion by 1.8-fold, compared to subjects with normal renal function. Therefore, once daily oral administration is recommended in patients with moderate renal impairment.

No appreciable change in systemic exposures to dextromethorphan, hydroxybupropion, and erythrohydroxybupropion; a 1.7-fold increase in exposure to bupropion; and a 1.4-fold increase in exposure to threohydroxybupropion were observed in patients with moderate hepatic impairment compared to subjects with normal hepatic function. Therefore, no dose adjustment is recommended in patients with moderate hepatic impairment.

The fact that the exposures to dextromethorphan were increased by approximately 2-fold in subjects with moderate renal impairment but not in subjects with moderate hepatic impairment may be due to the CYP2D6 inhibitory effects of bupropion active metabolites. The exposures to bupropion metabolites (i.e., threohydroxybupropion and erythrohydroxybupropion) are higher in subjects with moderate renal impairment compared to those with moderate hepatic impairment.

An approximately 3-fold increase in exposure ($C_{max,ss}$: 3-fold and $AUC_{0\text{-}12h,ss}$: 3.4-fold) to dextromethorphan and no change in exposures to bupropion and its metabolites were observed in three subjects who were CYP2D6 poor metabolizers compared to extensive metabolizers. Furthermore, in an open-label study, the steady state exposures to

dextromethorphan were increased by approximately 2.6-fold in 12 subjects who were CYP2D6 poor metabolizers compared to extensive metabolizers. Therefore, once daily oral administration is recommended in patients who are CYP2D6 poor metabolizers.

Refer to Section 15.3, Clinical Pharmacology for additional information.

Are there Clinically Relevant Food-Drug or Drug-Drug Interactions, and What is the Appropriate Management Strategy?

In a food effect study (AXS-05-107), a high-fat diet did not appreciably alter the systemic exposures to dextromethorphan (C_{max}: no change; AUC_{0-12h}: 14% lower) and bupropion (C_{max}: 3% higher; AUC_{0-12h}: 6% higher) following single-dose oral administration, compared to fasted conditions. Though the high-fat, high-calorie diet delayed the time to reach C_{max} (T_{max}) of AXS-05 from 3 hours to 4 hours, the impact on efficacy and safety is expected to be minimal, considering the onset of drug effect is slow and the indication is for a chronic disease. Therefore, AXS-05 can be administered with or without food.

Given that dextromethorphan is predominantly metabolized by CYP2D6, concomitant use of AXS-05 with the strong CYP2D6 inhibitor paroxetine showed an approximately 2.5-fold increase in systemic exposure (C_{max}: 2.4-fold and AUC_{0-12h}: 2.7-fold) to dextromethorphan compared to AXS-05 treatment alone (AXS-05-108). Because bupropion is mainly metabolized by CYP2B6, administration of AXS-05 with a strong CYP2D6 inhibitor showed no appreciable difference (<15% decrease) in systemic exposure to bupropion compared to AXS-05 treatment alone. The exposures to active metabolites were increased to a minor extent (hydroxybupropion: C_{max}: 21% and AUC_{0-12h}: 26%; threohydroxybupropion: C_{max}: 20% and AUC_{0-12h}: 23%; erythrohydroxybupropion: C_{max}: 40% and AUC_{0-12h}: 43%). Therefore, once daily oral administration of AXS-05 is recommended in patients coadministered AXS-05 with strong CYP2D6 inhibitors.

The weak CYP2B6 inhibitor clopidogrel showed minimal increases in exposures to bupropion (C_{max}: 27% and AUC_{0-12h}: 30%), erythrohydroxybupropion (C_{max}: 21% and AUC_{0-12h}: 24%), threohydroxybupropion (C_{max}: 22% and AUC_{0-12h}: 25%) and a decrease in exposures to hydroxybupropion: C_{max}: 42% and AUC_{0-12h}: 41%) compared to AXS-05 treatment alone (AXS-05-110). Following administration of AXS-05 with clopidogrel, minimal increase in exposure (C_{max}: 27% and AUC_{0-12h}: 29%) to dextromethorphan was observed compared to AXS-05 treatment alone. Therefore, no dose adjustment of AXS-05 is recommended when coadministered with weak CYP2B6 inhibitors.

Concomitant use of AXS-05 with the strong CYP2B6 inducer carbamazepine decreased systemic exposures to bupropion (C_{max}: 3.9-fold and AUC_{0-12h}: 4.2-fold) and its metabolites (hydroxybupropion: C_{max}: 1.5-fold and AUC_{0-12h}: 1.5-fold; threohydroxybupropion: C_{max}: 3.1-fold and AUC_{0-12h}: 3.2-fold; erythrohydroxybupropion: C_{max}: 2.6-fold and AUC_{0-12h}: 2.6-fold). Following administration of AXS-05 with carbamazepine, the exposure to dextromethorphan was reduced by approximately 2.5-fold (C_{max}: 2.4-fold and AUC_{0-12h}: 2.8-fold) compared to AXS-05 treatment alone (AXS-05-110). Given the efficacy and safety of AXS-05 were evaluated at only one dose level (i.e., 45 mg dextromethorphan-105 mg bupropion) in the pivotal studies,

and strong CYP2B6 inducers are expected to reduce the systemic exposures to dextromethorphan by more than half compared to AXS-05 treatment alone, the efficacy of AXS-05 for the treatment of MDD is expected to be significantly impacted when AXS-05 is coadministered with strong CYP2B6 inducers. Therefore, avoiding use of AXS-05 with strong CYP2B6 inducers is recommended.

Refer to Section 15.3, Clinical Pharmacology for additional information.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

For this application, data submitted to support efficacy consists of results from two 6-week controlled trials that enrolled subjects with MDD. Data submitted to support safety includes data from these two trials, from a third 6-week controlled trial that enrolled subjects with treatment-resistant depression (TRD) that did not meet its efficacy objective, and from a 1-year open-label trial of subjects with either MDD or TRD. A summary of the designs for the trials submitted is presented in Table 6.

Table 6. Summary of Designs for Trials Submitted

Trial Identity	NCT Number	Trial Design	Regimen and Schedule (All Dosing is by Mouth)	Study Endpoints	Treatment Duration and Follow-up (All Outpatients)	Number of Patients Enrolled	Study Population	Number of Centers and Countries
AXS-05-MDD-201	03595579	Randomized, double-blind, active-controlled	AXS-05 1 tablet daily for 3 days, then 1 tablet twice daily; bupropion SR 105 mg daily for 3 days, then 105 mg twice daily	Original Primary: mean change from baseline on MADRS total score, averaged across each time point in the study (Weeks 1 to 6) Draft Labeled Primary: mean change from baseline to Week 6 on MADRS total score	6-week treatment period; 1-week follow-up period	97	Adults with MDD	4 sites, all in the United States
AXS-05-MDD-301	04019704	Randomized, double-blind, placebo-controlled	AXS-05 1 tablet daily for 3 days, then 1 tablet twice daily; placebo daily for 3 days, then placebo twice daily	Primary: mean change from baseline to Week 6 on MADRS total score	6-week treatment period; 1-week follow-up period	327	Adults with MDD	43 sites, all in the United States

Trial Identity	NCT Number	Trial Design	Regimen and Schedule (All Dosing is by Mouth)	Study Endpoints	Treatment Duration and Follow-up (All Outpatients)	Number of Patients Enrolled	Study Population	Number of Centers and Countries
AXS-05-301	02741791	Randomized, double-blind, active-controlled	AXS-05 1 tablet daily for 3 days, then 1 tablet twice daily; bupropion SR 150 mg daily for 3 days, then 150 mg twice daily	Primary: mean change from baseline to Week 6 on MADRS total score	Open-label treatment: 6 weeks; Double-blind treatment: 6 weeks;	Open-label treatment: 799 Double-blind treatment: 312	Adults with TRD	93 sites, all in the United States
AXS-05-303	04039022	Open-label, uncontrolled study	AXS-05 1 tablet twice daily	Vital signs, clinical lab studies, adverse event reports	Up to 1 year of treatment	876	Adults with MDD or TRD	51 sites, all in the United States

Source: Generated by the Clinical Reviewer.
Abbreviations: NCT, national clinical trials; MADRS, Montgomery-Åsberg depression rating scale; MDD, major depressive disorder; TRD, treatment-resistant depression

7.2. Review Strategy

The assessment of efficacy included review of the clinical study reports (CSRs) and submitted datasets from the two 6-week controlled trials submitted by the Applicant as positive studies (AXS-05-MDD-201, AXS-05-MDD-301). The assessment of efficacy was a joint review between the clinical and biostatistics teams.

The assessment of safety included review of the CSRs and submitted datasets from all three 6-week controlled trials as well as from the long-term open-label safety trial.

As specified in the text, the presentation of efficacy and safety results includes analyses submitted by the Applicant as well as those performed by the review team.

7.3. Descriptions of Efficacy and Safety Assessments

The following is a description of the important efficacy and safety assessments used in the trials submitted to support the efficacy and safety of AXS-05. Not all assessment tools described were used in all the submitted studies.

Montgomery-Åsberg Depression Rating Scale

The Montgomery-Åsberg Depression Rating Scale (MADRS) is a 10-item scale used to measure symptoms of depression. The rating is based on a clinical interview in which the examiner asks the subject questions about the presence, frequency, and severity of symptoms of depression. The examiner also observes the subject's appearance and behavior. The examiner selects the score that best represents the subject's answers and the subject's overall presentation. Each item is scored from 0 to 6, where 0 indicates absence of a symptom and 6 indicates an extremely severe symptom. The range of the total MADRS score is from 0 to 60. The general interpretation of the total MADRS score is that a score from 0 to 6 indicates absence of depression; from 7 to 19 indicates mild depression; from 20 to 34 indicates moderate depression; and a score greater than 34 indicates severe depression. The mean change in total MADRS score from baseline to the end of treatment has been used frequently as a primary efficacy endpoint in clinical trials of drugs for the treatment of depression.

In Study AXS-05-MDD-201 and Study AXS-05-MDD-301, the MADRS was used to assess efficacy and also used during screening to confirm that a subject's most recent major depressive episode (MDE) was of at least moderate severity.

Quick Inventory of Depressive Symptomatology – Self-Rated

The Quick Inventory of Depressive Symptomatology – Self-Rated (QIDS-SR-16) is a 16-item self-report scale used to evaluate depressive symptoms during the 7 days prior to the examination. The questions cover nine symptom domains: sad mood, concentration, self-criticism, suicidal ideation, interest, energy/fatigue, sleep disturbance, appetite/weight change, and psychomotor agitation/retardation. Each item is scored on a scale from 0 to 3 points. Four items are used to assess the sleep domain (initial insomnia, middle insomnia, late insomnia, and hypersomnia).

Two items are used to gauge psychomotor activity (agitation and retardation). Four items assess the appetite/weight domain (appetite increase and decrease, weight increase and decrease). For each of these three domains, the highest rating on any one item is used to score the domain. Only one item is used to score the remaining six domains (sad mood, concentration, energy, interest, guilt, suicidal ideation). The total QIDS-SR-16 score is the sum of the scores for the nine symptom domains and ranges from 0 to 27.

In Study AXS-05-MDD-201 and Study AXS-05-MDD-301, a blinded independent assessor used the QIDS-SR-16 score as one of the criteria to confirm the diagnosis of MDD after the initial screening by study site personnel.

Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale (HAMD-17) is a clinician-rated scale for the assessment of depression severity in patients already diagnosed with a depressive disorder. The 17 items in the HAMD-17 have different scoring ranges, with items scored from 0 to 2, 0 to 3, or 0 to 4. In all cases, 0 indicates an absence of symptoms and the highest score indicates severe symptoms. The highest possible total score is 53. A score of 0 to 7 is generally considered to represent absence of depression or clinical remission. A score of 20 or higher is generally considered to represent depression of at least moderate severity.

In Study AXS-05-301, a blinded independent assessor used the HAMD-17 score as one of the criteria to confirm inadequate response to bupropion treatment after the initial assessment of treatment resistance by study site personnel.

Clinical Global Impression – Severity

The Clinical Global Impression – Severity (CGI-S) scale is a 7-point scale for rating symptom severity in patients with psychiatric disorders. The clinician rates the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Possible ratings are:

1. Normal; not at all ill
2. Borderline mentally ill
3. Mildly ill
4. Moderately ill
5. Markedly ill
6. Severely ill
7. Among the most extremely ill patients

In Study AXS-05-MDD-201 and Study AXS-05-MDD-301, the CGI-S score served as a secondary efficacy endpoint and was also used during screening to confirm that a subject's most recent MDE was of at least moderate severity.

Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire used to assess suicidal ideation and behavior. Suicidal ideation is assessed based on the subject's answers to five questions eliciting the subject's thought content on themes related to suicide:

1. The wish to be dead;
2. Nonspecific active suicidal thoughts;
3. Active suicidal ideation without intent to act;
4. Active suicidal ideation with some intent to act, without specific plan;
5. Active suicidal ideation with specific intent and plan.

The subject's score on the C-SSRS corresponds to the highest-numbered question to which the subject gives an answer of "Yes." Thus, score on the C-SSRS ranges from 0 (no "Yes" answers to any of the questions) to 5 ("Yes" answers to all questions). A score of 4 or 5 indicates a clinical assessment of high risk for suicide.

The C-SSRS also includes questions assessing for suicidal behavior, including:

1. Engagement in nonsuicidal self-injurious behavior;
2. Interrupted suicide attempt;
3. Aborted suicide attempt;
4. Preparatory acts or behavior towards suicide attempt;
5. Suicidal behavior, with actual and potential lethality assessed for suicide attempts;
6. Actual suicide attempt.

Several versions of the C-SSRS have been developed including the "Baseline" and "Screening" versions and a combined "Baseline/Screening" version that assesses suicidal ideation and behavior in a patient's lifetime and during a predefined time period. This version can assess a patient's lifetime suicidal ideation and behavior as well as eligibility based on inclusion/exclusion criteria. A separate "Since Last Visit" version of the scale has been developed, which is used to assess suicidal ideation and behavior since the patient's last visit. This version is meant to assess patients who have completed at least one initial C-SSRS assessment and can be used at each subsequent visit. The "Since Last Visit" of the C-SSRS addresses any suicidal thoughts or behaviors the patient may have had since the last time the C-SSRS was administered in the study.

In the three controlled trials, patients with a C-SSRS score ≥4 were excluded from the study. The C-SSRS was also one of the safety assessments performed in all of the clinical trials submitted.

8. Statistical and Clinical Efficacy and Safety Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

In this NDA the Applicant submitted results from Studies AXS-05-MDD-201 (Study MDD-201) and AXS-05-MDD-301 (Study MDD-301) to support the efficacy claim of AXS-05 for the

treatment of MDD in adults. Because AXS-05 is a fixed-dose combination drug, the Applicant needed to demonstrate that each component of the drug (i.e., dextromethorphan, bupropion) contributes to the claimed drug effect. Study MDD-301 was an adequate and well-controlled phase 3 trial that demonstrated the efficacy of AXS-05 compared to placebo. Study MDD-201 was initially conceived as an exploratory phase 2 study of the safety and tolerability of AXS-05 for subjects with MDD. This study provided supportive evidence of the efficacy of AXS-05 by demonstrating that the dextromethorphan component of the combination contributes to the antidepressant effect of the drug. Additional supportive evidence of efficacy was provided by previous studies conducted under NDA 020358 demonstrating superiority of the approved drug bupropion SR over placebo for the treatment of MDD.

8.1.1. Relevant Studies

Studies MDD-201 and MDD-301, the two trials submitted to support the efficacy of AXS-05 for the treatment of MDD, are described in this section. Study AXS-05-301 (Study 301), the trial that evaluated the use of AXS-05 for the treatment of TRD, did not meet its primary efficacy endpoint. However, data from that trial contribute to the evaluation of the safety of AXS-05. Data from Study AXS-05-303 (Study 303), the long-term, open-label safety trial, also contribute to the evaluation of the safety of AXS-05. The protocols for Study 301 and Study 303 are summarized in Section 8.2.2, *Review of the Safety Database*. Safety data from these two studies are presented in Section 8.2.4, *Safety Results*; Section 8.2.6, *Clinical Outcome Assessment Analyses Informing Safety/Tolerability*; and Section 8.2.7, *Safety Analyses by Demographic Subgroups*. Data from NDA 020358 demonstrating the efficacy of the approved drug bupropion SR over placebo will not be presented in this review.

8.1.1.1. Study AXS-05-MDD-201 (Study MDD-201; ClinicalTrials.Gov Identifier NCT03595579)

Overview and Objectives

Study Title

A Randomized, Double-Blind, Active-Controlled Trial of AXS-05 in Subjects with Major Depressive Disorder

Primary Objective

To assess the effect of AXS-05 versus bupropion as measured by the MADRS.

Secondary Objectives

To assess the effect of AXS-05 versus bupropion on:

- Quick Inventory of Depressive Symptomatology-Self-Rated (QIDS-SR-16);
- Clinical Global Impression-Improvement of Illness (CGI-I);
- Clinical Global Impression-Severity of Illness (CGI-S);
- Visual Analog Mood Scale (VAMS);
- Columbia-Suicide Severity Rating Scale (C-SSRS).

Safety Objectives

To assess safety of AXS-05 versus bupropion as measured by adverse events, vital signs, and laboratory assessments.

Trial Design

Study Design Overview

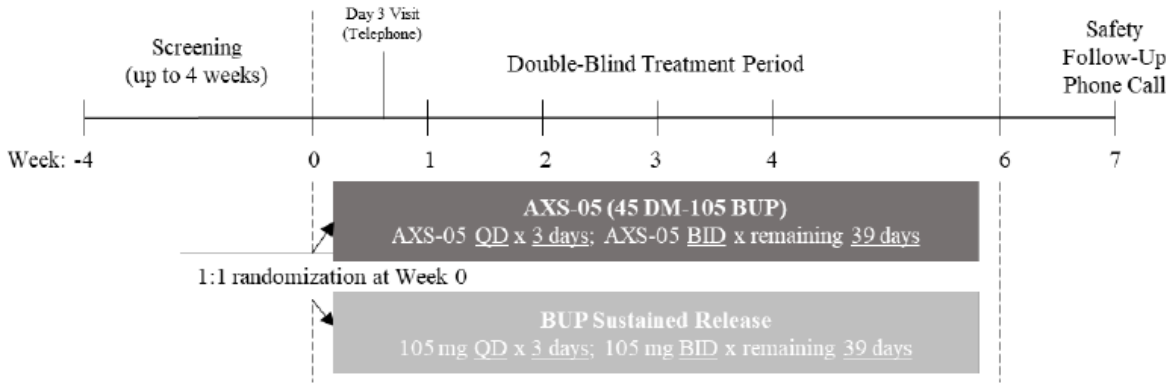
The study was a phase 2 trial conducted in subjects who were experiencing a current MDE. Subjects received either AXS-05 or bupropion 105 mg alone (active comparator), both dosed twice daily.

The study was divided into three periods:

- Screening: up to 4 weeks;
- Treatment: 6 weeks;
- Safety follow-up: 1 week.

See Figure 1.

Figure 1. Study MDD-201: Design Schematic



Source: AXS-05-MDD-201 Clinical Study Report, Figure 1, page 17.
Abbreviations: BID, twice daily, BUP, bupropion, DM, dextromethorphan; QD, once daily

Trial Locations

The trial was conducted at four sites, all in the United States.

Diagnostic Criteria

Eligible subjects were required to meet the DSM-5 criteria for MDD without psychotic features, based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Clinical Trials Version (SCID-5-CT). The current MDE was required to be of at least 4 weeks in duration and of moderate or greater severity based on a MADRS total score ≥25 and a CGI-S of ≥4.

Independent Assessment of Diagnosis

Diagnosis was confirmed by an independent assessor, based on a clinical review and a QIDS-SR-16 score of ≥13 at screening or baseline. Sites were blinded to the independent assessment and

the criteria for the assessment through use of a blinded protocol. Only subjects whose diagnosis was confirmed by the independent assessor were included in the prespecified efficacy analysis set (modified intent-to-treat [mITT] population). However, to maintain blinding of the site investigators, subjects failing the independent assessment were randomized, treated, and included in the safety population.

Blinding to Efficacy Objectives

The blinded protocol also blinded investigators to the efficacy objectives of the study. The blinded protocol stated that the objective of the trial was "To evaluate the safety and tolerability of AXS-05 and bupropion in subjects with MDD." The blinded protocol omitted all text discussing any efficacy analysis, including presentation of the primary and secondary efficacy endpoints, statistical methods, and powering assumptions. Discussion of any efficacy analysis was limited to the statistical analysis plan (SAP).

Key Inclusion Criteria

- Male or female outpatients, 18 to 65 years of age, inclusive.
- DSM-5 diagnosis of MDD without psychotic features.
- Current major depressive episode of at least 4 weeks in duration at screening.
- MADRS score ≥25 and CGI-S ≥4 at screening and baseline.
- Normal physical examination and clinical laboratory results at screening or abnormal results that were judged not clinically significant.
- Body mass index between 18 and 40 kg/m^2, inclusive.
- For females of childbearing potential, negative urine pregnancy test at screening and baseline, and use of an adequate method of birth control.
- For male subjects, use of an adequate method of birth control by the subject and by female sexual partners.

Key Exclusion Criteria

- History of psychotic symptoms, manic symptoms, neurocognitive disorder, or any anxiety disorder which has been the primary focus of treatment.
- History of treatment-resistant depression, defined as two or more failed treatments of adequate dose and duration in the current depressive episode.
- Other psychiatric disorder of sufficient severity to interfere with participation in the study.
- Substance use disorder (other than nicotine or caffeine), active within 1 year of screening.
- Psychiatric hospitalization within the current depressive episode.
- Psychiatric symptoms secondary to any other general medical condition.
- Clinically significant risk of suicide or harm to self or others.
- Initiation or termination of psychotherapy for depression within 3 months of screening, or a plan to initiate, terminate, or change such therapy during the study.
- History of seizure disorder; undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs; or any other condition that increases the risk of seizure such as stroke, significant head injury, tumor or infection of the central nervous system, arteriovenous malformation, neuroleptic malignant syndrome, serotonin syndrome, or

clinically significant metabolic disorders (e.g., hypoglycemia, hyponatremia, severe hepatic impairment, hypoxia).
- Female subjects of child-bearing potential who are pregnant, breastfeeding, planning to initiate pregnancy or breastfeeding, or not willing to practice a reliable method of contraception throughout the study.
- Positive serum ethanol test or urine drug screen for any prohibited medication or drugs of abuse at screening.
- Any current or recent medical, psychiatric, or social condition that was likely to interfere with the conduct of the study, to confound the interpretation of study results, or to endanger the subject's well-being.
- Hypertension defined as resting, sitting systolic blood pressure (BP) ≥150 mm Hg or diastolic BP ≥95 mm Hg. Subjects with high BP as defined above may have been accepted into the study if they subsequently had acceptable BP values on reassessment at least 30 minutes apart.
- Hypo-or hyper-thyroidism, unless stabilized on appropriate pharmacotherapy with no change in dosage for at least 1 month prior to screening.

Clinical Reviewer's Comment: *The inclusion and exclusion criteria were appropriate for screening of individuals being considered for entry into the study.*

Prohibited Recent Medications and Treatments

- Drugs that are strong inhibitors of CYP2D6 (e.g., fluoxetine, paroxetine, quinidine).
- Drugs that are inhibitors of CYP2B6 (e.g., clopidogrel, ticlopidine, prasugrel) or inducers of CYP2B6 (e.g., ritonavir, lopinavir, efavirenz).
- Current use, or use within 14 days before screening, of monoamine oxidase inhibitors.
- Use of dextromethorphan coadministered with quinidine (e.g., Nuedexta) within the past 4 weeks.
- Use of opioids within 14 days of screening.
- History of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation, or any experimental central nervous system treatment during the current depressive episode or in the 6 months prior to screening, whichever was longer.

Washout of Recent Medications

- Any of the prohibited medications listed in the protocol must have been discontinued within 1 week or five half-lives of the medication, whichever was longer, prior to the baseline visit.
- Lithium must have been tapered and followed by a 1-week washout.
- The safe withdrawal from benzodiazepine treatment was to be determined by the subject's treating clinician and monitored by the principal investigator.

Prohibited Concurrent Medications

- The protocol includes a list of prohibited medications, including antipsychotics, anticonvulsant mood stabilizers, anxiolytics, benzodiazepines, antidepressants, and antidepressant augmentation agents.

Allowable Concurrent Medications and Treatments

- Eszopiclone, zolpidem, zolpidem extended-release, zopiclone, or zaleplon for insomnia could be continued, provided the medication had been used in a consistent manner for 4 weeks prior to enrollment and at doses that did not exceed the maximum labeled amounts.
- Support meetings or counseling (e.g., marital counseling) were allowed provided they were no more frequent than weekly and did not have treatment of depression as their objective.

Assignment to Treatment

Subjects were randomized at the baseline visit (Visit 2) to receive either AXS-05 or bupropion SR in a 1:1 ratio for 6 weeks.

Study Treatments

- Treatment A: AXS-05 (105 mg bupropion HCl/45 mg dextromethorphan HBr) tablet, oral
- Treatment B: bupropion SR (105 mg) matching tablet, oral

Treatment Schedules

- Treatment A:
  - Days 1 to 3: AXS-05, one tablet daily
  - Days 4 to 42: AXS-05, one tablet twice daily
- Treatment B:
  - Days 1 to 3: bupropion SR 105 mg, one tablet daily
  - Days 4 to 42: bupropion SR 105 mg, one tablet twice daily

Procedures and Schedule

Subjects were provided a diary containing the VAMS and asked to complete it daily from baseline to the end of treatment. Study visits occurred at screening (Visit 1), baseline (Day 0, Visit 2), and on Days 3, 7, 14, 21, 28, 42, and 49 (Visits 3 to 9). Visit 3 (Day 3) was conducted by telephone. Subjects were reminded during Visit 3 to begin twice daily dosing on Day 4. There was no on-site or telephone visit scheduled for Day 35 (Week 5). All subjects who completed 6 weeks of treatment or subjects who discontinued from the study prematurely were required to complete a follow-up visit 1 week after the last dose of study drug. See Table 7 for the schedule of study events.

Table 7. Study MDD-201: Schedule of Events

Visit	Screening Visit 1	Baseline Visit 2	Phone Call Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 / ET	Visit 9 Follow-up[a]
Study Day	-28 to -1	0	3 (+1)	7 (±2)	14 (±2)	21 (±2)	28 (±2)	42 (±2)	49 (±2)
Week	-4 to -1			Week 1	Week 2	Week 3	Week 4	Week 6	Week 7
Informed Consent	X[b]								
Inclusion/Exclusion Criteria	X	X							
Demographics	X								
Medical/Psychiatric History	X								
Medication History	X								
Physical Examination	X							X	
Vital Signs, Height/Weight[c]	X	X		X	X	X	X	X	
Laboratory Tests[d]	X							X	
Urine Drug Screen[e]	X	X						X	
Serum Ethanol[e]	X							X	
Urine Pregnancy Test (all female subjects)	X	X						X	
Plasma Sample for Compliance[f]				X	X	X	X	X	
SCID-5-CT	X								
VAMS Completion/ Review[g]	X	X	X	X	X	X	X	X	
MADRS	X	X		X	X	X	X	X	
QIDS-SR-16	X	X		X	X	X	X	X	
CGI-S (Severity)	X	X		X	X	X	X	X	
CGI-I (Improvement)				X	X	X	X	X	
C-SSRS	X	X		X	X	X	X	X	X
Randomization		X							
Instruct to begin BID dosing			X						
Study Drug Dispensation[h]		X		X	X	X	X		
Study Drug Accountability			X	X	X	X	X	X	
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X

BID = twice daily; CGI-I = Clinical Global Impressions–Improvement; CGI-S = Clinical Global Impressions–Severity; C-SSRS = Columbia - Suicide Severity Rating Scale; ET = early termination; MADRS = Montgomery-Åsberg Depression Rating Scale; QIDS-SR-16 = Quick Inventory of Depressive Symptomatology-Self- Rated; SCID-5-CT = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Clinical Trials Version; VAMS = Visual Analog Mood Scale

[a] Safety follow-up visit was to be performed telephonically.
[b] Informed consent was signed prior to any study procedures being performed.
[c] Vital signs, including blood pressure, heart rate, respiratory rate, and oral body temperature, were measured after the subject has been in a seated position for at least 5 minutes. Height was measured at Visit 1 and weight at Visit 1 and Visit 8.
[d] Clinical laboratory tests included hematology, serum chemistry, urinalysis and thyroid panel.
[e] May have been performed at other study visits per investigator judgment. Subjects with positive urine drug screen or serum ethanol levels at Visit 1 may have been allowed in study depending on circumstances described to the Medical Monitor and a negative repeat urine drug screen was obtained before Visit 2.
[f] Bupropion concentrations were collected and analyzed throughout the study.
[g] A subject reported daily VAMS was collected from Screening through Week 6. At each visit, study personnel reviewed the VAMS diary for accurate completion and compliance.
[h] Subjects began to take study drug the morning of Day 1 (morning after Visit 2).

Source: AXS-05-MDD-201 Clinical Study Report, Table 3, page 29.

Study Endpoints

When the protocol for this study was submitted, the primary endpoints were safety and tolerability. Later, the Applicant specified a primary efficacy endpoint in the SAP—mean change from baseline to Week 6 in MADRS total score, averaged across all onsite study visits. As discussed in Section 3.2, this endpoint was discussed with the Applicant at the End-of-Phase 2 meeting because it has not previously been used to support regulatory approval of an antidepressant. In the Applicant's draft product labeling, the primary efficacy endpoint reported was the change from baseline to Week 6 in MADRS total score (b) (4) (b) (4)

Statistical Analysis Plan

The statistical plan was prespecified in the SAP. The Applicant did not prespecify an adjustment for multiplicity due to small sample size limitations.

Multiplicity Adjustment

No adjustments were made for multiple secondary endpoints.

Analysis Method

The prespecified primary efficacy analysis model was MMRM where missing values were imputed using last observation carried forward (LOCF) and within-subject covariance matrix of variance-components (VC) was assumed. The primary endpoint was change from baseline in MADRS, and the model included treatment, visit (Weeks 1 to 4 and Week 6), and treatment-by-visit interaction, baseline as a covariate, and subject as a random effect. The analysis population was mITT.

Statistical Reviewer's Comment: For the sake of clarity, because the Applicant uses MMRM with longitudinally LOCF imputed data, we refer to the analysis as MMRM_LOCF from here on.

Sample Size and Power

Approximately 120 subjects (60 per arm) were randomized in the study, with sample size estimated based on prior similar studies. Subjects who had MDD with a current MDE of moderate or greater severity, identified using a MADRS score of ≥25, CGI-S score ≥4, and QIDS-SR-16 score of ≥13 at screening or baseline, were included in the study.

Protocol Amendments

Original protocol: Version 1.0

Original protocol date: April 9, 2018

Protocol Version 2.0: June 28, 2018

- Addressed logistical issues:
  - Removed ketamine from urine drug screen panel due to logistical issues.

- Removed requirement for sites to wait for Applicant confirmation of bupropion compliance prior to continuing subject in study.

Protocol Version 2.1: November 5, 2018

- Provided measures to address potential site rater biases:
  - Incorporated a blinded independent assessor to confirm subject diagnosis of MDD with a major depressive episode of moderate or greater severity, based on clinical review and a QIDS-SR-16 score of ≥13 at screening or baseline.
  - Specified that the mITT population would consist of subjects whose diagnosis was confirmed by the independent assessor, who were randomized, took at least one dose of study drug, and had at least one postbaseline assessment.
  - To maintain blinding of study investigators to the efficacy objective of the trial, the investigators were blinded to this amendment.

Note that in all submitted versions of the protocol, the primary objective was listed as "to evaluate the safety and tolerability of AXS-05 and bupropion in subjects with MDD."

8.1.1.2. Study AXS-05-MDD-301 (Study MDD-301; ClinicalTrials.gov Identifier NCT04019704)

Overview and Objectives

Study Title

A Randomized, Double-Blind, Placebo-Controlled Trial of AXS-05 in Subjects with Major Depressive Disorder

Primary Objective

To evaluate the efficacy of AXS-05 as measured by the change from baseline in the MADRS total score with the primary timepoint at Week 6.

Key Secondary Objectives

To evaluate the efficacy of AXS-05 as measured by:

- Change in MADRS total score from baseline to Week 1.
- Change in MADRS total score from baseline to Week 2.
- Percentage of subjects achieving remission (MADRS total score ≤10) at Week 2.
- Percentage of responders (≥50% reduction in MADRS total score) at Week 6.

Other Secondary Efficacy Objectives

To evaluate the efficacy of AXS-05 as measured by:

- MADRS over time
- Clinical Global Impression – Improvement of Illness (CGI-I) over time
- Clinical Global Impression – Severity of Illness (CGI-S) over time
- Patient Global Impression – Improvement (PGI-I)

- Quick Inventory of Depressive Symptomatology – Self-Rated (QIDS-SR-16)
- Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form
- Sheehan Disability Scale
- Visual Analog Mood Scale (VAMS)
- MADRS-6 (MADRS six-item subscale)
- Response on MADRS (≥50% and ≥30% reductions from baseline)
- Remission on MADRS (MADRS ≤10 and ≤12) over time
- Response on MADRS-6 (≥50% reduction from baseline)

Safety Objectives

Safety endpoints included incidence of AEs, incidence of treatment-emergent adverse events (TEAEs), dropouts due to AEs, electrocardiogram (ECG) findings, clinical laboratory test results, vital sign measurements, physical examination findings, C-SSRS, and Physician Withdrawal Checklist (PWC-20).

Trial Design

Study Design Overview

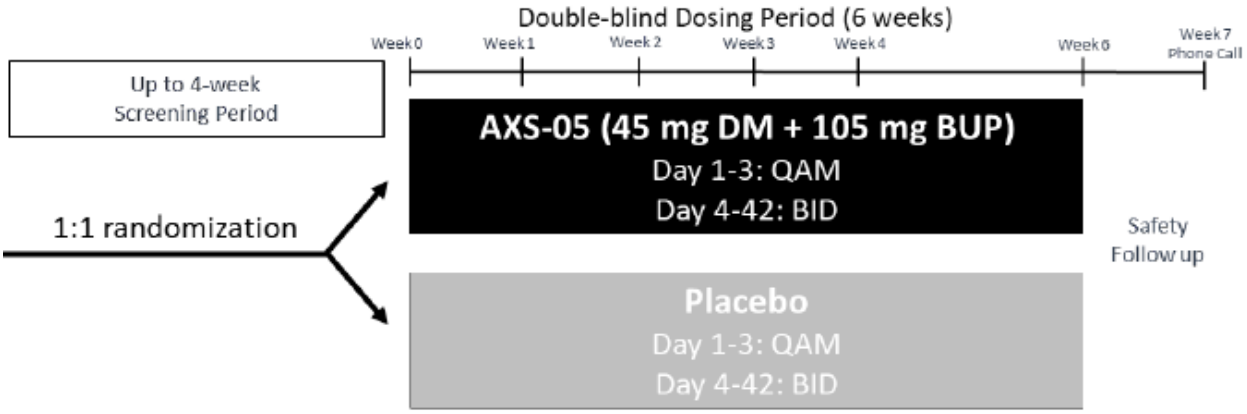
The study was a phase 3 trial conducted in subjects who were experiencing a current MDE. Subjects received either AXS-05 combination product or placebo, both dosed twice daily.

The study was divided into three periods:

- Screening: up to 4 weeks;
- Treatment: 6 weeks;
- Safety follow-up: 1 week.

See Figure 2.

Figure 2. Study MDD-301: Design Schematic



Source: AXS-05-MDD-301 Clinical Study Report, Figure 1, page 18.
Abbreviations: BID, twice daily, BUP, bupropion; DM, dextromethorphan; QAM, once daily in the morning

Trial Locations

The trial was conducted at 43 sites, all in the United States.

Diagnostic Criteria

Eligible subjects were required to meet the DSM-5 criteria for MDD without psychotic features, based on the SCID-5-CT. The current MDE was required to be of at least 4 weeks in duration and of moderate or greater severity based on a MADRS total score ≥25 and a CGI-S of ≥4.

Independent Assessment of Diagnosis

Diagnosis was confirmed by an independent assessor, based on a clinical review and a QIDS-SR-16 score of ≥13 at screening or baseline. Sites were blinded to the independent assessment and the criteria for the assessment through use of a blinded protocol. Only subjects whose diagnosis was confirmed by the independent assessor were included in the efficacy analysis set (mITT population), as prespecified. However, to maintain blinding of the site investigators, subjects failing the independent assessment were randomized, treated, and included in the safety population.

Blinding to Efficacy Objectives

The blinded protocol also blinded investigators to the efficacy objectives of the study. The blinded protocol stated that the objective of the trial was "To evaluate the safety of AXS-05 in subjects with MDD." The blinded protocol omitted all text discussing any efficacy analysis including presentation of the primary and secondary efficacy endpoints, statistical methods, and powering assumptions.

Key Inclusion Criteria

- Male or female outpatients, 18 to 65 years of age, inclusive.
- DSM-5 diagnosis of MDD without psychotic features.
- Current major depressive episode of at least 4 weeks in duration at screening.
- MADRS score ≥25 and CGI-S ≥4 at screening and baseline.
- Normal physical examination and clinical laboratory results at screening or abnormal results that were judged not clinically significant.
- Body mass index between 18 and 40 kg/m^2, inclusive.
- For females of childbearing potential, negative urine pregnancy test at screening and baseline, and use of two adequate methods of birth control.
- For male subjects, use of an adequate method of birth control by the subject and by female sexual partners.

Key Exclusion Criteria

- History of psychotic symptoms, manic symptoms, neurocognitive disorder, or any anxiety disorder which has been the primary focus of treatment.
- History of treatment-resistant depression, defined as two or more failed treatments of adequate dose and duration in the current depressive episode.
- Other psychiatric disorder of sufficient severity to interfere with participation in the study.
- Substance use disorder (other than nicotine or caffeine), active within 1 year of screening.
- Psychiatric hospitalization within the current depressive episode.
- Psychiatric symptoms secondary to any other general medical condition.

- Clinically significant risk of suicide or harm to self or others.
- Initiation or termination of psychotherapy for depression within 3 months of screening, or a plan to initiate, terminate, or change such therapy during the study.
- History of seizure disorder; undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs; or any other condition that increases the risk of seizure such as stroke, significant head injury, tumor or infection of the central nervous system, arteriovenous malformation, neuroleptic malignant syndrome, serotonin syndrome, or clinically significant metabolic disorders (e.g., hypoglycemia, hyponatremia, severe hepatic impairment, hypoxia).
- Female subjects of child-bearing potential who are pregnant, breastfeeding, planning to initiate pregnancy or breastfeeding, or not willing to practice a reliable method of contraception throughout the study.
- Positive serum ethanol test or urine drug screen for any prohibited medication or drugs of abuse at screening.
- Any current or recent medical, psychiatric, or social condition that was likely to interfere with the conduct of the study, to confound the interpretation of study results, or to endanger the subject's well-being.
- Hypertension defined as resting, sitting systolic blood pressure (BP) ≥150 mm Hg or diastolic BP ≥95 mm Hg. Subjects with high BP as defined above may have been accepted into the study if they subsequently had acceptable BP values on reassessment at least 30 minutes apart.
- Hypo-or hyper-thyroidism, unless stabilized on appropriate pharmacotherapy with no change in dosage for at least 1 month prior to screening.

Clinical Reviewer's Comment: The inclusion and exclusion criteria were appropriate for screening of individuals being considered for entry into the study.

Prohibited Recent Medications and Treatments

- Drugs that are strong inhibitors of CYP2D6 (e.g., fluoxetine, paroxetine, quinidine).
- Drugs that are inhibitors of CYP2B6 (e.g., clopidogrel, ticlopidine, prasugrel) or inducers of CYP2B6 (e.g., ritonavir, lopinavir, efavirenz).
- Current use, or use within 14 days before screening, of monoamine oxidase inhibitors.
- Use of dextromethorphan coadministered with quinidine (e.g., Nuedexta) within the past 4 weeks.
- Use of opioids within 14 days of screening.
- History of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation, or any experimental central nervous system treatment during the current depressive episode or in the 6 months prior to screening, whichever was longer.

Washout of Recent Medications

- Any of the prohibited medications listed in the protocol must have been discontinued within 1 week or 5 half-lives of the medication, whichever was longer, prior to the baseline visit.

- Lithium must have been tapered and followed by a 1-week washout.
- The safe withdrawal from benzodiazepine treatment was to be determined by the subject's treating clinician and monitored by the principal investigator.

Prohibited Concurrent Medications

- The protocol includes a list of prohibited medications, including antipsychotics, anticonvulsant mood stabilizers, anxiolytics, benzodiazepines, antidepressants, and antidepressant augmentation agents.

Allowable Concurrent Medications and Treatments

- Eszopiclone, zolpidem, zolpidem extended-release, zopiclone, or zaleplon for insomnia could be continued provided the medication had been used in a consistent manner for 4 weeks prior to enrollment and at doses that did not exceed the maximum labeled amounts.
- Support meetings or counseling (e.g., marital counseling) were allowed provided they were no more frequent than weekly and did not have treatment of depression as their objective.

Assignment to Treatment

Subjects were randomized at the baseline visit (Visit 2) to receive either AXS-05 or placebo in a 1:1 ratio for 6 weeks.

Study Treatments

- Treatment A: AXS-05 (105 mg bupropion HCl/45 mg dextromethorphan HBr) tablet, oral
- Treatment B: placebo matching tablet, oral

Clinical Reviewer's Comment: As per agreement with the Agency at the End-of-Phase 2 meeting (Section 3.2), Study MDD-301 was allowed to proceed with only a placebo control and no bupropion-only control. This decision was made based on the Applicant's analysis of data from Study MDD-201, which indicated that the dextromethorphan component of AXS-05 had an antidepressant effect that was independent of the antidepressant effect of bupropion. Study MDD-301 was not designed to allow assessment of the contribution of each component of AXS-05 to the overall antidepressant effect of the combination product.

Treatment Schedules

- Treatment A:
  - Days 1 to 3: AXS-05, one tablet daily
  - Days 4 to 42: AXS-05, one tablet twice daily
- Treatment B:
  - Days 1 to 3: placebo, one tablet daily
  - Days 4 to 42: placebo, one tablet twice daily

Procedures and Schedule

Subjects were provided a diary containing the VAMS and asked to complete it daily from baseline to the end of treatment. Study visits occurred at screening (Visit 1), baseline (Day 0, Visit 2), and on Days 4, 8, 15, 22, 29, 43, and 50 (Visits 3 to 9). Visit 3 (Day 4) was conducted by telephone. Subjects were reminded during Visit 3 to begin twice daily dosing on that day (Day 4). A 1-week safety follow-up visit (Visit 9) was conducted by telephone. Subjects who prematurely discontinued the study were encouraged to complete an early termination (ET) safety visit. See Table 8.

Table 8. Study MDD-301: Schedule of Events

Visit	Screening Visit 1	Baseline Visit 2	Phone Call Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 / ET	Visit 9 Follow-up[a]
Study Day	-28 to -1	1	4 (+1)	8 (±2)	15 (±2)	22 (±2)	29 (±2)	43 (±2)	50 (±2)
Week	-4 to 0			Week 1	Week 2	Week 3	Week 4	Week 6	Week 7
Informed consent	X[b]								
Subject registry	X								
Inclusion/exclusion criteria	X	X							
Demographics	X								
Medical/psychiatric history	X								
Medication history	X								
Physical examination	X							X	
Vital signs, height/weight[c]	X	X		X	X	X	X	X	
Laboratory tests[d]	X							X	
ECG	X					X[h]		X[h]	
Urine drug screen[e]	X	X							
Serum ethanol[e]	X								
Urine pregnancy test	X	X						X	
C-SSRS	X	X		X	X	X	X	X	X
SCID-5-CT	X								
VAMS completion/ review[g]	X	X	X	X	X	X	X	X	
MADRS	X	X		X	X	X	X	X	
QIDS-SR-16	X	X		X	X	X	X	X	
SDS		X		X	X	X	X	X	
Q-LES-Q-SF		X		X	X	X	X	X	
CGI-S (Severity)	X	X		X	X	X	X	X	
CGI-I (Improvement)				X	X	X	X	X	
PGI-I (Improvement)				X	X	X	X	X	
Randomization		X[j]							
Blood sample for compliance[f]				X	X	X	X	X	
First dose in clinic		X							

Visit	Screening Visit 1	Baseline Visit 2	Phone Call Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 / ET	Visit 9 Follow-up[a]
Study Day	-28 to -1	1	4 (+1)	8 (±2)	15 (±2)	22 (±2)	29 (±2)	43 (±2)	50 (±2)
Week	-4 to 0			Week 1	Week 2	Week 3	Week 4	Week 6	Week 7
Instruct to begin BID dosing			X						
Study drug dispensation[i]		X		X	X	X	X		
Study drug accountability			X	X	X	X	X	X	
PWC-20									X
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X

CBP = child bearing potential; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; C-SSRS = Columbia - Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = End of Study; ET = early termination; MADRS = Montgomery-Åsberg Depression Rating Scale; PGI-I = Patient Global Impression – Improvement; PWC-20 = Physicians Withdraw Criteria – 20 Item; QIDS-SR-16 = Quick Inventory of Depressive Symptomatology-Self- Rated; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; SCID-5-CT = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Clinical Trials Version; SDS = Sheehan disability scale; VAMS = Visual Analog Mood Scale

[a] Safety follow-up visit to be performed telephonically.
[b] Informed consent must be signed prior to any study procedures being performed.
[c] Vital signs, including blood pressure, heart rate, respiratory rate, and oral body temperature, was to be measured after the subject had been in a seated position for at least 5 minutes. Height was measured at Visit 1 and weight at Visit 1 and Visit 8 (EOS or ET).
[d] Clinical laboratory tests included hematology, serum chemistry, urinalysis and thyroid panel.
[e] May have been performed at other study visits per investigator judgment. Subjects with positive UDS or serum ethanol levels at Visit 1 may be allowed in study depending on circumstances described to the Medical Monitor and a negative repeat UDS is obtained before Visit 2.
[f] Axsome was to review drug concentrations throughout the study. Site would be contacted by Axsome if study drug non-compliance via blood draw is confirmed. *[Note: In order to maintain the blind, samples were not analyzed until the database was locked.]*
[g] A subject reported daily VAMS was used to collect a daily mood assessment starting from screening through Week 6. Study personnel showed subjects how to complete the VAMS. At each visit, study personnel reviewed VAMS data for accurate completion and compliance.
[h] Time of last study drug dose prior to ECG was collected.
[i] Study drug can be re-dispensed, when appropriate.
[j] Prior to randomization, subject eligibility must be reviewed by an independent clinical assessor.

Source: AXS-05-MDD-301 Clinical Study Report, Table 3, page 30.

Study Endpoints

The primary endpoint was the change from baseline to Week 6 in MADRS total score. The key secondary efficacy endpoints were:

- Change from baseline in MADRS total score at Week 2
- Percentage of subjects achieving remission (MADRS total score of ≤10) at Week 2
- Change from baseline in MADRS total score at Week 1
- Percentage of responders (≥50% reduction in MADRS total score) at Week 6

Statistical Analysis Plan

Multiplicity Adjustment

A fixed hierarchical testing strategy was specified to control the overall type 1 error rate. Testing begins with the primary endpoint. If the primary endpoint is statistically significant at α=0.05, then the first key secondary endpoint is tested. The process continues until a hypothesis fails to be rejected.

Analysis Method

The least squares mean change from baseline in MADRS total score was analyzed with the use of mixed-effect model for repeated measures (MMRM). The model contains treatment, week (Weeks 1 to 4 and Week 6), and treatment-by-week interaction as factors, baseline value as a covariate, and patient as a random effect. The analysis was based on the mITT analysis set which consists of all who are randomized, take at least one dose of study drug, and have at least one postbaseline assessment.

Sample Size and Power

Approximately 300 subjects (150 per arm) will provide 90% power at a significance level of 0.05 (two-sided) and assume an effect size of 0.31.

Protocol Amendments

The original statistical plan (version 1.0) was submitted on October 14, 2019. Although no protocol amendments were submitted, FDA statistical and clinical reviewers noted (SN 34, October 22, 2019) inconsistencies and changes in the key secondary endpoints in the updated protocol (May 31, 2019) submitted by the Applicant. The FDA conveyed to the Applicant that the responder and remission key secondary endpoints were not acceptable, but the change at Week 1 and change at Week 2 in MADRS total score as key secondary endpoints were acceptable because they provide useful clinical information.

8.1.2. Study Results

8.1.2.1. Study MDD-201

Compliance with Good Clinical Practices

Section 5.2, page 12 of the Clinical Study Report (CSR) states: "This study was designed and monitored in accordance with Axsome's procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki."

Financial Disclosure

No disclosable financial interests or arrangements were reported for any of the investigators participating in this study. See Section 15.2 for details.

Patient Disposition, mITT Population

All subjects deemed eligible by the investigator were randomized. A total of 97 subjects were randomized, 17 of whom failed the independent assessor evaluation, resulting in a total of 80 subjects in the mITT population (Table 9). Of the 17 subjects who failed the independent assessment, 16 failed because they did not meet the QIDS-SR-16 ≥13 criterion, and 1 failed because the subject did not have a primary diagnosis of MDD.

The mITT population consisted of subjects who met the following four criteria:

1. The independent assessor confirmed the subject's diagnosis of MDD and presence of a current MDE of moderate or greater severity based on clinical review and a QIDS-SR-16 score ≥13 at screening or baseline;
2. Subject was randomized;
3. Subject took at least one dose of study drug;
4. Subject had at least one postbaseline assessment.

Clinical Reviewer's Comment: The Applicant included 80 subjects in the mITT population. However, the Agency has concluded that four of these subjects did not meet all of the criteria for inclusion in the mITT population. This issue and its effects on the efficacy analysis are discussed below under Efficacy Results – Primary Endpoint.

Of the 80 subjects included in the mITT population by the Applicant, a total of 60 subjects (75.0%) completed the study; 34 subjects in the AXS-05 group and 26 subjects in the bupropion group. A total of 20 subjects (25.0%) discontinued the study. The most frequently reported reasons for discontinuation in the mITT population were AE (nine subjects), withdrew consent (four subjects), and lost to follow-up (three subjects). See Table 9.

Table 9. Study MDD-201: Subject Disposition, Applicant-Defined mITT Population

Status at End of Study	AXS-05 (N=43)	Bupropion (N=37)	Total (N=80)
Completed, n (%)	34 (79.1)	26 (70.3)	60 (75.0)
Discontinued, n (%)	9 (20.9)	11 (29.7)	20 (25.0)

Status at End of Study	AXS-05 (N=43)	Bupropion (N=37)	Total (N=80)
Primary reason for discontinuation, n (%)			
Adverse event	6 (14.0)	3 (8.1)	9 (11.3)
Lost to follow-up	0	3 (8.1)	3 (3.8)
Other; lost to follow-up for safety visit	0	1 (2.7)	1 (1.3)
Other; noncompliance with study drug	0	1 (2.7)	1 (1.3)
Other; noncompliance with study drug per lab analysis	1 (2.3)	0	1 (1.3)
Other; subject randomized but not treated with study drug	0	1 (2.7)	1 (1.3)
Withdrew consent	2 (4.7)	2 (5.4)	4 (5.0)

Source: AXS-05-MDD-201 Clinical Study Report, Table 8, page 48.
Abbreviation: mITT, modified intent-to-treat

Clinical Reviewer's Comment: The percentage of discontinuations for adverse events was higher in the AXS-05 group than in the bupropion group. This is consistent with the analyses presented in Section 8.2, which reveal a higher incidence of AEs in subjects treated with AXS-05 than in subjects treated with either bupropion or placebo. The percentage of subjects lost to follow-up was higher in the bupropion group. The reason for this difference is not clear.

Protocol Violations/Deviations

All major and minor protocol deviations were documented during the study. A total of three major deviations occurred. See Table 10.

Table 10. Study MDD-201: Major Protocol Deviations, All Randomized Subjects

Arm	Subject	Category	Description	Action Taken
AXS-05	(b) (6)	IP Compliance	At Visit 5, it was discovered that the subject had been taking 2 tabs in the AM in error.	Subject did not suffer any ill effects from the increased dose of study drug. Subject was counseled and continued in the study.
Bupropion	(b) (6)	Inclusion Criteria	The SCID was not completed at screening. It was completed after the subject completed the study.	Site reported deviation to the IRB.
Bupropion	(b) (6)	IP Compliance	Subject was not able to comply with the visit schedule, so site brought subject back 1 week early for Visit 6. Thus, the subject missed almost a full week of the treatment period.	The Investigator had not deemed this deviation to be reportable to the IRB.

Source: Generated by the Clinical Reviewer from AXS-05-MDD-201 Clinical Study Report, Listing 16.2.2.
Abbreviations: AM, morning; IP, investigational product; IRB, Institutional Review Board; SCID, Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders

Demographic Characteristics

In the Applicant-defined mITT population, the mean age was 37.3 years in the AXS-05 group and 37.7 years in the bupropion group. The majority of subjects in both treatment groups were female, white, and not Hispanic or Latino. The proportions of female subjects, black or African American subjects, and Hispanic or Latino subjects were higher in the bupropion group than in the AXS-05 group. See Table 11.

Table 11. Study MDD-201: Demographic Characteristics, Applicant-Defined mITT Population

Characteristic	AXS-05 (N=43)	Bupropion (N=37)	Total (N=80)
Age (years)			
Mean (SD)	37.3 (11.95)	37.7 (11.86)	37.5 (11.83)
Median	33.5	34.3	34.0
Minimum, maximum	19.6, 63.2	18.1, 61.7	18.1, 63.2
Sex, n (%)			
Female	25 (58.1)	26 (70.3)	51 (63.8)
Male	18 (41.9)	11 (29.7)	29 (36.3)
Race, n (%)			
White	30 (69.8)	20 (54.1)	50 (62.5)
Black or African American	12 (27.9)	14 (37.8)	26 (32.5)
Asian	1 (2.3)	0	1 (1.3)
Other	0	1 (2.7)	1 (1.3)
Multiracial	0	2 (5.4)	2 (2.5)
Ethnicity, n (%)			
Hispanic or Latino	6 (14.0)	11 (29.7)	17 (21.3)
Not Hispanic or Latino	37 (86.0)	26 (70.3)	63 (78.8)

Source: adapted from AXS-05-MDD-201 Clinical Study Report, Table 14.1.3.3., page 120.
Abbreviation: mITT, modified intent-to-treat

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

The baseline characteristics for the mITT population were generally similar between treatment groups. The mean age at onset of illness was 26.5 years for the AXS-05 group and 26.6 years for the bupropion group. In both groups, 51% of subjects had ≥3 MDEs prior to enrollment in the study. A greater proportion of subjects in the bupropion group had a family history of depression compared with the AXS-05 group. See Table 12.

Table 12. Study MDD-201: Clinical Characteristics, Applicant-Defined mITT Population

Characteristic	AXS-05 (N=43)	Bupropion (N=37)	Total (N=80)
Number of major depressive episodes, n (%)			
1	8 (18.6)	7 (18.9)	15 (18.8)
2	13 (30.2)	11 (29.7)	24 (30.0)
3	12 (27.9)	10 (27.0)	22 (27.5)
4	4 (9.3)	2 (5.4)	6 (7.5)
5	4 (9.3)	6 (16.2)	10 (12.5)
6	2 (4.7)	0	2 (2.5)
7	0	1 (2.7)	1 (1.3)
Onset age (years)			
Mean (SD)	26.5 (10.22)	26.6 (12.86)	26.6 (11.4)
Median	26.0	25.0	26.0
Minimum, maximum	12.0, 51.0	7.0, 54.0	7.0, 54.0
Family history, n (%)			
Yes	18 (41.9)	23 (62.2)	41 (51.3)
No	23 (53.5)	12 (32.4)	35 (43.8)
Not assessed	2 (4.7)	2 (5.4)	4 (5.0)

Characteristic	AXS-05 (N=43)	Bupropion (N=37)	Total (N=80)
Suicide risk, n (%)			
No	43 (100.0)	37 (100.0)	80 (100.0)

Source: Adapted from AXS-05-MDD-201 Clinical Study Report, Table 14.1.3.3, page 120.
Abbreviation: mITT, modified intent-to-treat

Baseline MADRS scores and CGI-S scores were similar for the AXS-05 and bupropion treatment groups, with subjects in both groups demonstrating moderate to severe depression. See Table 13.

Table 13. Study MDD-201: Baseline MADRS and CGI-S Scores, Applicant-Defined mITT Population

Baseline Assessment	AXS-05 (N=43)	Bupropion (N=37)
MADRS score		
Mean (SD)	31.8 (4.04)	32.3 (4.46)
Median	32.0	32.0
Minimum, maximum	25, 41	25, 41
CGI-S score		
Mean (SD)	4.4 (0.50)	4.5 (0.51)
Median	4	5
Minimum, maximum	4, 5	4, 5

Source: Adapted from AXS-05-MDD-201 Clinical Study Report, Table 14.2.1.2, page 138 (MADRS scores) and Table 14.2.4.2, page 147 (CGI-S scores).
Abbreviations: CGI-S, Clinical Global Impression – Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; SD, standard deviation

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was measured by counting the number of tablets dispensed and returned as well as by a subject's attainment of blood concentrations of bupropion and its metabolites that are consistent with steady state. Mean treatment compliance was 91.3% or higher each week in the mITT population for both the AXS-05 and bupropion groups.

Concomitant medication use was reported in 14 subjects (29.2%) in the AXS-05 group and 9 subjects (18.8%) in the bupropion group. The most frequently reported concomitant medications were antidepressants (five subjects [10.4%] in the AXS-05 group and three subjects [6.3%] in the bupropion group) and nonsteroidal anti-inflammatory drugs (three subjects [6.3%] in the AXS-05 group and two subjects [4.2%] in the bupropion group). The study protocol includes antidepressants in the list of prohibited concomitant medications. The eight subjects for whom an antidepressant was listed as a concomitant medication were all started on commercially-available bupropion or bupropion HCl on their last day of study drug, and thus did not begin taking an antidepressant until after their final efficacy assessments.

Efficacy Results – Primary Endpoint

As described in the protocol, the objective of this study was to evaluate the safety and tolerability of AXS-05 and bupropion in subjects with MDD. However, the SAP described analyses designed to demonstrate the efficacy of AXS-05 relative to an active comparator (bupropion). As discussed under Study Endpoints, the primary efficacy endpoint reported by

the Applicant [redacted] (b) (4) was change from baseline to Week 6 in MADRS total score. Scores range from 0 to 60, with higher scores indicating more severe depression. According to the Applicant's analysis, AXS-05 was statistically significantly superior to bupropion at Week 6 (Table 14, p=0.013; 95% confidence interval [CI]: 1.12 to 9.29).

Table 14. Applicant's Primary Efficacy Analysis Reported [redacted] (b) (4): MADRS Total Score Change From Baseline at Week 6 in mITT, Study MDD-201

Parameter	AXS-05 (N=43)	Bupropion (N=37)
Mean baseline score (SD)	31.8 (4.04)	32.2 (4.46)
Mean score at Week 6 (SD)	14.6 (11.82)	20.0 (10.36)
LS mean change from baseline (SE)	17.27 (1.41)	12.07 (1.52)
Bupropion-subtracted difference[1] (SE)	5.20 (2.08)	
95% CI	(1.12, 9.29)	
p-value	0.013	

Source: Tables 14.2.1.1 and 14.2.1.2 (Clinical Study Report, pages 137-138).
[1] Difference (drug minus bupropion) in least-squares mean change from baseline computed using mixed-effect model repeated measure analysis with missing outcomes imputed using the last observation carried forward method (MMRM_LOCF), with variance-components covariance matrix, maximum l kelihood estimation method
Abbreviations: CI, confidence interval; LS, least-squares; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; SD, standard deviation; SE, standard error

Although the Statistical Reviewer was able to replicate the Applicant's efficacy findings (Clinical Study Report; Table 13, page 53), there are concerns with the number of patients included in the Applicant's mITT population.

Statistical Reviewer's Note: The statistical and clinical teams did not review the protocol during the investigational new drug stage. The study was originally submitted to evaluate the safety and tolerability of AXS-05 and bupropion in subjects with MDD. Further, both the protocol and SAP appeared to be incorrectly coded when submitted to the Agency and were wrongly included in the human-pd-study folder. Because of the miscoding and the exploratory nature of the study, the protocol/SAP were not reviewed.

The SAP-specified primary endpoint was the average of mean change in the MADRS from baseline to each of the onsite visits from Weeks 1 to 6. The onsite visits occurred at the ends of Weeks 1, 2, 3, 4, and 6. The results are statistically significant (Table 15). [redacted] (b) (4) *the Applicant presents a conventional primary endpoint–change from baseline to end of treatment period. The change is based on FDA feedback at the pre-NDA meeting, at which the FDA communicated that the mean change from baseline in MADRS total score, averaged across all visits, has not been used previously to support regulatory approval of an antidepressant.*

Table 15. Applicant's Primary Efficacy Analysis: Average of Mean Change in MADRS Total Score From Baseline to Weeks 1 to 6 in mITT, Study MDD-201

Parameter	AXS-05 (N=43)	Bupropion (N=37)
Mean baseline score (SD)	31.8 (4.04)	32.2 (4.46)
LS mean change from baseline (SE)	13.66 (0.63)	8.76 (0.68)
Bupropion-subtracted difference[1] (SE)	4.90 (0.93)	
95% CI	(3.05, 6.75)	
p-value	<0.001	

Source: Table 13 (Clinical Study Report, page 53).
[1] Difference (drug minus bupropion) in least-squares mean change from baseline computed using mixed-effect model repeated measure analysis with missing outcomes imputed using the last observation carried forward method (MMRM_LOCF), with variance-components covariance matrix, maximum l kelihood estimation method
Abbreviations: CI, confidence interval; LS, least-squares; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; SD, standard deviation; SE, standard error

Reanalysis of Data Using MMRM Without Imputation

Following the initial review of the NDA, the FDA sent information requests (March 24 and March 29, 2021) to the Applicant to conduct the primary efficacy analysis based on MMRM without the LOCF imputation. Typically, the FDA accepts MMRM without imputation as the primary analysis for MDD trials and discourages a single value imputation approach, such as LOCF. The MMRM takes all observed values without imputing missing outcomes and assumes a missing-at-random missing data mechanism. The model parameters were to be estimated using the restricted maximum-likelihood (REML) method, with unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom. The REML approach produces unbiased estimates of variance and covariance parameters. Although there is no guarantee of a correct specification of covariance structure, the unstructured variance-covariance matrix is preferred unless a parsimonious covariance matrix is justified.

To address potential misspecification of the variance-components covariance matrix, the Applicant was requested to re-run additional analyses: (i) MMRM using a sandwich estimator for the *variance-components* covariance matrix and REML estimation method; (ii) MMRM with unstructured covariance matrix and REML estimation method. The Applicant responded to the request on March 30, 2021 (eCTD #0009).

The variance-components covariance structure assumes zero correlation between visits; that is, the off-diagonal elements in the correlation matrix are zero. In this study, the estimated correlation matrix (Figure 3) shows that the off-diagonal estimates are far from zero among the five time points and does not support the assumed variance-components covariance structure. This misspecification is likely to underestimate the standard error of the estimated treatment effect. Thus, to correct for the underestimation, the 'sandwich variance estimator' should be used to obtain a robust estimate of the variance of treatment effect; that is, the variance-components covariance matrix is used only as a 'working' covariance matrix.

Figure 3. Correlation Matrix Among the Five Timepoints

1	0.80	0.76	0.63	0.56
0.80	1	0.84	0.76	0.71
0.76	0.84	1	0.92	0.81
0.63	0.76	0.92	1	0.91
0.56	0.71	0.81	0.91	1

Source: FDA Biometrics Reviewer's analysis

The Applicant-conducted reanalysis (Response to Information Request, March 30, 2021), presented in Table 16, was confirmed by the Statistical Reviewer. The reanalysis conclusions did not meet the primary efficacy objective.

Table 16. Primary Efficacy Reanalysis (MMRM Without Imputation): MADRS Total Score Change From Baseline at Week 6 in Applicant's mITT, Study MDD-201

Parameter	AXS-05 (N=43)	Bupropion (N=37)
Mean baseline score (SD)	31.8 (4.04)	32.2 (4.46)
Mean score at Week 6 (SD)	11.8 (10.30)	17.7 (10.94)
LS mean change from baseline (SE)	20.16 (1.74)	14.92 (2.01)
Bupropion-subtracted difference[1] (SE)	5.24 (2.67)	
95% CI	(-0.02, 10.49)	
p-value	0.051	
LS mean change from baseline (SE)	19.35 (1.74)	15.18 (2.00)
Bupropion-subtracted difference[2] (SE)	4.17 (2.66)	
95% CI	(-1.12, 9.46)	
p-value	0.12	

Source: Information Request (March 29, 2021).
[1] Difference (drug minus bupropion) in least-squares mean change from baseline computed using MMRM with **variance-components covariance matrix, sandwich estimator,** REML (restricted maximum likelihood) estimation method
[2] Difference (drug minus bupropion) in least-squares mean change from baseline computed using MMRM **with unstructured covariance matrix**, REML (restricted maximum likelihood) estimation method
Abbreviations: CI, confidence interval; LS, least-squares; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; MMRM, mixed-effect model repeated measure; SD, standard deviation; SE, standard error

The prespecified primary efficacy analysis uses MMRM (with VC covariance structure and ML estimation method) where the longitudinal missing outcomes were imputed by the LOCF method. Although there was not a significant difference in the choice of estimation method, REML is used in the re-analyses of MMRM_LOCF below.

Reanalysis of MMRM_LOCF 1: Remove Three Subjects with Baseline Observations Only in the Bupropion Arm

While exploring the missing data patterns in the efficacy dataset, the FDA biometrics reviewer identified three subjects in the mITT population with no postbaseline MADRS scores (Table 17). The three subjects belonged to the bupropion arm, and their baseline MADRS total scores were carried forward and used in the efficacy analysis. Inclusion of these subjects appears to contradict the prespecified definition of the mITT population which specifies that subjects have "at least one dose of the study drug, and had *at least one postbaseline assessment.*" An information request was sent (June 14, 2021) to seek clarification and rationale as to why these patients were used in the analysis set. In response (June 17, 2021), the Applicant explained that

each patient's study site had made contact with patients during the first week to assess for adverse events. This postbaseline contact was made for safety assessment reasons and should not have met the definition of the mITT analysis set, which represents the efficacy population. Reanalysis of the efficacy data without these subjects resulted in a negative trial where the primary efficacy objective was not met.

Table 17. Missing Data Patterns, Study MDD-201

	Study Visit						
Group	**BL**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 6**	**N (%)**
1							61 (76.25)
Observed (X=yes, .=no)	X	X	X	X	X	X	
Mean	32.28	25.36	20.21	18.23	15.64	14.31	
2							2 (2.5)
Observed (X=yes, .=no)	X	X	X	X	.	.	
Mean	33.00	29.00	26.00	25.50	.	.	
3							3 (3.75)
Observed (X=yes, .=no)	X	X	X	.	.	.	
Mean	28.00	25.67	17.33	.	.	.	
4							11 (13.75)
Observed (X=yes, .=no)	X	X	.	.	.	.	
Mean	31.36	27.18	.	.	.	.	
5							3 (3.75)
Observed (X=yes, .=no)	X	.	.	.	.	.	
Mean	31.67	.	.	.	.	.	

Source: FDA Biometrics Reviewer's analysis.
Abbreviations: BL, baseline; FDA, Food and Drug Administration; X, observed value at a given timepoint; ., missing data

In Table 18, efficacy data were analyzed using MMRM_LOCF but removing the three subjects in the bupropion arm with no postbaseline observations. The top block in this table shows the results with VC covariance structure and the bottom block includes the results when adding a sandwich variance estimator. Removal of the three subjects under the two scenarios reveal a statistically nonsignificant primary efficacy result.

Table 18. FDA Primary Efficacy Reanalysis by Removing Three Subjects With No Postbaseline Observations: MADRS Total Score Change From Baseline at Week 6 (MMRM_LOCF, REML, mITT (as Defined in SAP), Study MDD-201)

Parameter	AXS-05 (N=43)	Bupropion (N=34)
Mean baseline score (SD)	31.8 (4.04)	32.2 (4.54)
Mean score at Week 6 (SD)	14.6 (11.82)	20.0 (10.36)
LS mean CFB (SE)	17.3 (1.43)	13.1 (1.61)
Bupropion-subtracted difference[1] (SE)	4.15 (2.15)	
95% CI	(-0.09, 8.39)	
p-value	0.06	
LS mean CFB (SE)	17.3 (1.76)	13.1 (1.70)
Bupropion-subtracted difference[2] (SE)	4.15 (2.45)	
95% CI	(-0.67, 8.97)	
p-value	0.09	

Source: FDA Biometrics Reviewer's analysis.
[1] Difference (drug minus bupropion) in least-squares mean change from baseline computed using mixed-effect model repeated measure analysis with missing outcomes imputed using the last observation carried forward method (MMRM_LOCF), with variance-components covariance matrix, REML (restricted maximum likelihood) estimation method
[2] Difference (drug minus bupropion) in least-squares mean change from baseline computed using MMRM_LOCF using **sandwich variance estimator** with variance-components covariance matrix, REML estimation method
Abbreviations: CFB, change from baseline; CI, confidence interval; FDA, Food and Drug Administration; LS, least-squares; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; SAP, statistical analysis plan; SD, standard deviation; SE, standard error

Reanalysis of MMRM_LOCF 2: Remove Four Subjects (Three Subjects With Baseline Observations Only in the Bupropion Arm and One Subject Who Was Not Dosed in the Bupropion Arm)

In addition to the three subjects who did not have postbaseline MADRS scores in the bupropion arm, one patient ((b) (6)) who did not dose in the bupropion arm was identified after data unblinding (CSR, page 56). These four subjects deviate from the predefined mITT population. Re-analysis of the efficacy data by removing all four subjects renders Study MDD-201 negative. This demonstrates that the four subjects had undue influence in the Applicant's reported primary efficacy result. In the Applicant's analysis, the four subjects from the bupropion arm might have undermined the effect of bupropion and showed that AXS-05 had a superior effect.

Table 19 reveals that the standard error estimates, using the robust variance sandwich estimator (bottom block of the table), are greater and the treatment estimates are almost identical compared to the analysis without the sandwich estimator (top block of the table). As summarized in Table 20, the results of the SAP-specified primary endpoint (the averaging endpoint) are still statistically significant.

Table 19. FDA Primary Efficacy Reanalysis by Removing Three Subjects With No Postbaseline Observations Plus One Subject With No Dose: MADRS Total Score Change From Baseline at Week 6 (MMRM_LOCF, REML, mITT (as Defined in SAP), Study MDD-201)

Parameter	AXS-05 (N=43)	Bupropion (N=33)
Mean baseline score (SD)	31.8 (4.04)	32.4 (4.42)
Mean score at Week 6 (SD)	14.6 (11.82)	18.79 (10.21)
LS mean CFB (SE)	17.3 (1.43)	13.52 (1.64)
Bupropion-subtracted difference[1] (SE)	3.78 (2.17)	
95% CI	(-1.51, 8.06)	
p-value	0.08	
LS mean CFB (SE)	17.3 (1.76)	13.52 (1.71)
Bupropion-subtracted difference[2] (SE)	3.78 (2.47)	
95% CI	(-1.08, 8.64)	
p-value	0.13	

Source: FDA Biometrics Reviewer's analysis.
[1] Difference (drug minus bupropion) in least-squares mean change from baseline computed using ANCOVA (LOCF) with variance-components covariance matrix, REML (restricted maximum likelihood) estimation method
[2] Difference (drug minus bupropion) in least-squares mean change from baseline computed using ANCOVA (LOCF) **using sandwich variance estimator** with variance-components covariance matrix, REML (restricted maximum l kelihood) estimation method
Abbreviations: ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; FDA, Food and Drug Administration; LOCF, last observation carried forward; LS, least-squares; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; MMRM_LOCF, mixed-effect model repeated measure analysis with missing outcomes imputed using the last observation carried forward method; SAP, statistical analysis plan; SD, standard deviation; SE, standard error

Table 20: FDA Primary Efficacy Reanalysis by Removing Three Subjects With No Postbaseline Observations Plus One Subject With No Dose: Average of Mean Change in MADRS Total Score From Baseline to Weeks 1 to 6 (MMRM_LOCF, REML, mITT (as Defined in SAP), Study MDD-

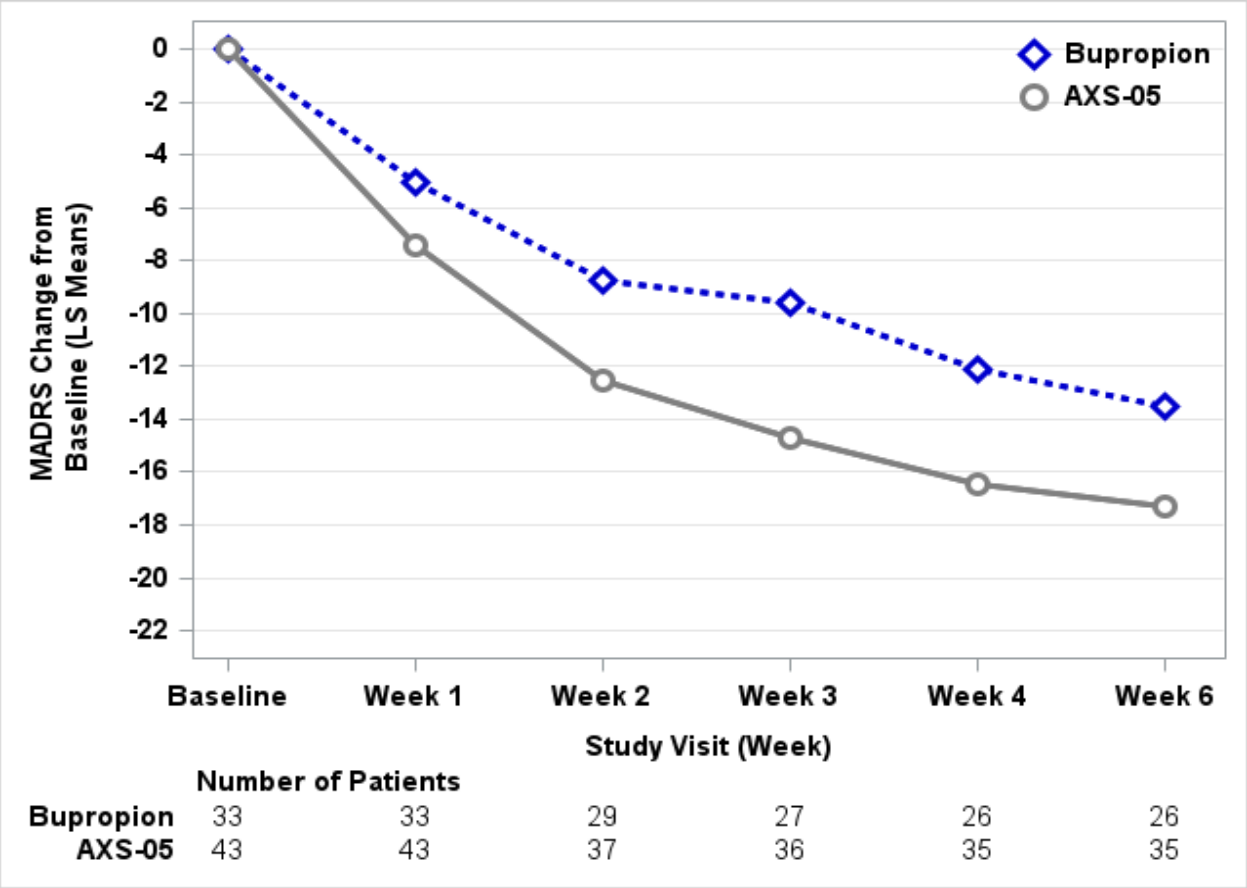
Parameter	AXS-05 (N=43)	Bupropion (N=33)
Mean baseline score (SD)	31.8 (4.04)	32.4 (4.42)
LS mean CFB (SE)	13.69 (0.64)	9.81 (0.73)
Bupropion-subtracted difference[1] (SE)	3.88 (0.97)	
95% CI	(1.94, 5.82)	
p-value	<0.001	
LS mean CFB (SE)	13.69 (1.35)	9.81 (1.27)
Bupropion-subtracted difference[2] (SE)	3.88 (1.86)	
95% CI	(0.18, 7.58)	
p-value	0.04	

Source: FDA Biometrics Reviewer's analysis.
[1] Difference (drug minus bupropion) in least-squares mean change from baseline computed using ANCOVA (LOCF) with variance-components covariance matrix, REML (restricted maximum likelihood) estimation method
[2] Difference (drug minus bupropion) in least-squares mean change from baseline computed using ANCOVA (LOCF) **using sandwich variance estimator** with variance-components covariance matrix, REML (restricted maximum l kelihood) estimation method
Abbreviations: ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; FDA, Food and Drug Administration; LOCF, last observation carried forward; LS, least-squares; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; MMRM_LOCF, mixed-effect model repeated measure analysis with missing outcomes imputed using the last observation carried forward method; SAP, statistical analysis plan; SD, standard deviation; SE, standard error

Figure 4 displays the least squares mean change from baseline in MADRS total score, by treatment group at each visit, using FDA's mITT analysis population (with the four subjects removed), using the prespecified primary statistical model (MMRM_LOCF with VC covariance

structure). Although the curves appear separate, the statistical evidence was not strong enough.

Figure 4. FDA's LS Mean Change From Baseline in MADRS Total Score (FDA's mITT With Four Subjects Removed; MMRM_LOCF), Study MDD-201



Number of Patients						
Bupropion	33	33	29	27	26	26
AXS-05	43	43	37	36	35	35

Source: FDA Biometrics Reviewer.
Based on the prespecified mixed-effect model repeated measure method last observation carried forward (MMRM_LOCF) model
Abbreviations: FDA, Food and Drug Administration; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat

Table 21 displays the longitudinal treatment effect across visits. The treatment effect was greatest at Week 3, followed by Week 4.

Table 21. FDA Primary Efficacy Reanalysis by Removing Three Subjects With No Postbaseline Observations Plus One Subject With No Dose: Longitudinal MADRS Total Score Change From Baseline Across Visits (MMRM_LOCF, REML, Sandwich Variance Estimator, mITT (as Defined in SAP), Study MDD-201)

Visit Treatment Arm	N	Change From Baseline	Treatment Difference (SE)	Lower 95% CI	Upper 95% CI
Week 1					
Bupropion	33	5.04	2.35 (1.52)	2.96	7.11
AXS-05	43	7.40		5.24	9.54
Week 2					
Bupropion	33	8.76	3.79 (2.01)	5.79	11.74
AXS-05	43	12.55		9.92	15.18
Week 3					
Bupropion	33	9.61	5.13 (2.11)	6.97	12.25
AXS-05	43	14.74		11.56	17.92
Week 4					
Bupropion	33	12.13	4.36 (2.30)	9.05	15.20
AXS-05	43	16.48		13.20	19.77
Week 6					
Bupropion	33	13.52	3.78 (2.47)	10.15	16.90
AXS-05	43	17.30		13.82	20.77

Source: FDA Biometrics Reviewer.
Abbreviations: CI, confidence interval; FDA, Food and Drug Administration; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; MMRM_LOCF, mixed-effect model repeated measure analysis with missing outcomes imputed using the last observation carried forward method; REML, restricted maximum l kelihood; SE, standard error

Statistical Reviewer's Note: In the pre-NDA meeting with the Applicant, FDA conveyed the following comments with regards to the acceptability of LOCF imputation:

> *The primary analysis, LOCF analysis of covariance, is also difficult to justify unless the dropout rate is negligible. In your NDA submission, you should include justifications for the suitability of the primary analysis as well as sensitivity analyses to assess the impact of the improbable missing data assumptions under the primary analysis. The acceptability of Study AXS-05-MDD-201 to support approval of your product will be a matter of review.*

The results of sensitivity analyses (random replacement method and tipping point analyses; Response to Information Request, March 30, 2021) that explored the impact of missing data on efficacy yielded the same conclusions as the primary efficacy analysis conducted by removing the four subjects.

Data Quality and Integrity

Page 38 of the CSR states: "Accurate and reliable data collection were ensured by verification and cross check of the case report forms (CRFs) against the investigator's records by the study monitor (source document verification) and by the maintenance of a drug-dispensing log by the investigator. Collected data were entered into a computer database and subject to electronic and manual quality assurance procedures."

Two clinical sites participating in this study were audited by the Agency's Office of Scientific Investigations (Section 4.1). No areas of concern regarding data quality or integrity were discovered during these investigations.

As mentioned previously, the Applicant recognized after database lock that a subject who had never taken the study drug had been included in the mITT population. The Applicant conducted a sensitivity analysis that suggested that removal of this subject from the mITT population would not affect the statistical significance of the efficacy results. However, the Agency disagrees with the Applicant's use of LOCF imputation for this subject and for three additional subjects who left the study prior to completion of any postbaseline efficacy assessments. The Agency's analyses omitting all four subjects who did not meet the criteria for inclusion in the mITT population are presented in Efficacy Results – Primary Endpoint.

Efficacy Results – Secondary and Other Relevant Endpoints

Only supportive secondary endpoints were specified in the protocol. No multiplicity adjustment was made for potential inclusion of the secondary endpoints in the label.

Dose/Dose Response

Evaluation of dose response was not conducted. AXS-05 has been developed as a fixed-dose combination tablet with the doses of bupropion and dextromethorphan determined during phase 1 studies. The Applicant intends to market only a single-dose combination: bupropion HCl 105 mg + dextromethorphan HBr 45 mg.

Durability of Response

Durability of response was not evaluated in the short-term clinical trials. Durability also was not evaluated in the long-term safety trial, which did not include a placebo arm or a randomized withdrawal period.

Persistence of Effect

Persistence of effect was not evaluated in any of the AXS-05 clinical trials.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

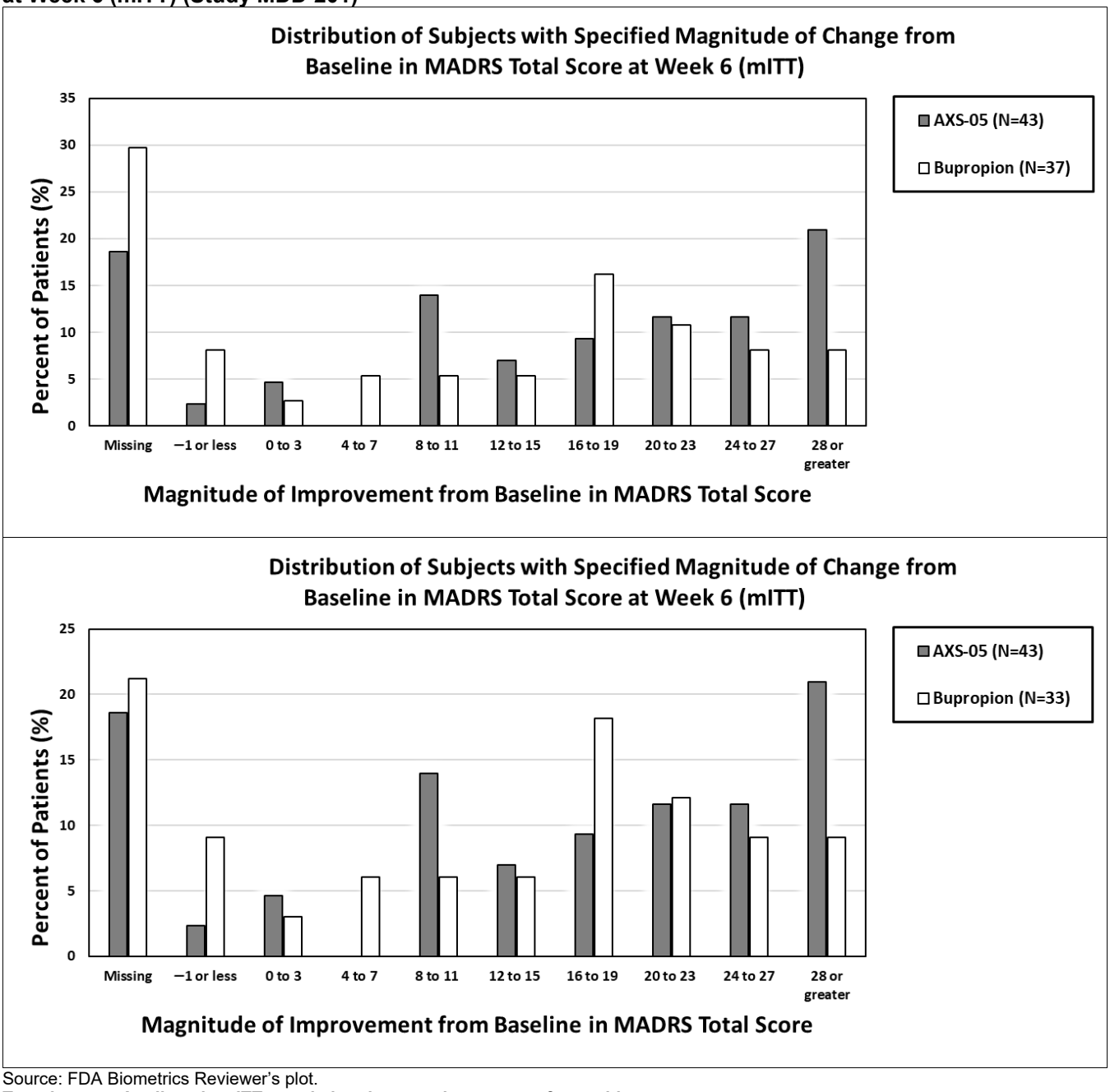
See Efficacy Results – Secondary and Other Relevant Endpoints. No exploratory Clinical Outcome Assessment (Patient-Reported Outcome) (COA [PRO]) endpoints were defined for this study.

Additional Analyses Conducted on the Individual Trials

Distribution of Proportion of Response and Cumulative Empirical Distribution

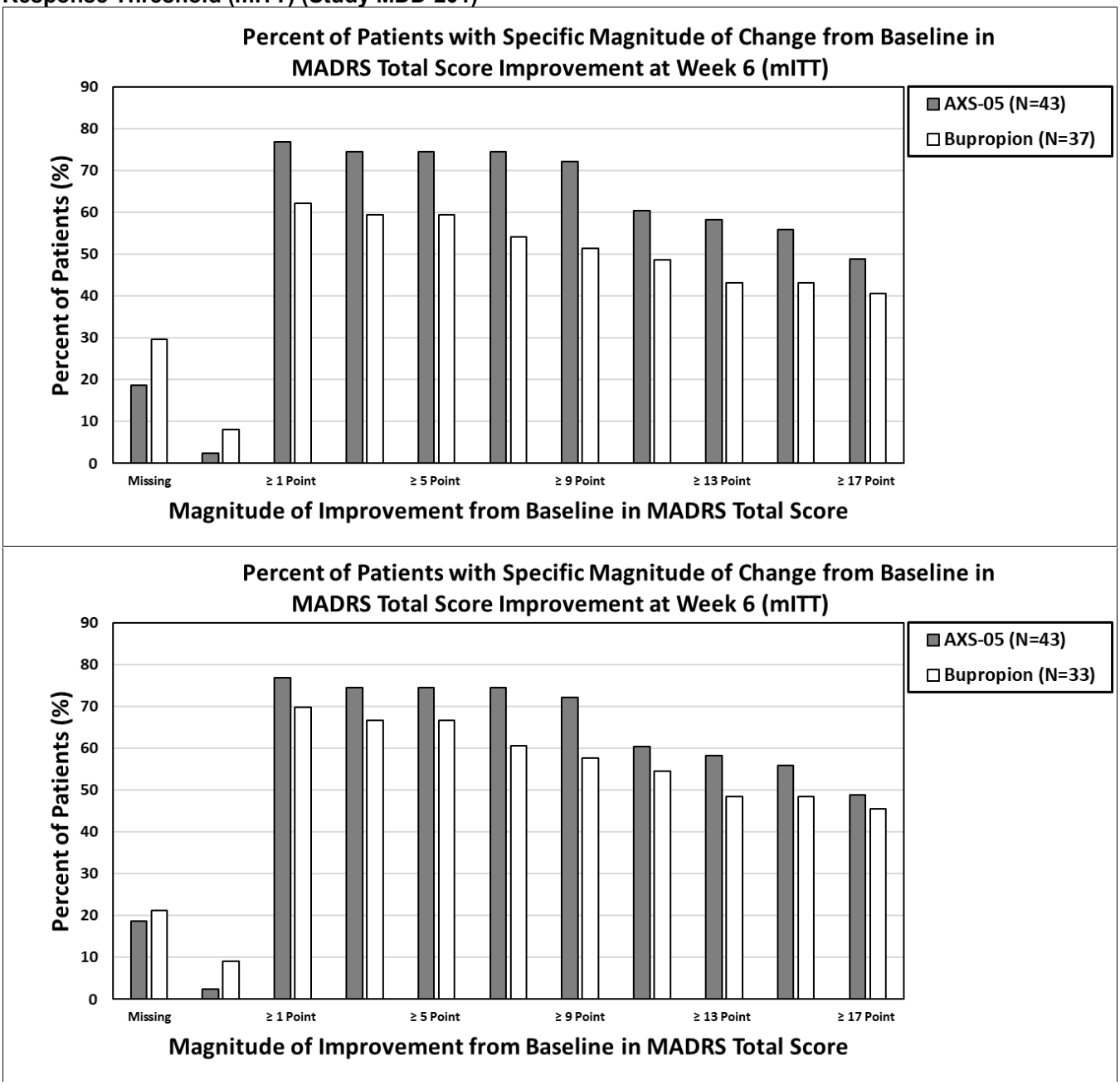
Figure 5 shows the distribution of the magnitude of change in MADRS total score for completers. The proportion of dropouts is presented at the left end of the plot. The proportion of subjects who showed improvement in depressive symptoms in the AXS-05 group was generally greater than that in the bupropion group. The cumulative distribution plot in Figure 6 shows that more subjects in the AXS-05 group showed improvement at Week 6, based on various MADRS response thresholds.

Figure 5. Percentage of Patients With a Specified Magnitude of MADRS Total Score Improvement at Week 6 (mITT) (Study MDD-201)



Source: FDA Biometrics Reviewer's plot.
Top plot uses Applicant's mITT population; bottom plot removes four subjects
Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat

Figure 6. Percentage of Response (MADRS Total Score) for Each Treatment Group at Week 6 by Response Threshold (mITT) (Study MDD-201)



Source: FDA Biometrics Reviewer's plot.
Top plot uses Applicant's mITT population; bottom plot removes four subjects
Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat

8.1.2.2. Study MDD-301

Compliance with Good Clinical Practices

Section 5.2, page 13 of the CSR states: "This study was designed and monitored in accordance with Axsome procedures, which comply with the ethical principles of GCP as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki."

Financial Disclosure

No disclosable financial interests or arrangements were reported for any of the investigators participating in this study. See Section 15.2 for details.

Patient Disposition

All subjects deemed eligible by the investigator were randomized. A total of 327 subjects was randomized, 9 of whom failed the independent assessor evaluation, resulting in a total of 318 subjects in the mITT population. The mITT population consisted of all randomized subjects whose diagnosis of MDD and of a current MDE of moderate or greater severity was confirmed by the independent assessor based on clinical review and a QIDS-SR-16 score ≥13 at screening or baseline, who took at least one dose of study drug, and who had at least one postbaseline assessment.

Of the 318 subjects in the mITT population, a total of 270 subjects (84.9%) completed the study; 123 subjects in the AXS-05 group and 147 subjects in the placebo group. A total of 48 subjects (15.1%) discontinued the study. The most frequently reported reasons for discontinuation in the mITT population were withdrawal by subject (19 subjects), lost to follow-up (15 subjects), and AE (7 subjects). See Table 22.

Table 22. Study MDD-301: Subject Disposition, mITT Population

Status at End of Study	AXS-05 (N=156)	Bupropion (N=162)	Total (N=318)
Completed, n (%)	123 (78.8)	147 (90.7)	270 (84.9)
Discontinued, n (%)	33 (21.2)	15 (9.3)	48 (15.1)
Primary reason for discontinuation, n (%)			
Adverse event	7 (4.5)	0 (0.0)	7 (2.2)
Investigator's decision	0 (0.0)	1 (0.6)	1 (0.3)
Lost to follow-up	9 (5.8)	6 (3.7)	15 (4.7)
Other	1 (0.6)[a]	3 (1.9)[b]	4 (1.3)
Protocol deviation	2 (1.3)	0 (0.0)	2 (0.6)
Withdrawal by subject	14 (9.0)[c]	5 (3.1)[d]	19 (6.0)

Source: AXS-05-MDD-301 Clinical Study Report, Table 6, page 51.
[a] Other included: noncompliant with study drug (one subject)
[b] Other included: noncompliant with study drug (one subject) and could not attend final study visit due to new job schedule (two subjects)
[c] Withdrawal by subject included: did not wish to continue study due to AE (two subjects), withdrew consent/no longer wished to participate (four subjects), moved and can no longer be in study (one subject), due to work schedule (four subjects), unable to make study visits (one subject), due to insomnia (one subject), "didn't like medication how feel" (one subject), and didn't l ke medication (one subject).
[d] Withdrawal by subject included: wanted to return to counseling (one subject), withdrew consent (one subject), travelled out of town with an unknown return (one subject), and lack of efficacy/no improvement (two subjects).
Abbreviation: mITT, modified intent-to-treat

Clinical Reviewer's Comment: The percentage of discontinuations because of withdrawal by subject, loss to follow-up, or AE were all higher in the AXS-05 group than in the placebo group. Of the 14 withdrawals by subject in the AXS-05 group, at least 4 were related to AEs. The relatively high rate of discontinuations for AEs in the AXS-05 group is consistent with the analyses presented in Section 8.2, which reveal a higher incidence of AEs in subjects treated with AXS-05 than in subjects treated with either bupropion or placebo.

Protocol Violations/Deviations

All major and minor protocol deviations were documented during the study. A total of 21 major protocol deviations occurred, 8 in the AXS-05 group and 21 in the placebo group. The largest number of major deviations was related to study drug dosing. Table 23 shows the number of major protocol deviations by study arm and category. Table 24 presents a description of each major protocol deviation.

Clinical Reviewer's Note: Deviations in dosing occurred mostly in the placebo group and all involved missed doses or running out of study drug. These deviations would not have affected the efficacy analysis.

Deviations in concomitant medications all involved subjects taking cough/cold medications containing dextromethorphan, which is a component of AXS-05 that the Applicant hypothesizes to have an antidepressant effect. Three such deviations occurred in the AXS-05 arm and one in the placebo arm. Although these deviations theoretically could have affected the efficacy analysis, the exposure durations were brief, and the number of subjects involved was small compared to the overall size of the randomized study population.

Table 23. Study MDD-301: Major Protocol Deviations, All Randomized Subjects (Summary)

Deviation Category	AXS-05 (N=163)	Placebo (N=164)	Total (N=327)
Total subjects with major deviations, n (%)	8 (4.9)	13 (7.9)	21 (6.4)
Dosing, n (%)	1 (0.6)	8 (4.9)	9 (5.5)
Exclusion criteria, n (%)	3 (1.8)	2 (1.2)	5 (3.1)
Concomitant medication, n (%)	3 (1.8)	1 (0.6)	4 (2.5)
Good clinical practices, n (%)	0 (0.0)	2 (1.2)	2 (1.2)
Study procedure/assessment, n (%)	1 (0.6)	0 (0.0)	1 (0.6)

Source: Generated by the Clinical Reviewer from the AXS-05-MDD-301 Clinical Study Report, Listing 16.2.2.

Table 24. Study MDD-301: Major Protocol Deviations, All Randomized Subjects (Details)

Arm	Subject	Category	Description
AXS-05	(b) (6)	Dosing	Subject stopped dosing 5 days before Visit 8 after running out of IP.
AXS-05	(b) (6)	Exclusion	Subject had been taking meloxicam 15 mg daily for arthritis since (b) (6) and continued this medication daily throughout the study. The list of prohibited medications states that nonsteroidal anti-inflammatory medications are allowed for episodic but not chronic use. Subjects taking a prohibited concomitant medication were to be excluded from the study.
AXS-05	(b) (6)	Exclusion	Subject was deemed ineligible by the independent assessor but was erroneously randomized.
AXS-05	(b) (6)	Exclusion	Subject was deemed ineligible by the independent assessor but was erroneously randomized. The error was caught before IP was dispensed.
AXS-05	(b) (6)	Concomitant medication	Subject took three doses of a cough/cold medication containing dextromethorphan (a prohibited medication), with the last dose taken the day before Visit 5.
AXS-05	(b) (6)	Concomitant medication	Subject took two doses of a cough/cold medication containing dextromethorphan (a prohibited medication) the day before Visit 4.
AXS-05	(b) (6)	Concomitant medication	Subject took one dose of a cough/cold medication containing dextromethorphan (a prohibited medication) the day before Visit 6.
AXS-05	(b) (6)	Study procedure / assessment	Visit 6 was not conducted.
Placebo	(b) (6)	Dosing	Subject was 40% compliant between Visit 2 and Visit 4. The day of her last dose, the subject stated that the bottle of IP had been stolen from her bag.
Placebo	(b) (6)	Dosing	Subject only took IP once per day from Visit 7 to Visit 8.
Placebo	(b) (6)	Dosing	Subject ran out of IP between Visit 7 and the end of treatment.
Placebo	(b) (6)	Dosing	Subject was found to be only 67% compliant with dosing between Visit 6 and Visit 7.
Placebo	(b) (6)	Dosing	Subject missed 4 days of IP between Visit 4 and Visit 6 after missing IP dispensing at Visit 5.
Placebo	(b) (6)	Dosing	Subject missed 11 days of IP dosing after running out of IP.
Placebo	(b) (6)	Dosing	Subject missed 2 weeks of dosing after running out of IP.
Placebo	(b) (6)	Dosing	Subject missed 1 week of dosing after running out of IP.
Placebo	(b) (6)	Exclusion	Subject met the exclusion criterion for ALT value >2× ULN but was randomized in error.
Placebo	(b) (6)	Exclusion	Subject has been on rivaroxaban (a prohibited medication) since (b) (6) and should have been excluded from the study.
Placebo	(b) (6)	Good Clinical Practices	It was noted that a subinvestigator was not delegated to perform physical exams. The subject's physical examination was performed by a different investigator.
Placebo	(b) (6)	Good Clinical Practices	The subinvestigator who administered the MADRS at Visit 4 was not approved or certified to do so.
Placebo	(b) (6)	Concomitant medication	Subject took a cough/cold medication containing dextromethorphan (a prohibited medication) for 6 days after Visit 6.

Source: Generated by the Clinical Reviewer from the AXS-05-MDD-301 Clinical Study Report, Listing 16.2.2.
Abbreviations: ALT, alanine aminotransferase; IP, investigational product; MADRS, Montgomery-Åsberg Depression Rating Scale; ULN, upper limit of normal

Table of Demographic Characteristics

In the mITT population, the mean age was 42.1 years in the AXS-05 group and 41.2 years in the placebo group. The majority of subjects in both treatment groups was female and white. The proportions of male subjects, black or African American subjects, Asian subjects, and multiple-race subjects were higher in the AXS-05 group than in the placebo group. See Table 25.

Table 25. Study MDD-301: Demographic Characteristics, mITT Population

Characteristic	AXS-05 (N=156)	Bupropion (N=162)	Total (N=318)
Age (years)			
Mean (SD)	42.1 (12.80)	41.2 (13.77)	41.7 (13.29)
Median	41	40	41
Minimum, maximum	18, 64	18, 65	18, 65
Sex, n (%)			
Female	95 (60.9)	117 (72.2)	212 (66.7)
Male	61 (39.1)	45 (27.8)	106 (33.3)
Race, n (%)			
White	84 (53.8)	92 (56.8)	176 (55.3)
Black or African American	58 (37.2)	54 (33.3)	112 (35.2)
Asian	9 (5.8)	8 (4.9)	17 (5.3)
Native Hawaiian or other Pacific Islander	1 (0.6)	2 (1.2)	3 (0.9)
American Indian or Alaska Native	1 (0.6)	1 (0.6)	2 (0.6)
Multiple	3 (1.9)	2 (1.2)	5 (1.6)
Other	0 (0.0)	2 (1.2)	2 (0.6)
Not reported	0 (0.0)	1 (0.6)	1 (0.3)
Ethnicity, n (%)			
Hispanic or Latino	25 (16.0)	28 (17.3)	53 (16.7)
Not Hispanic or Latino	131 (84.0)	134 (82.7)	265 (83.3)

Source: AXS-05-MDD-301 Clinical Study Report, Table 14.1.3.3., page 144.
Abbreviations: mITT, modified intent-to-treat; SD, standard deviation

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Baseline characteristics for the mITT population were generally similar between treatment groups. Mean baseline scores for the MADRS total, CGI-S, QIDS-SR-16, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form, and Sheehan Disability Scale were similar for the AXS-05 and placebo groups. The mean MADRS total score at baseline was 33.6 for the AXS-05 group and 33.2 for the placebo group. The mean CGI-S score was 4.6 for both the AXS-05 and placebo groups. See Table 26.

Table 26. Study MDD-301: Baseline Clinical Characteristics, mITT Population

Baseline Assessment	AXS-05 (N=156)	Bupropion (N=162)
MADRS total score		
Mean (SD)	33.6 (4.43)	33.2 (4.36)
Minimum, maximum	26, 48	25, 46
CGI-S score		
Mean (SD)	4.6 (0.59)	4.6 (0.57)
Minimum, maximum	4, 6	4, 6
QIDS-SR-16 score[a]		
Mean (SD)	16.3 (3.79)	15.9 (4.05)
Minimum, maximum	4, 27	7, 25
Q-LES-Q-SF (% of maximum)[b]		
Mean (SD)	34.0 (13.46)	36.0 (12.29)
Minimum, maximum	0.0, 76.8	10.7, 66.1
Sheehan Disability Scale total score[b]		
Mean (SD)	20.3 (5.96)	19.3 (5.82)
Minimum, maximum	2, 30	2, 30

Source: AXS-05-MDD-301 Clinical Study Report, Table 10, page 55.
[a] Independent assessor used the QIDS-SR-16 score at screening to confirm eligibility.
[b] These were secondary efficacy endpoints.
Abbreviations: CGI-S, Clinical Global Impression – Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; QIDS-SR-16, Quick Inventory of Depressive Symptomatology (16-Item); Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; SD, standard deviation

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance, measured by biweekly percentage of expected drug administration as well as by measuring concentrations of bupropion, dextromethorphan, and their metabolites, was similar in the AXS-05 group and placebo group and remained >80% throughout the study.

Concomitant medication use was reported in 203 subjects, 59.9% in the AXS-05 group and 64.6% in the placebo group. The most frequently reported concomitant medications were anti-inflammatory and antirheumatic drugs, vitamins, and analgesics. Concomitant antidepressant use was rare, with one subject taking duloxetine and one subject taking fluoxetine concomitantly; both subjects were in the AXS-05 group.

Efficacy Results – Primary Endpoint

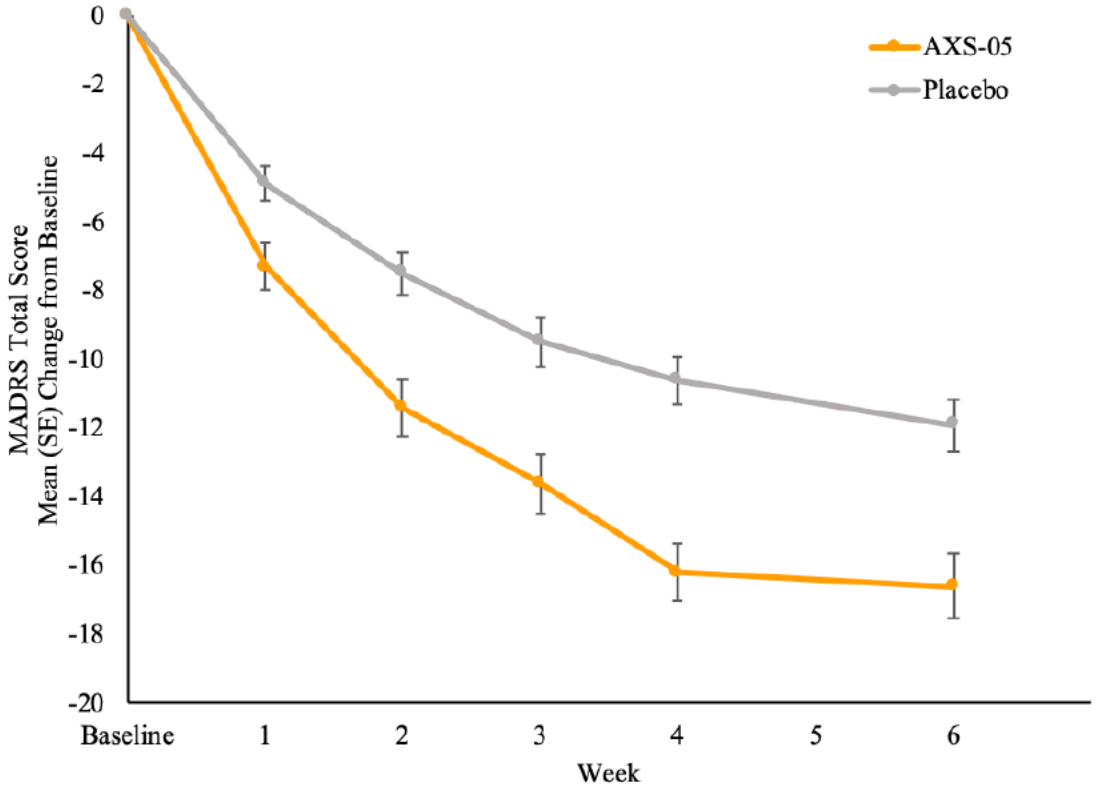
The mean MADRS score at baseline was 33.6 in the AXS-05 group and 33.2 in the placebo group. AXS-05 was statistically significantly superior to placebo at Week 6 (p=0.002; 95% CI: 1.39, 6.36) where the least-squares mean change from baseline in MADRS total score was 15.91 in the AXS-05 group and 12.04 in the placebo group, with a difference of 3.87 between treatment groups. See Table 27 and Figure 7.

Table 27. Primary Analysis of Primary Efficacy Endpoint: MADRS Total Score Change From Baseline at Week 6 in mITT, Study MDD-301

Parameter	AXS-05 (N=156)	Placebo (N=162)
Mean baseline score (SD)	33.6 (4.43)	33.2 (4.36)
Mean score at Week 6 (SD)	17.3 (12.83)	21.1 (10.24)
LS mean change from baseline (SE)	15.91 (0.92)	12.04 (0.86)
Placebo-subtracted difference[1] (SE)	3.87 (1.26)	
95% CI	(1.39, 6.36)	
p-value	0.002	

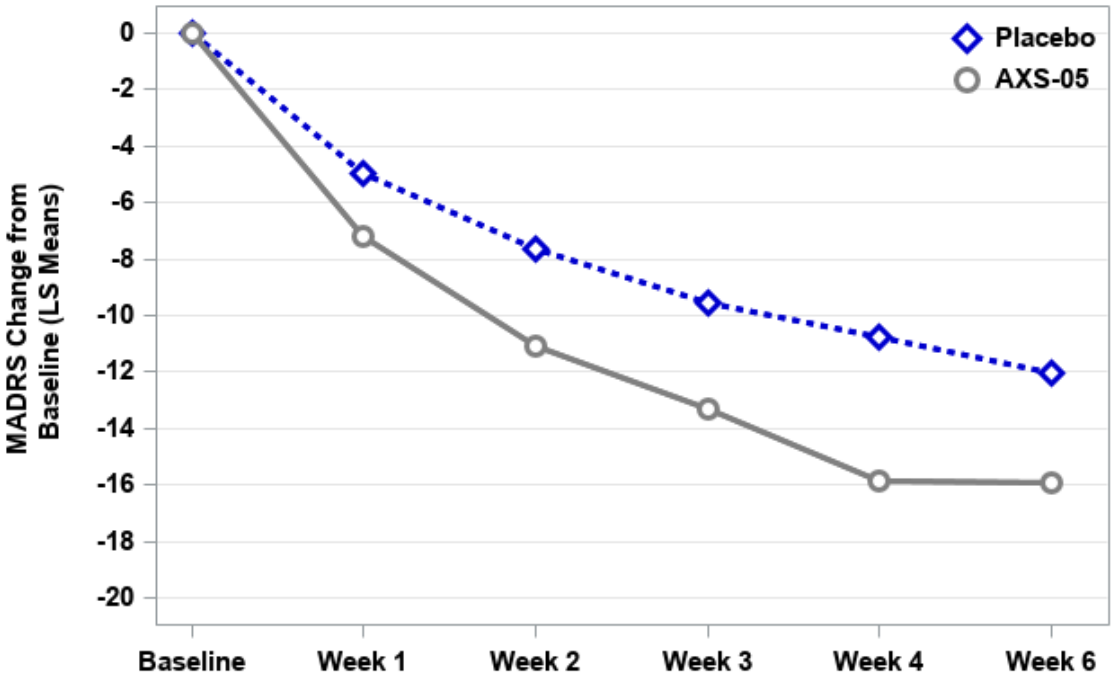
Source: Tables 14.2.1.1 and 14.2.1.2 (Clinical Study Report; pages 165-166), verified by the FDA Biometrics Reviewer.
[1] Difference (drug minus placebo) in least-squares mean change from baseline computed using mixed-effect model repeated measure method (MMRM) with unstructured covariance matrix
Abbreviations: CI, confidence interval; FDA, Food and Drug Administration; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; SD, standard deviation; SE, standard error

Figure 7. Applicant's Mean Change From Baseline in MADRS Total Score (mITT; MMRM) Study MDD-301



Source: Applicant's Figure 3 (Clinical Study Report; page 58).
Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; MMRM, mixed-effects model repeated measure method; SE, standard error

Figure 8. FDA's LS Mean Change From Baseline in MADRS Total Score (mITT; MMRM) Study MDD-301



Number of Patients						
Placebo	161	162	159	159	157	150
AXS-05	156	155	142	132	128	124

Source: FDA Biometrics Reviewer's analysis.
Abbreviations: LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; MMRM, mixed-effect model repeated measure method; SE, standard error

The Statistical Reviewer confirmed the Applicant's efficacy findings (Clinical Study Report; Table 12, page 58). The combination drug, AXS-05, was statistically significantly superior to placebo in the mean change from baseline in MADRS total score at Week 6, with a least-squares mean treatment differences to placebo of 3.87 (1.26) (p=0.002) (Figure 8).

Results of the sensitivity analysis for missing data (random replacement method and tipping point analyses; CSR, pages 60 to 61) were consistent with the primary efficacy results.

Statistical Reviewer's Note: Upon the recommendation of OSI, a sensitivity analysis with regard to the efficacy data from Dr. Hassman's site (Site #823) was conducted. The sensitivity analysis, by removing efficacy data from Site #823, did not change the overall efficacy conclusion for Study MDD-301 (3.01 [1.30]; p=0.02; 95% CI: 0.45, 5.56).

Data Quality and Integrity

Page 41 of the CSR states: "Accurate and reliable data collection were ensured by verification and cross check of the CRFs against the investigator's records by the study monitor (source document verification) and by the maintenance of a drug-dispensing log by the investigator. Collected data were entered into a computer database and subject to electronic and manual quality assurance procedures."

Two clinical sites participating in this study were audited by the Agency's Office of Scientific Investigations (Section 4.1). No areas of concern regarding data quality or integrity were discovered during these investigations.

Efficacy Results – Secondary and Other Relevant Endpoints

Adjusting for multiplicity using the fixed sequence approach, treatment with AXS-05 resulted in a favorable outcome at an earlier time than Week 6 based on the first key secondary endpoint, change from baseline in MADRS total score at Week 2 (p<0.001; 95% CI: 1.40, 5.47) with a least-squares mean difference of 3.44. At Week 2, the least-square mean reduction was 11.09 for AXS-05 and 7.66 for placebo. Although the second secondary endpoint in the hierarchy, percentage of subjects achieving remission (MADRS total score of ≤10) at Week 2 was positive with a least-squares mean difference 9.4 (p=0.013, CI: 1.96, 16.8), FDA does not accept it as a key secondary endpoint. The third key secondary endpoint in the hierarchical order, change from baseline in MADRS total score at Week 1, also achieved statistical significance (p=0.007; 95% CI: 0.60, 3.86) with a least-squares mean difference of 2.23 (Table 28).

Statistical Reviewer's Note: The reviewers conveyed to the Applicant during the protocol review (SN 34, October 22, 2019) that remission or responder rate endpoints cannot be considered as key secondary endpoints. Also pointed out were the limitations of the strength of evidence, in terms of support for regulatory claims, if significant findings from key secondary endpoints were derived from a single study.

Clinical Reviewer's Comment: Study MDD-301 only compared the onset of effect of AXS-05 to that of placebo. The study did not compare the onset of effect of AXS-05 to that of bupropion.

Table 28. Analysis of Key Secondary Efficacy Endpoints: MADRS Total Score Change From Baseline at Week 2 and Week 1 in mITT Population, Study MDD-301

Key secondary Endpoint	Parameter	AXS-05 (N=156)	Placebo (N=162)
	Mean baseline score (SD)	33.6 (4.43)	33.2 (4.36)
First key secondary endpoint	Mean score at Week 2 (SD)	22.3 (10.64)	25.5 (8.89)
	LS Mean change from baseline at Week 2 (SE)	11.09 (0.75)	7.66 (0.72)
	Placebo-subtracted difference[1] (SE)	3.44 (1.03)	
	95% CI	(1.40, 5.47)	
	p-value[2]	<0.001	
Third key secondary endpoint	Mean score at Week 1 (SD)	26.3 (8.60)	28.2 (7.52)
	LS Mean change from baseline at Week 1 (SE)	7.20 (0.59)	4.97 (0.58)
	Placebo-subtracted difference[1] (SE)	2.23 (0.83)	
	95% CI	(0.60, 3.86)	
	p-value[2]	0.007	

Source: Tables 14.2.1.1 and 14.2.1.2 (Clinical Study Report; pages 165-166).
[1] Difference (drug minus placebo) in least-squares mean change from baseline computed using mixed-effect model repeated measure method (MMRM) with uncovariance structure
[2] nominal p-value
Abbreviations: CI, confidence interval; LS, least-squares; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; MMRM, mixed-effect model repeated measure method; SD, standard deviation; SE, standard error

Dose/Dose Response

Evaluation of dose response was not conducted. AXS-05 has been developed as a fixed-dose tablet with the doses of bupropion and dextromethorphan determined during phase 1 studies. The Applicant intends to market only a single-dose combination: bupropion HCl 105 mg + dextromethorphan HBr 45 mg.

Durability of Response

Durability of response was not evaluated in the short-term clinical trials. Durability also was not evaluated in the long-term safety trial, which did not include a placebo arm or a randomized withdrawal period.

Persistence of Effect

Persistence of effect was not evaluated in any of the AXS-05 clinical trials.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

See Efficacy Results – Secondary and Other Relevant Endpoints

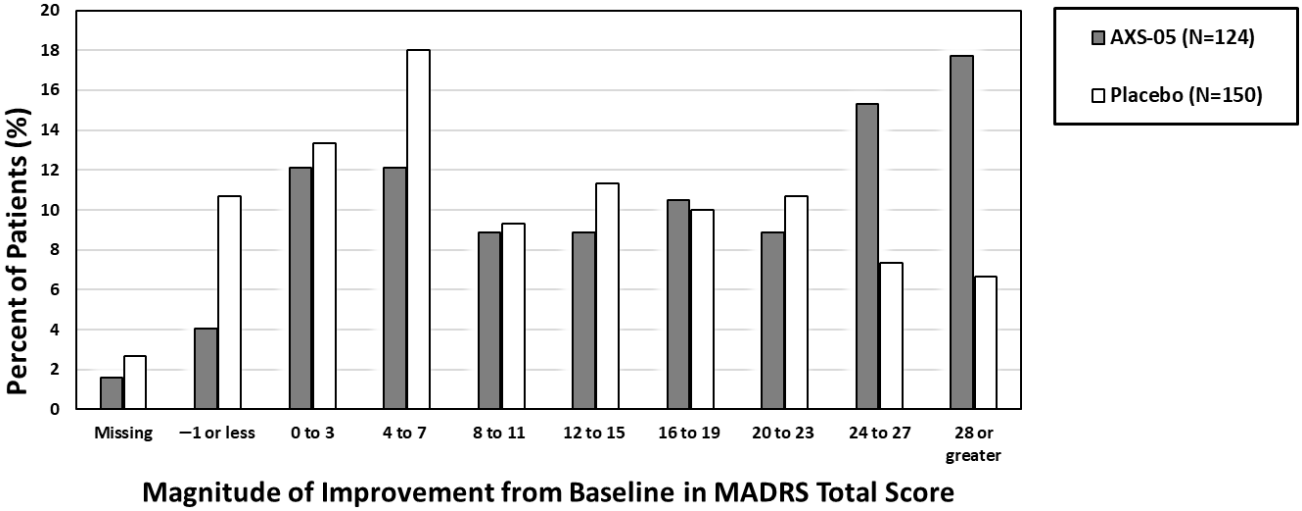
. No exploratory COA (PRO) endpoints were defined for this study.

Additional Analyses Conducted on the Individual Trial

Distribution of Proportion of Response and Empirical Cumulative Distribution for the Primary Endpoint

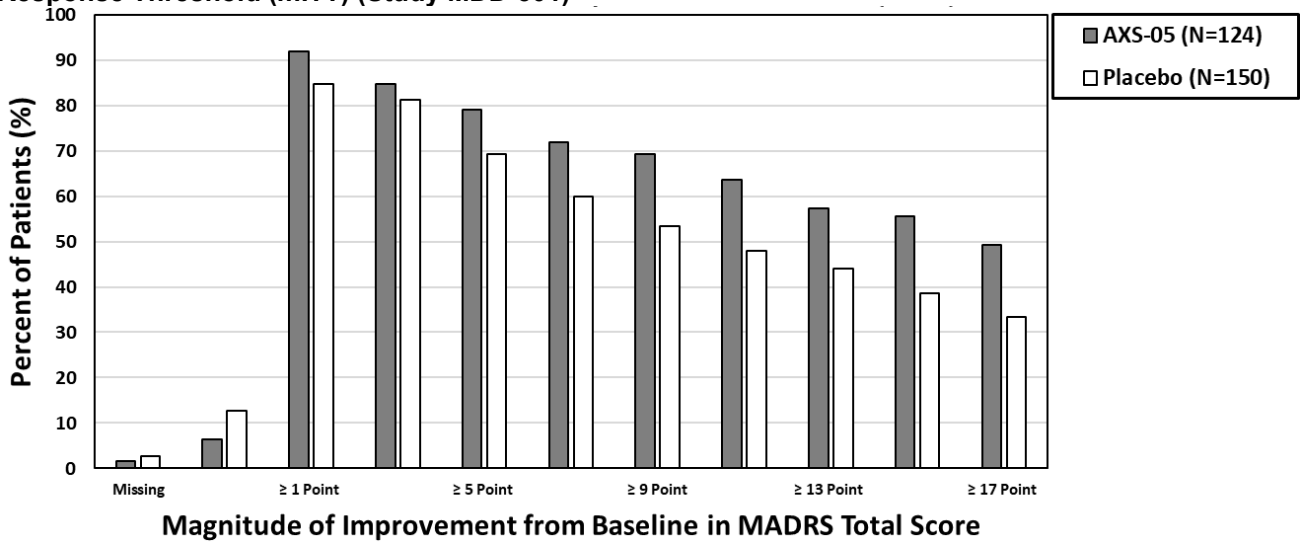
Figure 9 shows the distribution of the magnitude of change in MADRS total score for completers. Again, proportions of dropouts are presented at left. Compared to the placebo group, the proportion of subjects achieving improvement in the AXS-05 group generally increases as the magnitude of MADRS threshold increases. The cumulative distribution in Figure 10 shows that more subjects in AXS-05 group showed improvement at various predefined MADRS thresholds, defined as arbitrary clinical improvement above a certain treatment difference cutoff point.

Figure 9. Percentage of Patients With a Specified Magnitude of MADRS Total Score Improvement at Week 6 (mITT) (Study MDD-301)



Source: FDA Biometrics Reviewer's plot.
Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat

Figure 10. Percentage of Response (MADRS Total Score) for Each Treatment Group at Week 6 by Response Threshold (mITT) (Study MDD-301)



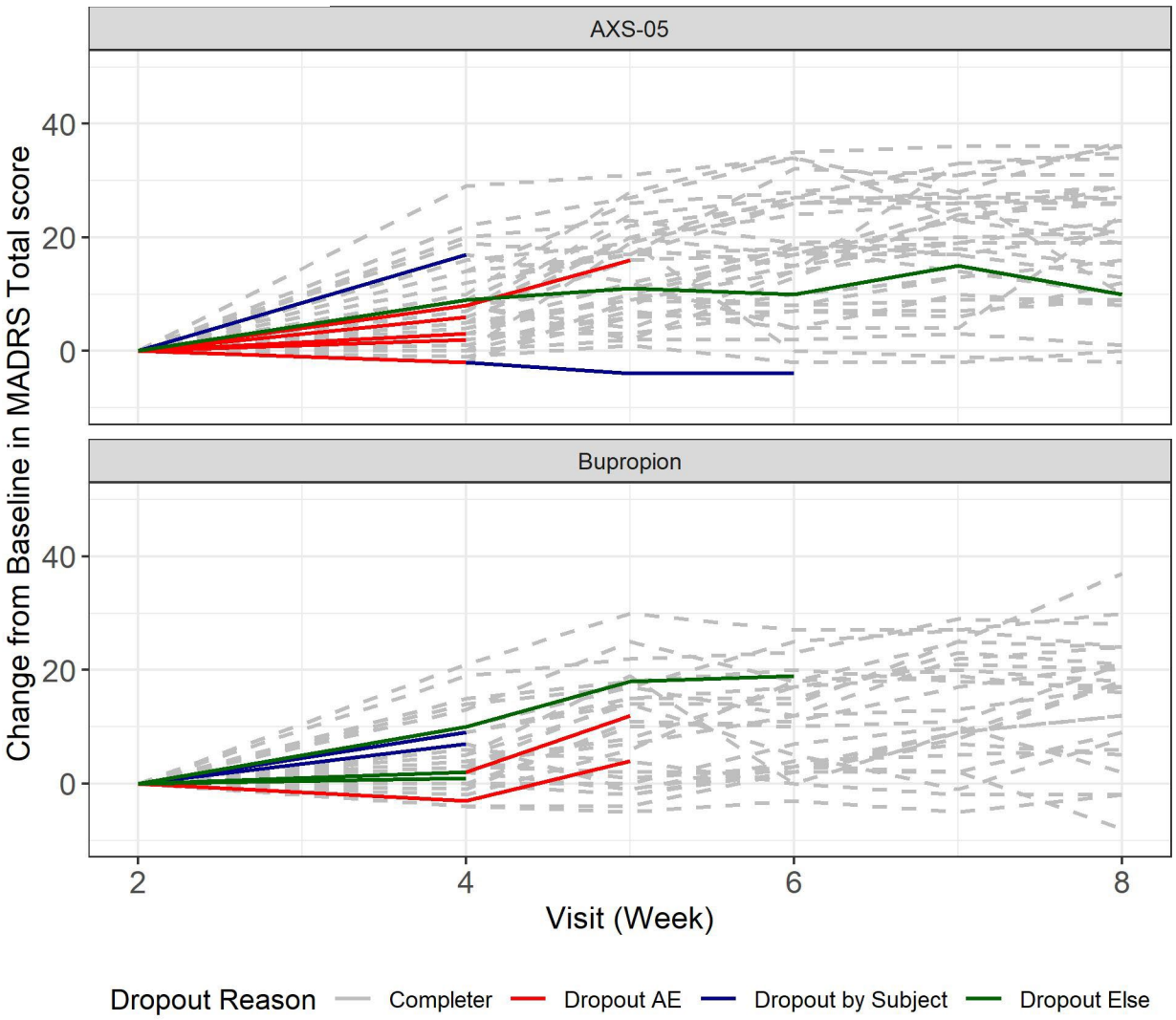
Source: FDA Biometrics Reviewer's plot.
Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat

8.1.3. Missing Data Patterns (Studies MDD-201 and MDD-301)

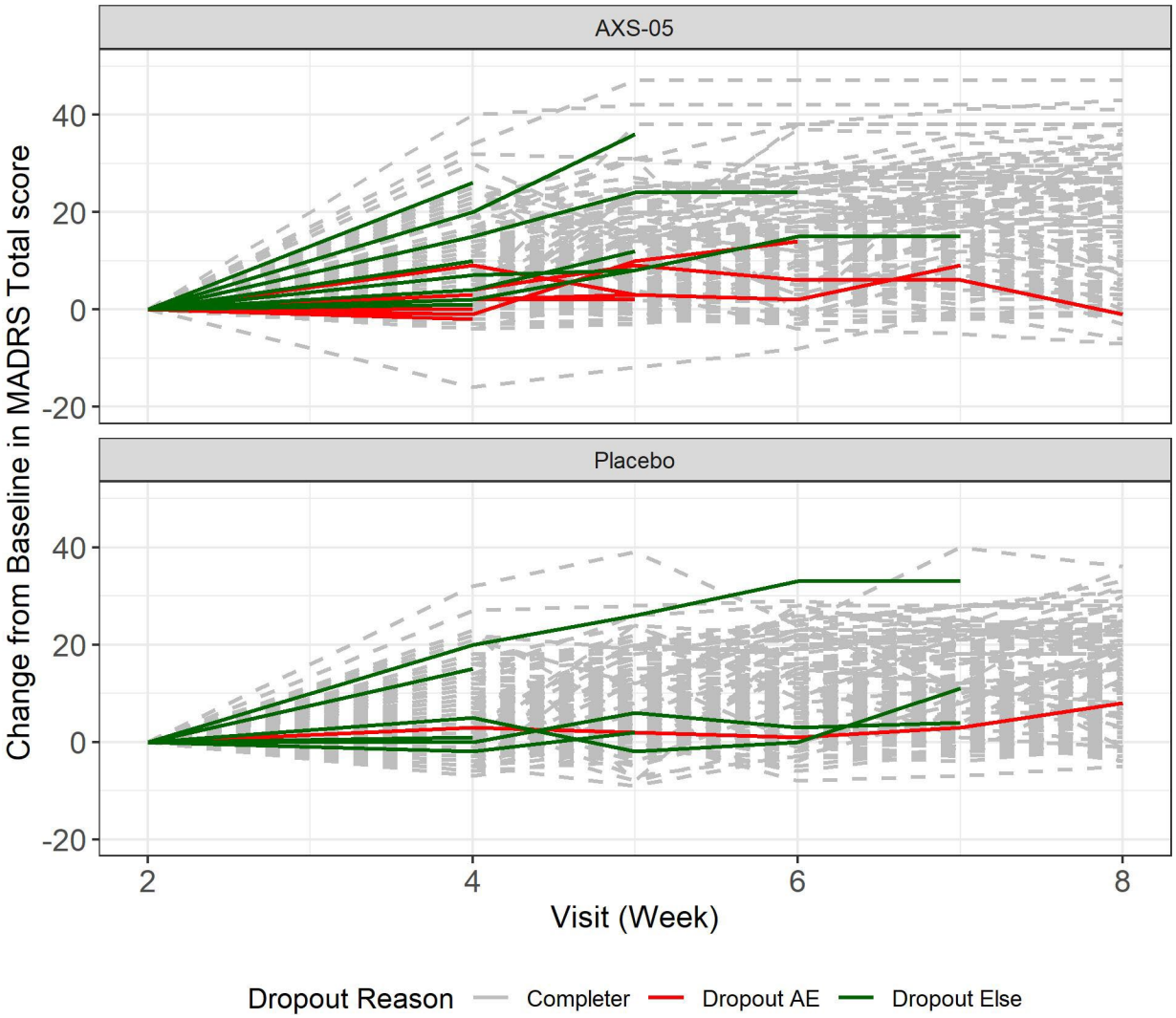
The reviewer assessed the plausibility of the MAR assumption in the MMRM model using visual inspection for Studies MDD-201 and MDD-301. The missing data pattern plots in Figure 11 suggest that subjects with missing MADRS total scores (due to AE, subjects dropping out due to individual reasons, or other reasons) would have evolved with MADRS outcome trajectories like those with similar subjects in the same respective treatment groups.

Figure 11. Missing Data Pattern (Studies MDD-201 and MDD-301)

Study MDD-201



Study MDD-301



Source: FDA Biometrics Reviewer's plot.
Abbreviations: AE, adverse event; MADRS, Montgomery-Åsberg Depression Rating Scale

8.1.4. Assessment of Efficacy Across Trials

Subgroup Analysis: Gender, Race, Age

The FDA Biometrics Reviewer conducted an exploratory subgroup analysis by race, gender, and age. For each study, the primary efficacy analysis model was used to investigate if treatment effects appeared consistent across subgroups. A sandwich variance estimator wasn't employed in the model.

In Study MDD-201, all the subjects fell in the age group ≤65 years (100%), and the majority were female (63.2%) and white (63.2%). Generally, there were no substantial differences between whites and non-whites, but females had numerically greater improvement than males for AXS-05 compared to placebo. See Table 29 (race) and Table 30 (gender).

In Study MDD-301, all the subjects fell in the age group ≤65 years (100%), the majority were females (66.6%), and there were slightly more whites (55.2%) than non-whites. Males had numerically better improvement than females in AXS-05 compared to placebo. See Table 31 (race) and Table 32 (gender).

Study MDD-201

Table 29. Study MDD-201 Subgroup Analysis by Race: MADRS Total Score (FDA mITT)

	Baseline		LS Mean Change From Baseline			LS Mean Difference From Placebo	
Treatment Group	N	Mean (SD)	N	Mean	SE	Mean	SE
Bupropion							
White	18	31.3 (4.37)	20	14.0	2.18	--	--
Non-white	15	33.7 (4.27)	17	13.1	2.35	--	--
AXS-05							
White	30	31.6 (4.40)	30	17.7	1.69	3.7	2.76
Non-white	13	32.5 (3.13)	13	16.1	2.53	3.1	3.46

Source: FDA Biometrics Reviewer's results.
Abbreviations: FDA, Food and Drug Administration; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; SD, standard deviation, SE, standard error

Table 30. Study MDD-201 Subgroup Analysis by Gender: MADRS Total Score (FDA mITT)

	Baseline		LS Mean Change From Baseline			LS Mean Difference From Placebo	
Treatment Group	N	Mean (SD)	N	Mean	SE	Mean	SE
Bupropion							
Male	10	33.1 (5.40)	10	12.8	2.73	--	--
Female	23	32.1 (4.03)	23	13.9	1.99	--	--
AXS-05							
Male	18	30.6 (4.12)	18	15.8	2.02	3.1	3.41
Female	25	32.8 (3.80)	25	18.3	1.92	4.4	2.77

Source: FDA Biometrics Reviewer's results.
Abbreviations: FDA, Food and Drug Administration; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; SD, standard deviation, SE, standard error

Study 301

Table 31. Study MDD-301 Subgroup Analysis by Race: MADRS Total Score (mITT)

	Baseline		LS Mean Change From Baseline			LS Mean Difference From Placebo	
Treatment Group	N	Mean (SD)	N	Mean	SE	Mean	SE
Placebo							
White	91	33.2 (4.28)	83	12.5	1.11	--	--
Non-white	70	33.1 (4.50)	67	11.4	1.35	--	--
AXS-05							
White	84	33.2 (4.15)	66	16.4	1.22	3.8	1.65
Non-white	72	34.1 (4.71)	58	15.4	1.40	3.9	1.95

Source: FDA Biometrics Reviewer's results.
Abbreviations: FDA, Food and Drug Administration; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; SD, standard deviation, SE, standard error

Table 32. Study MDD-301 Subgroup Analysis by Gender: MADRS Total Score (mITT)

	Baseline		LS Mean Change From Baseline			LS Mean Difference From Placebo	
Treatment Group	N	Mean (SD)	N	Mean	SE	Mean	SE
Placebo							
Male	45	33.0 (4.87)	42	10.3	1.56	--	--
Female	116	33.2 (4.17)	108	12.8	1.03	--	--
AXS-05							
Male	61	33.2 (4.30)	46	15.6	1.41	5.3	2.10
Female	95	33.9 (4.51)	78	16.0	1.20	3.2	1.58

Source: FDA Biometrics Reviewer's results.
Abbreviations: FDA, Food and Drug Administration; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; SD, standard deviation, SE, standard error

Additional Efficacy Considerations

No additional efficacy considerations were identified during this review.

8.1.5. Integrated Assessment of Effectiveness

AXS-05 is a fixed-dose combination drug comprised of dextromethorphan 45 mg and bupropion hydrochloride 105 mg, proposed to be administered by mouth twice daily. Bupropion is the active component of the listed drug Wellbutrin SR, which is approved for the treatment of MDD. The labeled usual adult target dose of Wellbutrin SR is 150 mg twice daily, and the maximum labeled effective dose is 200 mg twice daily. The Applicant proposes that dextromethorphan, as an NMDA antagonist, may exert its own antidepressant effect, but when given on its own would be metabolized too quickly by CYP2D6 to be able to exert this effect. The Applicant proposes that bupropion, as a CYP2D6 inhibitor, will prolong the exposure to dextromethorphan sufficiently so that dextromethorphan may contribute its own antidepressant effect. Assessment of the effectiveness of AXS-05 is complicated by the fact that each component could potentially contribute an antidepressant effect to the combination. The controlled trials submitted with the NDA were reviewed to assess whether AXS-05 is an effective antidepressant and whether each component makes a contribution to the overall effect.

Studies MDD-301, MDD-201, and 301 have some similarities in design. All had a 6-week treatment duration after randomization, and all used the same dose of study drug in the AXS-05 arm. The three studies also had important differences in design, including treatment comparator, diagnostic inclusion criteria, and primary endpoint selection. These factors necessitate taking a careful approach to integrating the efficacy data from the individual studies in order to assess the effectiveness of AXS-05 for the treatment of MDD.

Study MDD-301 was an adequate and well-controlled trial and was positive. The Division of Psychiatry accepted the Applicant's proposal for the study to proceed with no bupropion arm and only an AXS-05 arm and a placebo arm. This decision was made under the assumption that Study MDD-201 had demonstrated that dextromethorphan contributed to the antidepressant effect of AXS-05 and that it was unnecessary to demonstrate its contribution in a second study.

Study 301 was a negative trial enrolling patients with TRD, a patient population different from the population enrolled in either Study MDD-201 or Study MDD-301. Although all patients with TRD also met the criteria for the diagnosis of MDD, patients with TRD have symptoms that are more difficult to treat. This could help to explain why a treatment effect was not demonstrated in Study 301. A possible additional factor is that the dose of bupropion used in the bupropion arm of the study (150 mg twice daily) was 43% higher than that used in the AXS-05 arm (105 mg twice daily). Prior to randomization, all patients received open-label bupropion (150 mg twice daily) for 6 weeks. For subjects randomized to receive AXS-05, the decrease in bupropion dose after randomization may have made it difficult for the combination drug to demonstrate a larger treatment effect than that seen in subjects randomized to continue receiving bupropion 150 mg twice daily. Regardless of the reason, the failure of Study 301 precluded the submission of this study as an additional positive trial in a population of patients who met criteria for the diagnosis of MDD (as well as the criteria for TRD).

Study MDD-201, initially conceived as an exploratory phase 2 study of the safety and tolerability of AXS-05 in subjects with MDD, was markedly smaller than the other two controlled trials. This study included two treatment arms: AXS-05 twice daily and bupropion SR 105 mg twice daily. The daily bupropion dose in each arm was lower than the labeled usual adult target dose for Wellbutrin SR. However, because each treatment arm included the same dose of bupropion, this study allowed for the assessment of the independent contribution of dextromethorphan to the therapeutic effect of the combination product.

The efficacy analysis population pre-specified in the SAP was the mITT population, defined as subjects who were randomized, took at least one dose of study drug, and had at least one post-baseline assessment. This study was positive on the Applicant's pre-specified primary efficacy endpoint (mean change in MADRS total score from baseline to each time point from Week 1 to Week 6). The Agency identified four subjects who should not have been included in the Applicant's pre-specified efficacy analysis population, all of whom were randomized to receive the comparator treatment (bupropion). Of the four subjects, one did not receive study drug and three had no post-baseline efficacy assessments (see Section 8.1.2.1).

With regard to the primary efficacy endpoint in Study MDD-201, the Agency communicated to the Applicant at the pre-NDA meeting held on June 11, 2020, that the Agency has more typically used the mean change in MADRS score from baseline to the end of treatment, without averaging at the intermediate time points ("non-averaging endpoint"), to support regulatory approval of an antidepressant. (b) (4) Using the non-averaging endpoint, Study MDD-201 would be negative if the four subjects were appropriately removed from the mITT population. However, using the Applicant's pre-specified efficacy endpoint, Study MDD-201 remains positive even if the four subjects mentioned above are removed from the mITT population. Using a study endpoint that averages the change from baseline across multiple intermediate time points could overestimate the overall treatment effect if drug-treated subjects tended to show improvement compared to comparator-treated subjects early in the study. In this case, the larger treatment difference at early timepoints is consistent with the rationale for the combination product. The team concluded that the statistically significant

improvement on the Applicant's pre-specified primary efficacy endpoint, along with the magnitudes of separation between AXS-05 and bupropion on MADRS scores at early time points in the study, were sufficient to demonstrate the contribution of dextromethorphan to AXS-05 as well as provide supportive evidence for the effectiveness of AXS-05.

To summarize, Study MDD-301 was an adequate and well-controlled trial that demonstrated the efficacy of AXS-05 compared to placebo in the treatment of MDD. The contribution of the dextromethorphan component was demonstrated by Study MDD-201, a phase 2 study that demonstrated statistically significant separation of AXS-05 from bupropion on the Applicant's pre-specified primary efficacy endpoint. The contribution of the bupropion component is evident, in part, because dextromethorphan could not have had an antidepressant effect on its own at this dose without the inhibition of CYP2D6 by bupropion, given its otherwise rapid metabolism by CYP2D6 as shown by PK data in Study AXS-05-101 (Figure 12). Additionally, bupropion is an approved antidepressant.

In conclusion, substantial evidence of effectiveness of AXS-05 for the treatment of MDD has been demonstrated by one adequate and well-controlled clinical trial, Study MDD-301, plus confirmatory evidence. In addition, the Applicant has demonstrated that each component of the fixed-dose combination drug contributes to the claimed effects.

The benefits of AXS-05 are expected to be clinically meaningful to patients. The clinical research literature suggests that a 6- to 9-point reduction in MADRS total score is considered to be clinically meaningful to patients with MDD. In Study MDD-301, over 70% of subjects receiving AXS-05 experienced a ≥7-point reduction of MADRS total score by Week 6 (Figure 10). Further, the statistically significant differences between AXS-05-treated and placebo-treated subjects at Week 1 and Week 2 (key secondary endpoints) suggest that patients may experience a clinically meaningful improvement in symptoms more quickly than the 2- to 4-week time frame that is typical for most approved antidepressant medications.

To present the efficacy evidence in product labeling, the results of Study MDD-301 will be described in both tabular format as well as a time course figure. The supportive results of Study MDD-201 will be described in Section 14 in paragraph format. The proposed product labeling will be discussed in more detail in Section 11, Labeling Recommendations.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review was focused on analyzing data from the three controlled trials and the long-term, open-label safety trial (see Section 7.1, Table 6). Phase 1 trials of AXS-05, including dose-ranging studies, drug-drug interaction studies, a food-effect study, and studies in renal impairment and hepatic impairment were not included in this review because of the small sizes of the study populations and the use of doses of the two drug components that were sometimes higher than the doses proposed for marketing. Bupropion doses used in the phase 1 trials ranged from 75 mg to 150 mg and dextromethorphan doses ranged from 30 mg to 60 mg. There were no deaths or serious adverse events in any of the phase 1 trials. The most common

adverse events in the phase 1 trials were headache, dizziness, nausea, and insomnia. This list is very similar to the list of most common adverse events observed in the three controlled trials and the open-label safety trial.

Some safety analyses are based on pooled datasets created by the Applicant to combine safety data from multiple trials. The pooled dataset of controlled trials includes data from subjects who participated in Studies MDD-201, MDD-301, and 301. This pooled dataset includes trials that all had a 6-week duration and that all used the same dose of AXS-05 in the active drug arm. This pooling is useful for comparing adverse events across treatment arms. It is important to note that the doses of bupropion are not the same in the two studies that included a bupropion arm. In Study MDD-201, the dose in the bupropion arm was 210 mg/day. This was the same as the dose of bupropion taken by subjects in the AXS-05 arm. In Study 301, the dose in the bupropion arm was 300 mg/day. Thus, subjects in the bupropion arm received a higher dose of bupropion than those in the AXS-05 arm. Because Study 301 was a larger study than Study MDD-201, the pooled dataset compares subjects who were taking 210 mg bupropion plus 90 mg dextromethorphan daily to subjects who were mostly taking 300 mg bupropion daily. This pooling would appear to give bupropion a comparative disadvantage, as one might expect that subjects taking the higher bupropion dose would be more susceptible to adverse effects of bupropion. However, the safety analyses presented later will show that AXS-05 demonstrated a higher frequency of adverse events for almost all preferred terms used to code AEs in the controlled trials, even though it was being compared to a higher dose of bupropion than the bupropion dose included in AXS-05.

The pooled dataset of overall AXS-05 exposure includes data from subjects who participated in the controlled trials and in the long-term safety trial, Study 303. This pooling is useful for analysis of SAEs and AESIs because these adverse events occurred in small numbers of subjects.

Whether the safety analyses are based on specific studies or pooled data is described in the text.

8.2.2. Review of the Safety Database

Overall Exposure

At the time of submission of the application (February 21, 2021), 1114 subjects had been exposed to at least one dose of AXS-05 in the three controlled trials and the open-label trial that are the focus of this safety review. This includes 364 subjects who received AXS-05 in the three controlled trials, 611 subjects who entered the open-label Study 303 as newly treated patients, and 139 subjects who entered the open-label Study 303 after participating in the control arm of a previous AXS-05 trial.

An additional 492 subjects have been exposed to AXS-05 in other clinical trials. These include 52 subjects who entered the open-label trial AXS-05-TRD-202 as newly treated patients, 281 subjects who participated in phase 1 trials, and 159 subjects who participated in Study AXS-05-AD-301 evaluating AXS-05 for the treatment of agitation associated with Alzheimer disease. Thus, a total of 1606 subjects across all clinical trials had been exposed to at least one dose of

AXS-05 at the time of submission of the application.

Submitted Trials Contributing Safety Data Only

Two clinical trials submitted with the application did not provide data in support of efficacy of AXS-05 but did provide safety data.

Study AXS-05-301 (Study 301: ClinicalTrials.gov Identifier NCT02741791)

Study Title

A Randomized, Double-Blind, Active-Controlled Trial to Assess the Efficacy and Safety of AXS-05 Administered Orally to Subjects with Treatment-Resistant Major Depressive Disorder

Study Design Overview

The study was a phase 2/3 trial conducted in subjects with TRD who were experiencing a current major depressive episode (MDE). Subjects received either AXS-05 combination product or bupropion 105 mg alone (active comparator), both dosed twice daily.

The study was divided into three periods:

- Screening period (up to 2 weeks): The inclusion criteria comprised age 18 to 65 years inclusive, absence of any clinically significant physical examination or laboratory findings, meeting the DSM-5 criteria for MDD without psychotic features, and score of ≥18 on the Hamilton Depression Rating Scale (HAMD-17) at screening. Eligible subjects must have had a previous inadequate response (<50% symptom reduction) after an adequate trial of one or two antidepressant treatments (ADTs) as determined by administration of the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (ATRQ). At least one of the ADTs must have been a medication other than bupropion.
- Open-label treatment period (6 weeks): To confirm treatment resistance, all subjects received open-label bupropion 150 mg orally once daily for 1 week and then bupropion 150 mg orally twice daily for the subsequent 5 weeks. Subjects were assessed for response to bupropion at the end of 6 weeks of treatment. Inadequate response was defined as <30% improvement on the MADRS total score compared to baseline at Weeks 3, 5, and 6. Inadequate response was confirmed by an independent rater based on a <30% improvement in the HAMD-17 total score compared to baseline at Week 6. Subjects assessed by the independent rater as adequate responders were discontinued from the study and were referred for follow-up clinical care. Additionally, subjects who were not treatment compliant, as evidenced by the absence of detectable serum or plasma concentrations of bupropion at Week 3, were discontinued from the study and were referred for follow-up clinical care.
- Double-blind treatment period (6 weeks): Treatment-compliant subjects confirmed to have an inadequate response to open-label bupropion treatment were randomized in a 1:1 ratio to either continue bupropion 150 mg twice daily or AXS-05 (bupropion 105 mg + dextromethorphan 45 mg) twice daily. The primary efficacy endpoint was the change in

MADRS total score from randomization to the end of the 6-week double-blind treatment period.

Clinical Reviewer's Comment: As mentioned in Section 8.2.1., the dose of bupropion that subjects in the bupropion arm of the study received was higher than the dose of bupropion that subjects in the AXS-05 arm received. The Applicant's choice of bupropion 300 mg daily as the dose used to confirm treatment resistance during the open-label treatment period is justifiable because this is the recommended target dose for treatment of depression in the Wellbutrin SR label. However, interpretation of the efficacy results of the study may be confounded by the fact that subjects randomized to AXS-05 experienced a reduction in bupropion dose at the time of randomization.

The Schedule of Assessments is provided to show the timing of assessments. See Table 33.

Table 33. Study 301: Schedule of Assessments

	Screening	Period 1 Open-Label Bupropion 6 Weeks				Period 2 Double-Blind Study Drug 6 Weeks				Early Term Visit[11]	1-week Follow-up
		Day 0 (±2)	Day 21 (±2)	Day 35 (±2)	Day 42 (±2) Randomization	Day 49 (±2)	Day 56 (±2)	Day 70 (±2)	EOS Day 84 (±2)		Day 91
Study visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**ET**	**10**
End of week	**-2 to -1[12]**	**0**	**3**	**5**	**6**	**7**	**8**	**10**	**12**		**13**
Study Week					**Baseline**	**1**	**2**	**4**	**6**		**7**
Informed consent	X										
Demographic info	X										
Obtain SID via e-tablets	X										
Inc./Exc. criteria	X	X			X						
Medical, surgical and psychiatric history	X										
Medication history	X										
Physical examination[1]	X								X	X	
ECG	X				X				X	X	
Vital signs[2]	X	X	X	X	X	X	X	X	X	X	X
Height and weight[3]	X				X				X	X	
Laboratory tests[4]	X	X			X				X	X	
CYP2D6 genotyping			X								
PK sample [14]			X						X	X	
Thyroid function test	X										
Urine drug screen and blood alcohol [5]	X	X			X				X		
Pregnancy test[6]	X	X			X				X	X	
Hepatitis serology	X										
SCID-5	X										
Schedule remote independent rater interview	X[7]			X[8]							

	Screening	Period 1 Open-Label Bupropion 6 Weeks				Period 2 Double-Blind Study Drug 6 Weeks				Early Term Visit[11]	1-week Follow-up
		Day 0 (±2)	Day 21 (±2)	Day 35 (±2)	Day 42 (±2) Randomization	Day 49 (±2)	Day 56 (±2)	Day 70 (±2)	EOS Day 84 (±2)		Day 91
Independent rater interview	X[9]				X						
MADRS	X	X	X	X	X	X	X	X	X	X	
ATRQ	X										
QIDS-SR-16	X	X	X	X	X	X	X	X	X	X	
CGI-S (Severity)	X		X		X	X	X	X	X	X	
CGI-I (Improvement)			X		X	X	X	X	X	X	
CPFQ	X	X	X		X	X	X	X	X	X	
BPRS 13 Factor 1 Items	X				X	X	X	X	X	X	
HAM-A	X		X		X		X		X	X	
HAMD-17[10]	X				X				X	X	
SDS	X	X			X		X	X	X	X	
e-C-SSRS	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X
Concomitant meds		X	X	X	X	X	X	X	X	X	X
Study drug dispensed		X	X	X	X	X	X	X			
Study drug compliance			X	X	X	X	X	X	X	X	

ATRQ = (Massachusetts General Hospital) Antidepressant Treatment Response Questionnaire; BPRS = Brief Psychiatric Rating Scale; C-SSRS = Columbia - Suicide Severity Rating Scale CGI-I = Clinical Global Impressions–Improvement; CGI-S = Clinical Global Impressions–Severity; CPFQ = (Massachusetts General Hospital) Cognitive and Physical Functioning Questionnaire; ECG = electrocardiogram; EOS = End of Study; ET = early termination; HAM-A= Hamilton Rating Scale for Anxiety; HAMD-17 = Hamilton Depression Rating Scale - 17 items; Inc./Exc. = inclusion/exclusion; MADRS = Montgomery-Åsberg Depression Rating Scale; PK = pharmacokinetic; QIDS-SR-16 = Quick Inventory of Depressive Symptomatology-Self-Rated; SAFER = Scale for Assessment of Family Enjoyment within Routines; SCID-5 = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; SDS = Sheehan Disability Scale; SID = subject identification; UDS = urine drug screen.

1. A complete physical examination (general appearance; head, ears, eyes, nose, throat; dermatological; abdominal; respiratory; cardiovascular; musculoskeletal; neurological; other) was performed by a licensed physician or health professional licensed to perform physical examinations, (e.g., nurse practitioner) at screening (Visit 1) and Visit 9 or ET.
2. Vital signs, including blood pressure, heart rate, respiratory rate, and oral body temperature, was measured after the subject had been in a seated position for at least 5 minutes.
3. Height was measured only at Visit 1. Weight was assessed at Visits 1, 5, and 9 or ET.
4. Clinical findings upon termination were to be followed until the condition returned to pre-trial status or could be explained as unrelated to study drug. If needed, follow-up visits were to be scheduled.
5. Urine drug screen and blood alcohol were required to be performed at other study visits per investigator's judgment. Subjects with positive urine drug screen at Visit 1 may have been allowed in study depending on circumstances described to the Medical Monitor and a negative repeat UDS was obtained before both Visit 2 and Visit 5.
6. Serum β–human chorionic gonadotropin pregnancy tests were performed at screening (Visit 1) and Visit 5, urine pregnancy tests at Visits 2, 5 and 9 or ET.
7. The site scheduled the first independent remote rater interview at Visit 1, once eligibility was determined (i.e. all site screening assessments conducted first). Interview occurred remotely after Visit 1 but before Visit 2 to obtain results before enrollment. It consisted of the SAFER, ATRQ and HAMD-17 scales. Results from remote interview confirmed or denied whether subject was eligible for enrollment into Period 1, which started at Visit 2.
8. The second independent remote rater interview was scheduled at Visit 4 (which occurred while the subject was on site at Visit 5). This interview confirmed if the subject was an inadequate responder and consisted of the HAMD-17.
9. The screening independent rater interview was completed such that results were available by Visit 2 and before Day 1 of dosing.
10. The HAMD-17 was completed by site rater and independent rater at Visit 1; Only by independent rater at Visit 5 and only site rater at Visit 9 or ET
11. Early Termination Visit completed and subject referred to follow-up clinical care. Subjects were also requested to complete the 1-week Follow-up Visit.

12. The time between Visit 1 to Visit 2 was to be 1 week, however, extension of the one-week time frame was allowed for washout.
13. The clinician obtained only Factor 1 (Reality Distortion) items (Suspiciousness, Hallucinatory Behavior and Unusual Thought Content) in the BPRS.
14. Assessment of compliance

Source: AXS-05-301 Clinical Study Report, Table 3, pages 26-28.

Study Results

A total of 312 subjects was randomized, 156 in each treatment group, comprising the mITT population. Two subjects were randomized to receive AXS-05 but did not receive a dose of study drug and were therefore excluded from all analysis populations. One subject in the bupropion group was excluded from the mITT population due to not having at least one postrandomization efficacy assessment.

The primary efficacy endpoint of the trial, change in total MADRS from baseline to Week 6, was not met. In the mITT population, the mean MADRS total score at baseline was 33.4 points for the AXS-05 group and 33.2 points for the bupropion group. At Week 6, the mean reduction from baseline was 11.43 points for the AXS-05 group and 9.71 points for the bupropion group (p=0.117). See Table 34.

Table 34. Study 301: Change From Baseline in MADRS Total Score by Week, mITT Population

Visit Statistic	AXS-05 (N=154)	Bupropion (N=155)	Difference (AXS-05 Minus Bupropion)	p-Value
Week 1				
LS Mean (SE)	5.19 (0.468)	3.65 (0.467)	1.54 (0.661)	0.020
95% CI	[4.27, 6.11]	[2.73, 4.56]	[0.24, 2.84]	
Week 2				
LS Mean (SE)	7.98 (0.611)	6.17 (0.597)	1.81 (0.854)	0.035
95% CI	[6.78, 9.19]	[5,00, 7.35]	[0.13, 3.49]	
Week 4				
LS Mean (SE)	9.56 (0.676)	8.02 (0.663)	1.54 (0.947)	0.105
95% CI	[8.22, 10.89]	[6.71, 9.32]	[-0.33, 3.40]	
Week 6				
LS Mean (SE)	11.43 (0.786)	9.71 (0.769)	1.73 (1.099)	0.117
95% CI	[9.89, 12.98]	[8.19, 11.22]	[-0.44, 3.89]	

Source: AXS-05-301 Clinical Study Report, Table 11, page 53.
Abbreviations: CI, confidence interval; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; SE, standard error

Study AXS-05-303 (Study 303: ClinicalTrials.gov Identifier NCT04039022)

Study Title

An Open-Label Study to Assess the Long-Term Safety of AXS-05 in Subjects with Major Depressive Disorder

Study Design Overview

The study was designed to evaluate the long-term safety and efficacy of AXS-05 in subjects with a diagnosis of MDD. Both roll-over subjects and de novo subjects were eligible. Roll-over subjects must have completed a prior AXS-05 MDD study (Study MDD-301) or TRD study (Study

301) immediately prior to enrollment. Direct roll-over from Study MDD-201 was not possible because of the duration of time that had passed between the conclusion of Study MDD-201 and the initiation of Study 303. De novo subjects must have met the DSM-5 criteria for MDD without psychotic features and must have had a MADRS total score of ≥25, indicating at least moderately severe depression at the time of entry into the study.

Subjects who met the eligibility criteria received AXS-05 once daily for the first 3 days of treatment and then twice daily for up to 12 months. Subjects returned to the study site every week for 2 weeks, then every 2 weeks for the first 2 months, and monthly thereafter. Safety was assessed at all visits by the incidence of AEs, vital signs, and administration of the C-SSRS. Clinical laboratory examinations, electrocardiograms (ECGs), and physical examinations were also performed at the first study visit and at Months 3, 6, 9, and 12.

At Week 6, subjects who had not previously participated in a study with AXS-05 were assessed for clinical improvement, defined as a ≥25% improvement from baseline in MADRS score. Subjects who did not improve were discontinued from the study and completed early termination assessments during Week 6.

The Schedule of Assessments is provided to show the timing of assessments. See Table 35.

Table 35. Study 303: Schedule of Assessments

Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16 / ETV
Study Day	D1[f]	Wk 1 (± 2d)	Wk 2 (± 2d)	Wk 4 (± 3d)	Wk 6 (± 3d)	Mo 2 (± 7d)	Mo 3 (± 7d)	Mo 4 (± 7d)	Mo 5 (± 7d)	Mo 6 (± 7d)	Mo 7 (± 7d)	Mo 8 (± 7d)	Mo 9 (± 7d)	Mo 10 (± 7d)	Mo 11 (± 7d)	Mo 12 (± 7d)
Informed Consent	X															
Inclusion/Exclusion Criteria	X															
Demographics	X															
Medical History	X															
Physical Examination	X						X			X			X			X
ECG[d]	X						X			X			X			X
Laboratory Tests[b]	X						X			X			X			X
Blood Sample for CYP2D6 Genotyping[h]	X															
Blood Sample for Study Drug Concentrations		X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]
Vital Signs, Height/Weight[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test (females of childbearing potential)	X			X		X	X	X	X	X	X	X	X	X	X	X
SDS	X	X	X	X	X	X	X			X			X			X
MADRS	X	X	X	X	X[g]	X	X			X			X			X
Q-LES-Q-SF	X	X	X	X	X	X	X			X			X			X
CGI-I		X	X	X	X	X	X			X			X			X
CGI-S	X	X	X	X	X	X	X			X			X			X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensation[c]	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Accountability		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: CGI-I = Clinical Global Impression of Improvement; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia - Suicide Severity Rating Scale; D = day; ECG = electrocardiogram; ETV = early termination visit; MADRS = Montgomery-Åsberg Depression Rating Scale; Mo = month; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; SDS = Sheehan Disability Scale; V = visit.

a. Vital signs, including blood pressure, pulse, respiratory rate, and oral body temperature, were measured after the subject had been in a seated position for at least 5 minutes. Weight was measured at each visit and height was only measured at Visit 1.
b. Clinical laboratory tests included hematology, serum chemistry, and urinalysis.
c. Study drug could be re-dispensed, when appropriate.
d. Subjects were to rest in the supine position for at least 2 minutes prior to performing ECG.

e. The first dose was to be taken in clinic. Subject were instructed to take one dose each morning for the next 2 days. On the 4th day of dosing, the subject began twice daily dosing.
f. Day 1 assessments could have taken place over multiple days to ensure safety measurements were reviewed prior to enrollment. Subsequent visits dates were triggered off the date of first dose.
g. Subjects must have had a ≥25% improvement in MADRS at Week 6 to continue participation. Subjects who did not meet the improvement criteria completed the remaining Early Termination assessments.
h. Subjects enrolled prior to Amendment 2 had the genotyping collected at the next study visit.
i Site recorded the date and time of the most recent dose of study drug prior to sample collection.

Source: AXS-05-303 Clinical Study Report, Table 4, pages 23-24.

Controlled Clinical Trial Safety Population, Pooled Dataset

For the Applicant's analyses, the overall safety population was defined as subjects in both the three controlled trials and the open-label trial who received at least one dose of AXS-05. For this review, the phrases "pooled dataset" and "pooled safety population" refer to the dataset resulting from combining data on subjects from the safety populations of only the three controlled trials. In the event of subjects receiving treatment that differed from the treatment assigned according to the randomization schedule, the safety analyses were conducted according to the treatment received rather than according to the randomization group. Table 36 presents the demographics of the controlled clinical trial pooled safety population.

Clinical Reviewer's Comments: The higher percentage of females than males in the pooled safety dataset is consistent with the higher frequency of the diagnosis of MDD in females than in males in the United States.

The United States Census Bureau's most recent estimates of racial and ethnic demographics in the United States are as follows[8]: white, 76.3%; Hispanic or Latino, 18.5%; black or African American, 13.4%; Asian, 5.9%; multiracial, 2.8%; American Indian and Alaska Native, 1.3%; Native Hawaiian and Other Pacific Islander, 0.2%. The percentage of black or African American subjects in the pooled safety dataset (31.0%) is higher than the United States Census Bureau estimate of the percentage of the United States population declaring their race as black or African American. This suggests that safety data from the AXS-05 clinical trials may have some generalizability to the clinical population of patients of African descent in the United States seeking treatment for depression. The representation in the pooled safety dataset of subjects declaring races other than white, black or African American, and of subjects declaring their ethnicity as Hispanic or Latino is very low, leaving much uncertainty about the generalizability of the safety findings to patients of those races and ethnicities.

Table 36. Demographics, Controlled Clinical Trial Safety Population, Pooled Dataset

Characteristic	AXS-05 Pooled (N=364)	Bupropion Pooled (N=204)	Placebo (N=164)	Total (N=732)
Age (years)				
Mean (SD)	42.5 (12.55)	43.6 (12.79)	41.1 (13.78)	42.5 (12.91)
Median	42.0	43.5	40.0	42.0
Minimum, maximum	18, 65	18, 65	18, 65	18, 65
Sex, n (%)				
Female	226 (62.1)	130 (63.7)	117 (71.3)	473 (64.6)
Male	138 (37.9)	74 (36.3)	47 (28.7)	259 (35.4)

[8] United States Census Bureau QuickFacts: 2010-2019 Census. Accessed 8/2/2021 from https://www.census.gov/quickfacts/fact/table/US/PST045219.

Characteristic	AXS-05 Pooled (N=364)	Bupropion Pooled (N=204)	Placebo (N=164)	Total (N=732)
Race, n (%)				
White	219 (60.2)	135 (66.2)	92 (56.1)	446 (60.9)
Black or African American	117 (32.1)	55 (27.0)	55 (33.5)	227 (31.0)
Asian	12 (3.3)	6 (2.9)	8 (4.9)	26 (3.6)
Other	7 (1.9)	3 (1.5)	2 (1.2)	12 (1.6)
Multiple	3 (0.8)	2 (1.0)	3 (1.8)	8 (1.1)
Native Hawaiian or Other Pacific Islander	3 (0.8)	0	2 (1.2)	5 (0.7)
American Indian or Alaska Native	2 (0.5)	3 (1.5)	1 (0.6)	6 (0.8)
Not reported	1 (0.3)	0	1 (0.6)	2 (0.3)
Ethnicity[a], n (%)				
Hispanic or Latino	33 (9.1)	12 (5.9)	28 (17.1)	73 (10.0)
Not Hispanic or Latino	177 (48.6)	36 (17.6)	136 (82.9)	349 (47.7)
Not reported	154 (42.3)	156 (76.5)	0	310 (42.3)

Source: Generated by the Clinical Reviewer.
[a] The percentages of subjects with ethnicity not reported in the AXS-05 and bupropion arms and in the total population are very large because ethnicity was not captured in Study 301.
Abbreviation: SD, standard deviation

Long-Term Trial Safety Population

A total of 876 subjects was enrolled in Study 303, an open-label study in which subjects received up to 12 months of exposure to AXS-05. Subjects entered the long-term safety trial either from one of the three short-term controlled trials or as de novo subjects with MDD who did not participate in a previous AXS-05 trial.

The Applicant defined the primary safety population as subjects who continued beyond Week 6 (n=707) and the overall safety population as all subjects who participated in the study (n=876). This review will analyze safety data from the overall safety population. Table 37 presents the demographics of the overall long-term safety population.

Table 37. Study 303: Demographics, Overall Long-Term Safety Population

	Prior Study Treatment			Newly Treated	
Characteristic	AXS-05 (N=126)	Bupropion (N=25)	Placebo (N=114)	Naïve (N=611)	Total (N=876)
Age, years					
Mean (SD)	43.6 (12.52)	43.5 (14.90)	42.2 (13.84)	42.4 (13.60)	42.5 (13.50)
Median	43	50	42	43	43
Minimum, maximum	18, 65	21, 66	18, 65	18, 65	18, 66
Sex, n (%)					
Female	81 (64.3)	16 (64.0)	82 (71.9)	381 (62.4)	560 (63.9)
Male	45 (35.7)	9 (36.0)	32 (28.1)	230 (37.6)	316 (36.1)

Characteristic	Prior Study Treatment			Newly Treated	Total
	AXS-05 (N=126)	Bupropion (N=25)	Placebo (N=114)	Naïve (N=611)	(N=876)
Race, n (%)					
White	71 (56.3)	15 (60.0)	67 (58.8)	356 (58.3)	509 (58.1)
Black or African American	42 (33.3)	8 (32.0)	34 (29.8)	217 (35.5)	301 (34.4)
Multiple	2 (1.6)	0	1 (0.9)	7 (1.1)	10 (1.1)
Asian	8 (6.3)	2 (8.0)	7 (6.1)	12 (2.0)	29 (3.3)
Not reported	2 (1.6)	0	0	3 (0.5)	5 (0.6)
American Indian or Alaskan Native	0	0	1 (0.9)	2 (0.3)	3 (0.3)
Native Hawaiian or Other Pacific Islander	1 (0.8)	0	2 (1.8)	1 (0.2)	4 (0.5)
Other	0	0	2 (1.8)	13 (2.1)	15 (1.7)
Ethnicity, n (%)					
Hispanic or Latino	16 (12.7)	2 (8.0)	14 (12.3)	119 (19.5)	151 (17.2)
Not Hispanic or Latino	110 (87.3)	23 (92.0)	100 (87.7)	491 (80.4)	724 (82.6)
Not reported	0	0	0	1 (0.2)	1 (0.1)

Source: AXS-05-303 Clinical Study Report, Table 8, page 41.
Abbreviation: SD, standard deviation

Clinical Reviewer's Comment: Notably, 725 subjects (83%) enrolled in the long-term safety trial had not previously been exposed to AXS-05 (114 subjects who entered from the placebo arm of Study MDD-301 and 611 subjects who had not participated in a previous AXS-05 trial). The percentage of subjects who would have already accommodated to adverse effects of either AXS-05 or bupropion at the time of entry into the study should be low.

In the long-term overall safety population, 597 subjects (68.2%) were treated for at least 6 months, and 110 subjects (12.6%) were treated for at least 12 months. See Table 38.

Table 38. Study 303: Summary of Drug Exposure, Long-Term Safety Population

Duration of Exposure	AXS-05 (N=876) n (%)
<6 weeks	121 (13.8)
≥6 weeks	755 (86.2)
≥3 months	666 (76.0)
≥9 months	383 (43.7)
≥12 months	110 (12.6)

Source: NDA 215430 Summary of Clinical Safety, Table 8, page 33.

Adequacy of the Safety Database

Per the ICH E1 Guideline, the safety database should include at least 1500 subjects with short-term exposure to the investigational drug, 300 to 600 subjects with exposure for at least 6 months, and 100 subjects with exposure for at least 12 months. The Applicant's safety database meets the ICH E1 Guideline for subject exposures to the study drug.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant provided original Case Report Forms for all deaths, SAEs, and AEs leading to discontinuation. It appears that adverse events were coded appropriately, based on review of the AE data files for each of the pivotal trials. The organizational structure of the submitted data allowed for adequate review of the safety data.

The Applicant's review of data for Study MDD-201 after database lock revealed that one subject randomized to the bupropion arm of the study was never dosed. The patient was included in the Applicant's primary efficacy analysis dataset but was excluded from the safety dataset.

There were no issues with data integrity or submission quality that had a significant effect on the safety review.

Categorization of Adverse Events

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) to classify events by primary system organ class and preferred term (PT). The MedDRA versions used to code AEs for Studies MDD-201, MDD-301, and 301 were versions 21.0, 22.1, and 22.0, respectively. The MedDRA version used to code AEs for Study 303 was not specified. The Applicant defined a TEAE as an AE that developed or worsened during the on-treatment period. The on-treatment period was defined as the time from first dose of study medication up to X days after the last dose of study medication, where X equals 5 for nonserious AEs and 30 for SAEs.

In addition to reviewing AEs by PT and system organ class, the Clinical Reviewer performed an exploratory analysis using FDA Medical Query version 1.1, which is aligned to MedDRA version 22.0. FDA Medical Query is a set of standardized groupings of similar AE terms designed to assist with the identification of potential safety issues during the review of AE data. The FDA Medical Query groupings are similar to Standardized MedDRA Query groupings produced by MedDRA but are designed with terms and clinical concepts that FDA reviewers encounter frequently.

Routine Clinical Tests

Clinical laboratory analyses were conducted for hematology, chemistry, and urinalysis according to schedules presented in the reviews of Studies MDD-201, MDD-301, 301, and 303. For each continuous laboratory parameter, the baseline, actual value, and change from baseline at last on-treatment assessment were summarized using descriptive statistics. For hematology and chemistry parameters, mean changes from baseline to minimum and maximum postbaseline values (outlier analyses) were also summarized. Markedly abnormal laboratory values were identified using criteria specified in the Statistical Analysis Plan. The Applicant's schedule of laboratory assessments and plan for analysis of laboratory data were acceptable.

8.2.4. Safety Results

Deaths: Controlled Clinical Trials

No deaths occurred in Study MDD-201, Study MDD-301, or Study 301.

Deaths: Long-Term Safety Trial

Two deaths occurred in Study 303 and are detailed below.

Subject (b) (6), Study 303: Aortic Dissection

The subject was a 39-year-old male who had not participated in a prior AXS-05 study. The site attempted to contact the subject by telephone and by mail after he missed a study visit. His mother contacted the study site and reported that the subject died suddenly at home on what would have been Day 143 of the study. The subject's mother verbally gave the cause of death as an aortic dissection tear. The subject had no known risk factors for aortic dissection. Autopsy and toxicology reports are not available. The Investigator and Applicant assessed the subject's death as not related to the study drug.

Clinical Reviewer's Comment: A relationship between the study drug and the subject's death cannot definitively be ruled out. The subject reported no known history of any medical illnesses at the time of entry into the study. His death from aortic dissection raises the question of whether he had any risk factors for aortic dissection, such as uncontrolled hypertension, atherosclerosis, a pre-existing aortic aneurysm, an aortic valve defect, or aortic coarctation. The subject may have had pre-existing aortic pathology but may not have known that he did.

The American College of Cardiology/American Heart Association Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017) defines hypertension as a systolic blood pressure of 130 mm Hg or higher and diastolic blood pressure of 80 mm Hg or higher. The subject's blood pressure readings at Study Visits 1, 2, 3, 4, 5, and 6 were 135/78, 138/87, 149/89, 143/91, 154/97, and 142/96, respectively. This degree of hypertension might not ordinarily have a fatal outcome, but it might for an individual who also has unknown pre-existing aortic pathology.

According to the subject's CRFs, vital signs were not measured at Study Visits 7 and 8, although the Schedule of Assessments in the study protocol indicates that vital signs were scheduled to be checked at every study visit. The subject attended Study Visit 8 on (b) (6). The aortic dissection causing his death occurred on (b) (6).

The subject's cholesterol level was in the normal range at Visit 1. There are no laboratory results for Visit 7, although the Schedule of Assessments indicates that labs were scheduled to be checked at Visit 7. The subject participated in Study 303 for 20 weeks. It is possible that the subject's worsening hypertension over the course of the study was related to exposure to the study drug. Whether AXS-05 might be related to onset and/or worsening of hypertension will be explored further in the sections in this review on and Vital Signs.

Subject (b) (6), Study 303: Unknown Cause of Death

The subject was a 62-year-old male who had not participated in a previous AXS-05 study. The subject attended a final study visit on Day 271 after the Applicant's decision to close the study. The subject elected not to continue the study drug after close of the study. A family member of the subject subsequently informed the site via voicemail that the subject had died on what would have been Day 285 of the study. No other information about the subject's death was provided to the study site. The Applicant assessed the death as not related to the study drug.

Clinical Reviewer's Comment: Any relationship of the study drug to the subject's death is unclear because of the lack of information about the cause of death. However, the occurrence of death 2 weeks after the last dose of study drug mitigates against a causal relationship between the subject's death and the study drug. The possibility of death related to a withdrawal effect is a consideration. However, the evaluation of adverse events in the short-term and long-term clinical trials did not reveal any adverse events that appeared to be related to withdrawal.

Serious Adverse Events: Controlled Clinical Trials

Four SAEs occurred in the controlled clinical trials. Each SAE occurred in one subject. Three of the SAEs occurred in the Study 301, the TRD study.

Clinical Reviewer's Comment: A factor that may have contributed to the higher frequency of SAEs occurring in the TRD study is that subjects with treatment-resistant depression typically have more severe and more disabling symptoms than subjects with major depression and thus may be more likely to have SAEs related to their underlying psychiatric diagnosis.

Subject (b) (6), Study 301: Overdose

The subject was a 48-year-old male in the AXS-05 arm of the study. On Day 10 of the study, he was brought to the emergency room following an overdose of study drug. The quantity of tablets ingested was not known. The subject reported several psychosocial stressors prior to the hospitalization, including his mother and sister being killed in an automobile accident 1 month before his overdose and his apartment burning down 1 day before his overdose. The subject remained in the hospital for 4 days. He was discharged from the hospital on Day 14 of the study. The subject was discontinued from the study as a result of this SAE. The Investigator assessed the SAE as possibly related to the study drug. However, the Applicant assessed the SAE as not related to the study drug in light of the multiple psychosocial stressors preceding the overdose.

Clinical Reviewer's Comment: The narrative included in the Clinical Study Report does not provide much detail about this incident. The narrative does not state whether the patient had a previous history of suicide attempts, nor does it indicate the severity of suicidal ideation at the time of the emergency room evaluation. The narrative states that the subject was responsive and was admitted to the hospital "secondary to concerns about possibility of study drug lowering seizure threshold." This suggests the possibility that the patient might not have been hospitalized if the risk of a lowered seizure threshold was not present. The narrative uses only the term "overdose" to describe the incident and does not use terms such as "suicidal ideation"

or "suicide attempt" anywhere in the text. It is not clear whether the subject's intent in taking more study drug than prescribed was to end his life or to try to relieve his depression more quickly.

Suicidal ideation and suicide attempt are known symptoms of patients with the diagnosis of major depression. In addition, the labels of all antidepressants approved by the FDA include a boxed warning for increased risk of suicidal ideation and behavior. In the AXS-05 controlled trials, AEs of suicidal ideation occurred at rates of 0.5%, 1.0%, and 0.0% in patients treated with AXS-05, bupropion, and placebo, respectively. Thus, it is possible that the study drug was causally related to the SAE of overdose, although the risk appears to be low. The recent psychosocial stressors of the deaths of two family members and loss of housing following a fire may have been important contributors to the subject's overdose.

Subject (b) (6), Study 301: Suicidal Ideation

The subject was a 35-year-old female in the AXS-05 arm of the study. Eight days after completion of the treatment period, she reported suicidal ideation with intent to act. She was hospitalized involuntarily. The narrative states that she had not had any previous similar episodes. She reported that marital issues were the cause of her suicidal ideation. She was discharged from the hospital after 7 days. The Investigator assessed the incident as possibly related to discontinuation of the study drug. The Applicant assessed the incident as not related to the study drug, as the study drug had been discontinued 8 days prior to the incident and the subject reported that psychosocial stressors were the cause of her suicidal ideation.

Clinical Reviewer's Comment: In contrast to Subject (b) (6), Subject (b) (6) reported suicidal thoughts and an intent to act on those thoughts. It is possible that discontinuation of the study drug left her at risk for worsening of depressive symptoms. However, her report of a causal relationship between her suicidal thoughts and a psychosocial stressor adds plausibility to the Applicant's assessment that the SAE of suicidal ideation was not related to discontinuation of the study drug.

Subject (b) (6), Study 301: Migraine

The subject was a 39-year-old female in the AXS-05 arm of the study. On Day 42 of the study, she experienced syncope, a fall, dysarthria, diffuse weakness, leg pain, and headache. She was hospitalized. Echocardiogram, telemetry, computed tomography of the head, and magnetic resonance imaging of the head were normal. She was diagnosed with a migraine headache. She was started on topiramate, and her symptoms resolved by Day 44 of the study. During the hospitalization she was also diagnosed with a urinary tract infection, which was treated with ciprofloxacin. The study drug was discontinued. The Investigator and the Applicant assessed the SAE of migraine as possibly related to the study drug.

Clinical Reviewer's Comment: I agree with the Investigator and the Applicant that this SAE may have been related to the study drug. AEs of headache and migraine have occurred at rates higher than placebo in the bupropion clinical trials. In the AXS-05 controlled trials, AEs of headache occurred at rates of 6.6%, 6.4%, and 3.7% in patients treated with AXS-05, bupropion, and placebo, respectively. Also, in the AXS-05 controlled trials, AEs of migraine occurred at rates

of 0.8%, 0.5%, and 0.0% in patients treated with AXS-05, bupropion, and placebo, respectively. Thus, headaches and migraine both occurred in the controlled trials at higher rates in subjects treated with AXS-05 than in subjects treated with either bupropion or placebo.

Subject (b) (6), Study MDD-301: Pancreatitis

The subject was a 39-year-old male in the AXS-05 arm of the study. He developed abdominal pain on Day 43. The pain worsened over the subsequent 3 days. He was hospitalized on Day 46 and was diagnosed with pancreatitis. He was discharged from hospital on Day 48 of the study. The presence of any risk factors for pancreatitis are not known because the subject refused to give consent for disclosure of his hospital records. The subject was lost to follow-up and for this reason was discontinued from the study. The Investigator and the Applicant assessed this SAE as not related to the study drug.

Clinical Reviewer's Comment: Factors that may have contributed to the onset of pancreatitis are not known because the subject refused to give consent for review of his hospital records. Review of the AE data from the development program did not reveal a pattern of occurrence of pancreatitis related to exposure to AXS-05. Additionally, the pharmacological action of the study drug does not suggest a plausible mechanism for causation of pancreatitis.

Discontinuations Due to Serious Adverse Effects: Controlled Clinical Trials

One subject (0.3%) in the controlled clinical trials had an SAE of overdose that led to discontinuation from the study (Subject (b) (6), Study 301).

Discontinuations Due to Serious Adverse Effects: Long-Term Safety Trials

A total of seven subjects (0.8%) in the long-term safety trial had an SAE that led to discontinuation from the study (Table 39).

Serious Adverse Events: Long-Term Safety Trial

In the overall safety population in Study 303, 21 subjects (2.4%) experienced 22 SAEs. One subject reported two SAEs, chest pain and peripheral artery occlusion. All other SAEs were reported by one subject each; thus, each SAE had a frequency of 0.1%. See Table 39. In the table, columns Relationship, Outcome, and Action Taken reflect assessments and actions reported by the Applicant. The SAEs are numbered to simplify correlating SAEs in the table to the narrative descriptions that follow.

Table 39. Study 303: Treatment-Emergent Serious Adverse Events, Overall Safety Population

System Organ Class		Preferred Term	Subject ID	Sex	Age	Applicant's Assessment of Relatedness	Outcome	Action Taken
Cardiac disorders								
	[1]	Acute myocardial infarction	(b) (6)	F	52	Not related	R/R	Dose not changed
	[2]	Coronary artery disease	(b) (6)	F	45	Not related	R/R	Dose not changed
	[3]	Left ventricular hypertrophy	(b) (6)	F	57	Not related	NR/NR	Drug withdrawn
Eye disorders								
	[4]	Eye inflammation	(b) (6)	F	19	Unlikely	R/R	Drug interrupted
Gastrointestinal disorders								
	[5]	Nausea	(b) (6)	F	41	Not related	R/R	Drug interrupted
General disorders and administration site conditions								
	[6]	Chest pain (plus peripheral artery occlusion)	(b) (6)	F	50	Not related	R/R	Drug interrupted
	[7]	Death	(b) (6)	M	62	Not related	Fatal	Not applicable
Hepatobiliary disorders								
	[8]	Cholelithiasis	(b) (6)	F	47	Not related	R/R	Dose not changed
Infections and infestations								
	[9]	Cellulitis	(b) (6)	F	28	Not related	R/R	Drug interrupted
	[10]	Diverticulitis	(b) (6)	F	63	Not related	R/R	Dose not changed
Injury, poisoning and procedural complications								
	[11]	Fall	(b) (6)	F	62	Not related	R/R	Dose not changed
*	[12]	Road traffic accident	(b) (6)	M	28	Not related	R/R	Drug withdrawn
Musculoskeletal and connective tissue disorders								
	[13]	Intervertebral disc protrusion	(b) (6)	F	45	Not related	R/R	Dose not changed
Neoplasms benign, malignant, and unspecified								
*	[14]	Breast cancer	(b) (6)	F	59	Not related	NR/NR	Drug withdrawn
Nervous system disorders								
*	[15]	Cerebrovascular accident	(b) (6)	F	39	Unlikely	NR/NR	Drug withdrawn
*	[16]	Seizure	(b) (6)	M	24	Possibly	R/R	Drug withdrawn

System Organ Class	Preferred Term	Subject ID	Sex	Age	Applicant's Assessment of Relatedness	Outcome	Action Taken
Psychiatric disorders							
[17]	Depression	(b) (6)	F	23	Not related	R/R	Not applicable
[18]	Mental disorder	(b) (6)	F	54	Unlikely	R/R	Drug withdrawn
* [19]	Suicidal ideation	(b) (6)	F	45	Possibly	R/R	Drug withdrawn
Respiratory, thoracic, and mediastinal disorders							
* [20]	Pulmonary embolism	(b) (6)	M	55	Not related	R/R	Drug withdrawn
Vascular disorders							
* [21]	Aortic dissection	(b) (6)	M	39	Not related	Fatal	Not applicable
[22]	Peripheral artery occlusion (plus chest pain)	(b) (6)	F	50	Not related	R/R	Drug interrupted

Source: Generated by the Clinical Reviewer from the following Applicant submissions: Study 303 Clinical Study Report, Table 14.3.5.1, page 460; NDA 215430 Summary of Clinical Safety, Table 24, page 50.
* An asterisk marks SAEs that resulted in study discontinuation.
Abbreviations: F, female; ID, identification; M, male; NR/NR, not recovered/not resolved; R/R, recovered/resolved; SAE, serious adverse event

The two deaths that occurred in Study 303 were discussed previously. The rest of the SAEs that occurred during the long-term study are described below.

[1] Subject (b) (6), Study 303: Acute Myocardial Infarction

The subject was a 52-year-old female who had not participated in a prior AXS-05 study. Her previous medical history included hypertension, hyperlipidemia, sleep apnea, and obesity requiring bariatric surgery. On Study Day 49, the subject woke up with bilateral chest pain. In the emergency room, an electrocardiogram showed evidence of ST elevation myocardial infarction. She was hospitalized, and ST elevation myocardial infarction protocol was initiated. Cardiac workup showed elevated cardiac enzymes. Lipid profile showed elevated triglycerides and cholesterol. Cardiac catheterization showed 100% occlusion of the distal circumflex coronary artery and 50% occlusion of the right coronary artery. Stent implantation was performed. The subject's postoperative course was good. She missed 1 day of study medication but continued in the study. The Applicant assessed the SAE as not related to the study drug.

Clinical Reviewer's Comment: Agree with the Applicant's assessment that the SAE was not related to the study drug. According to the subject's CRFs, she had a history of hypertension and hyperlipidemia beginning in (b) (6). She was taking lisinopril and atorvastatin at the time of entry into the study. Her blood pressure was 145/83 at Study Visit 1 and was as high as 160/87 at Study Visit 3. Both her systolic and diastolic blood pressure readings showed a decreasing trend over subsequent visits. Thus, the subject did not demonstrate a trend of worsening blood pressure over the course of exposure to the study drug. Although increases in blood pressure can be an effect of bupropion, the subject's long history of hypertension and hyperlipidemia provides

a more plausible explanation for the extent of cardiac pathology reported in the narrative of this SAE.

[2] Subject (b) (6), Study 303: Coronary Artery Disease

The subject was a 45-year-old female who had not participated in a prior AXS-05 study. She was a former smoker who had a family history of coronary artery disease and obesity. On Study Day 112, the subject experienced shortness of breath after walking 4 miles. The shortness of breath resolved with rest but returned while walking up stairs. In the emergency room, she was tachycardic. Electrocardiogram revealed ST segment elevation, and echocardiography revealed three-vessel coronary artery disease. The troponin level was elevated. She was scheduled for cardiac catheterization. Angioplasty was performed and two stents were placed. She was diagnosed with an ST elevated myocardial infarction and three-vessel coronary artery disease. She was also diagnosed with hypertension and hyperlipidemia during the hospitalization. The subject continued in the study. The Applicant assessed the SAE as not related to the study drug.

Clinical Reviewer's Comment: It is not clear that this SAE was not related to the study drug. The subject's diagnoses of hypertension and hyperlipidemia, which were newly made during this hospitalization, are plausible causes for this SAE. Neither bupropion nor dextromethorphan is known to cause hyperlipidemia. However, hypertension is a known risk of bupropion. Subject (b) (6) began to have cardiac symptoms after 16 weeks of exposure to AXS-05. Her blood pressure readings recorded in the CRF were mostly within the normal range. The highest blood pressure recorded at study visits was 130/85 at Visit 4. Her CRF does not reflect a trend of increasing blood pressure over the course of the study. However, this may be because the subject was started on metoprolol (along with atorvastatin) after her hospitalization for shortness of breath. It is possible that the subject developed new-onset hypertension over the course of exposure to the study drug. It is also possible that the subject had pre-existing hypertension that had not previously been diagnosed and that was exacerbated by the study drug.

[3] Subject (b) (6), Study 303: Left Ventricular Hypertrophy

The subject was a 57-year-old female who had received 6 weeks of blinded AXS-05 in Study AXS-05-MDD-301. Her previous medical history included hypertension and obesity. Her concomitant medications included hydrochlorothiazide for hypertension. However, she stopped taking this medication at some point during the month of her entry into the study. On Study Day 274, the subject went to the emergency room and was hospitalized for intermittent chest pain with dyspnea, dizziness, and diaphoresis. She was diagnosed with left ventricular hypertrophy. She was discharged on Study Day 277. She restarted her hydrochlorothiazide at some point after discharge. The Applicant assessed the SAE as not related to the study drug, proposing her untreated hypertension as a plausible cause for the incident.

Clinical Reviewer's Comment: It is possible that the subject's left ventricular hypertrophy may have been related to a period of untreated hypertension. The subject's blood pressure was 124/87 at Study Visit 1 and was 149/86 at Study Visit 13, which occurred 1 week before her hospitalization. Her diastolic blood pressure fluctuated in the range from 81 to 92 over the

course of the study with no trend of consistent increase over time. Although these values could be attributed entirely to untreated hypertension, it is possible that the subject's hypertension may have been exacerbated to some degree by the study drug. Whether AXS-05 might be related to worsening of hypertension will be explored further in the sections in this review on and Vital Signs.

[4] Subject (b) (6), Study 303: Eye Inflammation

The subject was a 19-year-old female who had not participated in a previous AXS-05 study. Her concomitant medications included the Nexplanon contraceptive implant. The subject woke up with a swollen eye on Study Day 145. In the emergency room it was determined that she had a blood clot behind her eye and required surgery. She was discharged from the hospital on Study Day 150. The Applicant assessed the SAE as not related to the study drug because of the known risk of blood clot with the use of Nexplanon.

Clinical Reviewer's Comment: Agree with the Applicant's assessment. There were no other incidents of eye inflammation or blood clots in the AXS-05 controlled trials or the long-term trial. Blood clot is not a known risk of either dextromethorphan or bupropion but is a known risk of Nexplanon.

[5] Subject (b) (6), Study 303: Nausea

The subject was a 41-year-old female who had not participated in a previous AXS-05 study. She presented to the emergency room on Study Day 7 with nausea, vomiting, and intermittent palpitations. The nausea and vomiting began 1 week prior to her entry into the study. The subject had not participated in a prior AXS-05 study. The subject had pre-existing medical conditions that could contribute to nausea, including irritable bowel syndrome and chronic interstitial cystitis. The Applicant assessed the SAE as not related to the study drug because symptoms began prior to the first dose of study drug.

Clinical Reviewer's Comment: Agree with the Applicant's assessment. There was no temporal relationship between the onset of symptoms and the first dose of study drug.

[6] Subject (b) (6), Study 303: Chest Pain and Peripheral Artery Occlusion

The subject was a 50-year-old female who had received blinded placebo for 6 weeks in Study AXS-05-MDD-301. She had a past history of type II diabetes mellitus, left leg deep-vein thrombosis, and pulmonary embolism. She had not reported past diagnoses of hypertension and hyperlipidemia during her screening for the study but did report these during her hospitalization for this AE. On Study Day 71, the subject went to the emergency room with complaint of left-sided chest pain. She stated that she had been having the pain for the past 3 to 4 weeks and had been seen in the emergency room a few weeks prior for chest pain. She was hospitalized for cardiac workup and monitoring. Chest X-ray showed borderline cardiomegaly. A Lexiscan stress test (myocardial perfusion imaging) showed reversible myocardial ischemia. The subject's chest pain was believed to be attributable to unstable angina. She underwent cardiac catheterization through the right femoral artery. Left ventricle systolic function, ejection fraction, and all coronary arteries were found to be normal with no stenosis. Following the procedure, the subject reported paresthesia, decreased sensation, and

decreased movement in her right leg. Computed tomography of the right lower extremity showed occlusion of the right popliteal artery and proximal tibial arteries, believed to be due to a thrombus. She was taken to surgery. Right femoral artery exploration revealed a large amount of thrombo-embolus and a portion of the collagen plug from a vascular closure device within the lumen of the proximal superficial femoral artery, which were retrieved. A stent was placed. It was determined that the subject had thrombus formation due to right superficial femoral artery injury during the cardiac catheterization procedure. The subject recovered and was discharged home on Study Day 77. The chest pain continued after discharge but resolved by Study Day 105. The Applicant assessed the SAE of chest pain as not related to the study drug and more likely related to the subject's previous history of hypertension and hyperlipidemia. Additionally, the Applicant assessed the SAE of peripheral artery occlusion as not related to the study drug but related to an iatrogenic event in the course of her cardiac catheterization.

Clinical Reviewer's Comment: It is unlikely that the subject's chest pain was related to the study drug. Her chest pain also may not have been related to either hypertension or hyperlipidemia. According to the subject's CRF, her blood pressure was in the normal range at the time of entry into the study and was not elevated at any visits prior to or immediately after her hospitalization. Her cholesterol level was in the normal range at the time of entry into the study. She was not taking medications for hypertension or hyperlipidemia at the time of her hospitalization. The lab database for Study 303 does not show any elevated cholesterol levels until the Visit 10 lab results on Study Da 100. The subject's blood glucose levels were also in the normal range at all study visits. However, she was taking metformin at the time of entry into the study, so these normal values may represent adequate treatment of her diabetes. Her previous history of deep vein thrombosis and pulmonary embolism and the detection of reversible myocardial ischemia during her hospitalization suggest that she had vascular disease that may not have been related to her hypertension or hyperlipidemia but that may have been the cause of her chest pain. It is possible that the vascular disease may have been related to her diagnosis of type II diabetes.

Agree with the Applicant that the SAE of peripheral artery occlusion was not related to the study drug but was the result of an iatrogenic event in the course of her cardiac catheterization.

[7] Subject (b) (6), Study 303: Death, Cause Unknown

Clinical Reviewer's Comment: This SAE is discussed above under Deaths: Long-Term Safety Trial.

[8] Subject (b) (6), Study 303: Cholelithiasis

The subject was a 47-year-old female who had not participated in a previous AXS-05 study. She had a previous history of hypertension, hypercholesterolemia, steatohepatitis, and episodes of abdominal pain. On Study Day 19, the subject began vomiting. She went to the emergency room the following day for ongoing vomiting, nausea, and abdominal pain over the previous 8 days. Computed tomography of the abdomen and pelvis revealed cholelithiasis without acute cholecystitis. She was hospitalized for intravenous hydration. Her symptoms gradually improved. She was discharged on Study Day 23. However, the subject had a recurrence of epigastric pain, nausea, and vomiting. She was rehospitalized on Study Day 31 and underwent

laparoscopic cholecystectomy. Intraoperative cholangiogram shows no filling defect in the biliary tracts and no inflammation of the gallbladder. The subject had some continued nausea after the surgery, but this gradually improved. The SAE was considered resolved by Study Day 33. The Applicant assessed the SAE as not related to the study drug because the subject had a history of similar episodes for several years before entry into the study.

Clinical Reviewer's Comment: Agree with the Applicant's assessment. The subject had a previous history of episodes of similar symptoms in (b) (6) *and* (b) (6)*, both preceding her entry into the study in* (b) (6)*, and both characterized by negative workup and spontaneous resolution of symptoms. The time course of symptoms suggests that this problem was not related to the study drug.*

[9] Subject (b) (6), Study 303: Cellulitis

The subject was a 28-year-old female who had not participated in a prior AXS-05 study. On Study Day 52, she began experiencing fever, headache, nausea, epigastric pain, and back pain. She presented to the emergency room on Study Day 54. Physical examination revealed diffuse left upper quadrant abdominal tenderness and an area of erythema, warmth to touch, and tenderness in the mid right upper back. Her white blood cell count was elevated. The subject was diagnosed with right upper back cellulitis with abscess-associated methicillin-resistant *Staphylococcus aureus*. Incision and drainage of the abscess was performed. She was hospitalized and received intravenous antibiotics, intravenous fluids, and sepsis syndrome care. Her symptoms resolved. She was discharged home on oral antibiotics on Study Day 58. The Applicant accessed the SAE as not related to the study drug because the patient had a previous history of abscess in the year prior to her entry into the study.

Clinical Reviewer's Comment: It is unlikely that this SAE is related to the study drug. In Study 303, the frequency of adverse events coded with the preferred term 'cellulitis' was 0.3, which is very low. Additionally, the pharmacological action of the study drug does not suggest a plausible mechanism for causation of cellulitis.

[10] Subject (b) (6), Study 303: Diverticulitis

The subject was a 63-year-old female who had received 6 weeks of blinded AXS-05 in Study AXS-05-301. She had a previous episode of colitis and diverticulitis in 2016, 3 years prior to her entry into Study 303. On Study Day 283, she was transported to the emergency room with left lower quadrant abdominal pain, nausea, vomiting, and diarrhea with bright red blood per rectum which had started the previous night. Computed tomography of the abdomen was consistent with colitis and sigmoid diverticulosis. She was started on intravenous antibiotics and hospitalized. Colonoscopy on Study Day 285 showed mild colitis and moderate diverticulosis. Biopsy ruled out ischemic colitis. She had no further bleeding on that day. She was discharged the same day with instructions to continue a course of oral antibiotics. The Applicant assessed the SAE as not related to the study drug.

Clinical Reviewer's Comment: Agree with the Applicant's assessment that this SAE was not likely to be related to the study drug. The subject has a history of a previous episode of colitis and diverticulitis. In Study 303, the frequency of adverse events coded with the preferred term

'diverticulitis' was 0.2, which is very low. The subjects affected were aged 62 and 63 years, and age is a known predisposing factor for diverticulosis. Additionally, the pharmacological action of the study drug does not suggest a plausible mechanism for causation of diverticulitis.

[11] Subject (b) (6), Study 303: Fall

The subject was a 62-year-old female who had not participated in a prior AXS-05 study. Her medical history included a diagnosis of hypertension. On Study Day 47 she tripped while getting out of her car and hit her head on the sidewalk, resulting in loss of consciousness and a forehead laceration. She had another episode of loss of consciousness later that day. She went to the emergency room and was admitted for observation and cardiac evaluation. She was hypotensive, with blood pressures in the range 88/68 to 101/56 mm Hg. Cardiac enzymes, two electrocardiograms, and transthoracic echocardiogram were normal. Hospital staff recommended that she hold her antihypertensive medications until she could be evaluated by her outpatient health care provider. The SAE was considered to be resolved on Study Day 48. The Applicant assessed the SAE as not related to the study drug due to "the mechanical nature of her fall by tripping on a curb and the mild hypotension."

Clinical Reviewer's Comment: It is difficult to definitively rule out a role for the study drug in the causation of this SAE. The AE most frequently reported in both the AXS-05 controlled trials and the long-term trial is dizziness. The narrative of the SAE does not indicate whether the subject reported dizziness prior to either the first or second episode of loss of consciousness.

The subject's CRF includes an AE of weight loss reported on Study Day 15, but with a notation that the subject was intentionally dieting. The hypotension the subject experienced may have been related to a need for some adjustment in her antihypertensive regimen following her weight loss. However, it is possible that the subject's fall and the episodes of loss of consciousness were related to the combined effect of her hypotensive state and any dizziness that may have been caused by the study drug.

[12] Subject (b) (6), Study 303: Road Traffic Accident

The subject was a 28-year-old male who had not participated in a previous AXS-05 study. On Study Day 63, he was involved in a motorcycle accident that resulted in dislocation of the left knee, open fracture of the left knee, open fracture of the right ankle, and laceration of the perineum. Details of the accident are not provided in the Clinical Study Report narrative. The subject was discontinued early from the study because of this adverse event. The Applicant assessed the SAE as not related to the study drug.

Clinical Reviewer's Comment: Because of the limited information provided in the CSR narrative, it is difficult to assess whether the study drug may have had any causal role in the motorcycle accident. Notably, the subject reported the AE of "mental fogginess" on Study Day 2. The end date recorded in the CRF for the AE of "mental fogginess" is 12 days after the last dose of study drug. It would be instructive to know whether the subject felt that the "mental fogginess" he experienced had any role in the causation of the motorcycle accident.

[13] Subject (b) (6), Study 303: Intervertebral Disc Protrusion

The subject was a 45-year-old female who had not participated in a previous AXS-05 study. Her previous medical history included osteoarthritis and degenerative disc disease requiring a lumbar disc replacement in (b) (6) and a cervical disc fusion in (b) (6). On Study Day 140, she presented to the emergency room with severe neck pain. Magnetic resonance imaging and computed tomography of the cervical spine revealed cervical disc hernia compression at the C4 to C5 level. The subject was hospitalized on Study Day 143 and underwent cervical disc fusion surgery. She was discharged from the hospital on Study Day 144. The Applicant assessed the SAE as not related to the study drug and more likely related to the subject's pre-existing degenerative disc disease.

Clinical Reviewer's Comment: *Agree with the Applicant's assessment. This SAE is most likely related to the subject's long history of osteoarthritis and degenerative disc disease.*

[14] Subject (b) (6), Study 303: Breast Cancer

The subject was a 59-year-old female who had not participated in a previous AXS-05 study. On an unknown date, a breast lump was discovered after the subject had a routine mammogram. Biopsy on Study Day 162 revealed that she had breast cancer. The subject was discontinued early from the study because of this diagnosis. The Applicant did not receive information regarding further plans for the subject's treatment. The Applicant assessed this SAE as not related to the study drug because the timeline of cancer development was not consistent with the timeline of study participation.

Clinical Reviewer's Comment: Agree with the Applicant's assessment. There is no evidence of increased breast cancer risk or risk of other malignancies with exposure to either bupropion or dextromethorphan. There were no other incidents of new malignancies diagnosed in either the AXS-05 controlled trials or in the long-term trial.

[15] Subject (b) (6), Study 303: Cerebrovascular Accident

The subject was a 39-year-old male who had not participated in a previous AXS-05 study. His past medical history included borderline hypertension. The only concomitant medication recorded for the subject is calcium carbonate as needed for intermittent indigestion. On Study Day 267 he woke up in the middle of the night with a tingling sensation and muscle weakness in his upper and lower left extremities. He also had diplopia, dysarthria, and dysphagia. He had not had any similar episodes or transient ischemic attacks in the past. He was admitted to the hospital for evaluation. Details of the neurological workup are not included in the CSR narrative. Reportedly, no etiology could be identified for the subject's symptoms. He was started on atorvastatin and an anticoagulant and was discharged to a rehabilitation facility with continued paresis and paresthesia in the left upper and lower extremities. The subject was discontinued early from the study as a result of this SAE. The Applicant assessed the SAE as unlikely to be related to the study drug because of the subject's history of untreated borderline hypertension.

Clinical Reviewer's Comment: The limited amount of information provided in the narrative makes it difficult to assess whether the study drug had any causal relationship to this SAE. His blood pressure at Study Visit 1 was 158/94 and remained high at all study visits. The highest

reading was 168/108 at Study Visit 7. According to The American College of Cardiology/American Heart Association Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017), the subject would be diagnosed with stage 2 hypertension and not-borderline hypertension (a designation not included in the American College of Cardiology/American Heart Association Guideline). His body mass index at Study Visit 1 was 33.9 kg/m^2, which according to the Centers for Disease Control and Prevention places him in the category of obese. The subject thus had two risk factors for stroke. Increased blood pressure is a known risk of bupropion. The subject participated in the study for 9 months. It is possible that the study drug may have been related to this SAE by increasing the blood pressure in a subject with untreated hypertension.

[16] Subject (b) (6), Study 303: Seizure

The subject was a 24-year-old male who had not participated in a prior AXS-05 study. He was not receiving any concomitant medications at the time of entry into the study. At the time of screening, he did not disclose that he had a history of head trauma secondary to a motor vehicle accident with a seizure at the time of the head trauma. On Study Day 27, the subject had a seizure lasting 60 seconds while at work. He was taken to the emergency room. He was given Zofran for nausea and sent back home after approximately 5 hours of observation. The emergency-room physician recommended discontinuation of the study drug. After returning home, the subject continued to take the study drug until Study Day 30. He visited the site on Study Day 31. At that visit, the subject was discontinued from the study as a result of this SAE. The Applicant assessed the SAE as possibly related to the study drug due to the known risk of seizures with bupropion.

Clinical Reviewer's Comment: *Agree with the Applicant's assessment that the study drug may have been related to this SAE. In addition to the known epileptogenic potential of bupropion, the subject had a previous history of seizure and thus may have been vulnerable to medication-induced seizures. The narrative in the CSR notes that the subject would have been excluded from the study if the history of seizure had been revealed during his screening for entry into the study.*

[17] Subject (b) (6), Study 303: Depression

The subject was a 23-year-old female who had not participated in a previous AXS-05 trial. She had shown improvements in MADRS scores at study visits on Study Days 49 and 63. The narrative in the CSR reports that the subject discontinued the study drug on Study Day 88. However, the subject's reason for discontinuing the medication is not given. On Study Day 90, the subject's family brought her to the emergency room because of sleep disturbances and loss of appetite. The subject reported worsening depression with feelings of hopelessness and worthlessness, passive suicidal ideation, anhedonia, limited motivation, poor appetite, increased alcohol consumption, hypersomnia, worsening nightmares, intrusive thoughts, hypervigilance, and irritability. She was admitted to the hospital. The subject stated that the depression started 1 month prior to her emergency room visit after a difficult visit with her family. She reported multiple stressors included chaotic family situation, job-related problems, lack of money, and stress of the coronavirus disease-2019 (COVID-19) pandemic. During the hospitalization she was started on fluoxetine for depression and trazodone for sleep. Her mood

improved during the hospitalization. Her suicidal ideation resolved. Her mood, affect, sleep pattern, and appetite all improved. She requested discharge and was discharged on Study Day 96. The Applicant assessed the SAE as unlikely to be related to the study drug and more likely related to worsening of her underlying mood disorder.

Clinical Reviewer's Comment: Agree with the Applicant that the SAE is not likely to be related to the study drug. The labels of approved antidepressants, including bupropion, include a warning regarding the risk of increased suicidal ideation and behavior in children, adolescents, and young adults. However, the subject had shown improvement in MADRS scores during the first 2 months of exposure to the study drug. The worsening of her depression began shortly after a stressful visit with her family. The time course of worsening of the subject's depression appears more consistent with a response to life stresses than with an effect of the study drug.

[18] Subject (b) (6), Study 303: Mental Disorder

The subject was a 54-year-old female who had not participated in a previous AXS-05 study. On Study Day 25, her MADRS score was 25 points (moderate depression) and results of the Columbia-Suicide Severity Rating Scale (C-SSRS) ruled out suicidal ideation or behavior. She had reported family problems at that visit. The following day, she requested psychiatric hospitalization and was admitted. During the hospitalization she was instructed to stop the study drug and was prescribed venlafaxine. She was discharged from the hospital on Study Day 33. One week after discharge, she became a victim of domestic violence. The Applicant assessed the SAE as unlikely related to the study drug and more likely related to the stress of the subject's family situation.

Clinical Reviewer's Comment: The details of the narrative in the CSR are limited. There is no discussion of the symptoms the subject reported when she requested psychiatric hospitalization. Although the labels of approved antidepressants include a warning regarding the risk of increased suicidal ideation and behavior, this is more applicable to children, adolescents, and young adults than to older adults. Agree with the Applicant that the hospitalization is more likely related to the subject's psychosocial stressors than to an adverse effect of the study drug.

[19] Subject (b) (6), Study 303: Suicidal Ideation

The subject was a 45-year-old female who had received blinded placebo for 6 weeks in Study AXS-05-MDD-301. She was not receiving any concomitant medications at the time of entry into the study. On Study Day 275, the subject requested psychiatric hospitalization. She reported feeling very depressed, with thoughts of suicide by crashing her car, and stated that she was scared that she was going to hurt herself. She also reported hypersomnia, anhedonia, feelings of guilt and worthlessness, loss of concentration, loss of appetite, psychomotor retardation, and feeling unable to function. She could not describe any recent stressor that might have caused worsening of her depression. At the time of hospitalization, the subject had a urine drug screen that was positive for opiates. However, she denied taking any opiates. The subject reported that she had not had suicidal ideation in the past and had not had any suicidal ideation during the course of the study. Previous antidepressants that she had been prescribed included sertraline, fluoxetine, citalopram, escitalopram, venlafaxine, duloxetine, and

bupropion. She stated that all had worked for 2 to 3 months but then stopped working. On the day after admission to the hospital the study drug was discontinued, and she was started on a combination of bupropion and venlafaxine. The subject was discharged from the hospital on Study Day 281. The subject was discontinued from the study as a result of this SAE. The Applicant assessed the SAE as possibly related to the study drug, given that the subject had not previously had suicidal ideation and had not had any recent psychosocial stressor.

Clinical Reviewer's Comment: The subject appears to be suffering from a clinically recognized phenomenon by which an antidepressant initially helps with depressive symptoms but over time loses its effectiveness. Although the labels of approved antidepressants include a warning regarding the risk of increased suicidal ideation and behavior, this typically occurs early in the course of treatment, whereas the subject received treatment for 9 months before her depression worsened. The warning is also more applicable to children, adolescents, and young adults than to older adults. The subject had taken bupropion before with no elicitation of suicidal ideation, but she had no previous exposure to the combination of bupropion and dextromethorphan. The onset of suicidal ideation with the combination of bupropion and dextromethorphan, with no other antidepressant treatment, and in the absence of any psychosocial stressor suggest a possible relationship between the study drug and the subject's worsening of depression. It is possible that the subject's positive drug screen was a false positive caused by structural similarities between dextromethorphan and some opiates such as morphine and codeine.

[20] Subject (b) (6), Study 303: Pulmonary Embolism

The subject was a 55-year-old male who had not participated in a previous AXS-05 study. His previous medical history included seasonal allergies, obesity, hypertension, and left knee osteoarthritis. Following evaluation for mild shortness of breath, he was diagnosed with bronchitis and was treated with doxycycline and azithromycin. On Study Day 81, the correct diagnosis of COVID-19 was made. On Study Day 86, he was discontinued from the study drug because of the COVID-19 diagnosis. On Study Day 93, he was evaluated for persistent cough and dyspnea. Computed tomography angiography of the chest showed bilateral pulmonary emboli with moderate to large clot burden. The subject was diagnosed with pulmonary embolism. He was treated with methylprednisolone and intravenous heparin drip. Lower extremity venous duplex scan was negative for acute deep or superficial thrombosis. The subject was discharged home on Study Day 96. He was continued on apixaban (anticoagulant) and losartan (antihypertensive) after discharge. The subject was discontinued from the study as a result of this SAE. The Applicant assessed the SAE as not related to the study drug and more likely related to COVID-19 infection.

Clinical Reviewer's Comment: Agree with the Applicant's assessment. There was no pattern of pulmonary embolism occurring in either the AXS-05 controlled trials or the long-term trial; this was the only case. Additionally, the pharmacological action of the study drug does not suggest a plausible mechanism for causation of pulmonary embolism. Pulmonary embolism is a known risk of COVID-19 infection.

[21] Subject (b) (6), Study 303: Aortic Dissection

Clinical Reviewer's Comment: This SAE was discussed under Deaths: Long-Term Safety Trial.

[22] Subject (b) (6), Study 303: Peripheral Artery Occlusion and Chest Pain

Clinical Reviewer's Comment: This SAE was discussed under SAE [6].

Discontinuations Due to Adverse Effects: Controlled Clinical Trials

In the pooled dataset from the AXS-05 controlled trials, 16 subjects (4.4%) treated with AXS-05 reported 18 TEAEs that led to discontinuation from the study, and 6 subjects (2.9%) treated with bupropion reported 8 TEAEs that led to discontinuation from the study. There were no TEAEs that led to discontinuation from the study in subjects treated with placebo. In the AXS-05 pooled group, anxiety led to discontinuation in five subjects (1.4%) and dizziness led to discontinuation in two subjects (0.5%). In the bupropion pooled group, nausea led to discontinuation in two subjects (1.0%). All other TEAEs were reported by one subject each. Depression was the reason for discontinuation in one subject in both the AXS-05 pooled group and the bupropion pooled group. See Table 40.

Table 40. TEAEs Leading to Discontinuation, Pooled Controlled Clinical Trials Safety Population

Preferred Term	AXS-05 Pooled (N=364) n (%)	Bupropion Pooled (N=204) n (%)	Placebo (N=164) n (%)
At least 1 TEAE leading to discontinuation from the study	16 (4.4)	6 (2.9)	0
Anxiety	5 (1.4)	0	0
Dizziness	2 (0.5)	0	0
Nausea	1 (0.3)	2 (1.0)	0
Swollen tongue	1 (0.3)	0	0
Frequent bowel movements	0	1 (0.5)	0
Abdominal pain	0	1 (0.5)	0
Overdose	1 (0.3)	0	0
Disturbance in attention	1 (0.3)	0	0
Feeling abnormal	1 (0.3)	0	0
Initial insomnia	1 (0.3)	0	0
Depression	1 (0.3)	1 (0.5)	0
Insomnia	0	1 (0.5)	0
Psychomotor retardation	1 (0.3)	0	0
Psychotic disorder	0	1 (0.5)	0
Restlessness	1 (0.3)	0	0
Suicidal ideation	1 (0.3)	0	0
Dyspnea	0	1 (0.5)	0
Hypertension	1 (0.3)	0	0

Source: generated by Clinical Reviewer from NDA 215430 Integrated Summary of Safety, Table 2.6, Errata Report submitted by the Applicant on January 18, 2022.
Abbreviations: TEAE, treatment-emergent adverse event

Discontinuations Due to Adverse Effects: Long-Term Safety Trial

In the long-term safety trial, 74 subjects (8.4%) reported 127 TEAEs that led to discontinuation from the study. The most frequently reported TEAEs leading to discontinuation were dizziness (1.5%), nausea (1.1%), headache (1.0%), anxiety (0.8%), and decreased appetite (0.6%) (Table 41).

Table 41. Summary of TEAEs Leading to Discontinuation and Occurring in ≥3 Subjects, Long-Term Safety Population

Preferred Term	AXS-05 Long-Term (N=876) n (%)
At least 1 TEAE leading to discontinuation from the study	74 (8.4)
Dizziness	13 (1.5)
Nausea	10 (1.1)
Headache	9 (1.0)
Anxiety	7 (0.8)
Decreased appetite	5 (0.6)
Dry mouth	4 (0.5)
Insomnia	4 (0.5)
Palpitations	3 (0.3)
Somnolence	3 (0.3)
Suicidal ideation	3 (0.3)

Source: NDA 215430 Summary of Clinical Safety, Table 26, page 53.
Abbreviation: TEAE, treatment-emergent adverse event

Adverse Events of Special Interest

AESIs are AEs with special scientific and medical concern that are known to be associated with, or have the potential to be associated with, either of the components of AXS-05 (dextromethorphan and bupropion) or the MDD indication. Analysis of AESIs will be based on the overall pooled dataset of subjects who participated in controlled trials MDD-201, MDD-301, or 301 and long-term safety trial 303. This dataset includes 1114 subjects treated with AXS-05, 204 subjects treated with bupropion, and 164 subjects treated with placebo.

Adverse Events of Special Interest: Abuse Potential

There were no PTs of drug abuse or substance abuse in any treatment group. Further details of the Applicant's analysis of the abuse potential of AXS-05 is presented in this review under Assessment of the Abuse Potential for AXS-05.

Adverse Events of Special Interest: Serotonin Syndrome

There were no AEs coded with the preferred term *serotonin syndrome* in the AXS-05 overall exposure dataset.

The Clinical Reviewer searched the adverse event data from the short-term clinical trials pooled safety population and from the long-term trial safety population for occurrence of the following preferred terms potentially related to serotonin syndrome: *agitation, chills, confusional state, coordination abnormal, diarrhoea, headache, hyperhidrosis, hyperreflexia, muscle twitching, mydriasis, myoclonus, psychomotor hyperactivity, restlessness,* and *tremor*. See Table 42 and Table 43.

Table 42. TEAEs Potentially Related to Serotonin Syndrome, Controlled Clinical Trial Safety Population, Pooled Dataset

Preferred Term, n (%)	AXS-05 Pooled (N=876)	Bupropion Pooled (n=204)	Placebo (N=164)
Headache	24 (6.6)	13 (6.4)	6 (3.7)
Diarrhoea	15 (4.1)	2 (1.0)	5 (3.0)
Restlessness	2 (0.5)	2 (1.0)	1 (0.6)
Tremor	2 (0.5)	2 (1.0)	0 (0.0)
Chills	1 (0.3)	0 (0.0)	0 (0.0)
Muscle twitching	1 (0.3)	0 (0.0)	0 (0.0)
Mydriasis	1 (0.3)	0 (0.0)	0 (0.0)
Myoclonus	1 (0.3)	0 (0.0)	0 (0.0)
Agitation	0 (0.0)	2 (1.0)	1 (0.6)

Source: Generated by the Clinical Reviewer.
Abbreviation: TEAE, treatment-emergent adverse event

Table 43. TEAEs Potentially Related to Serotonin Syndrome, Long-Term Safety Population

Preferred Term, n (%)	AXS-05 (N=876)
Headache	77 (8.8)
Diarrhoea	33 (3.8)
Tremor	12 (1.4)
Restlessness	8 (0.9)
Agitation	6 (0.7)
Confusional state	4 (0.5)
Muscle twitching	2 (0.2)
Myoclonus	2 (0.2)
Chills	1 (0.1)
Coordination abnormal	1 (0.1)

Source: Generated by the Clinical Reviewer.
Abbreviation: TEAE, treatment-emergent adverse event

In both the short-term and long-term clinical trials, the most frequent TEAEs potentially related to serotonin syndrome, headache and diarrhea, have many possible causes other than serotonin syndrome. The other TEAEs occurred at very low frequencies and all have possible causes other than serotonin syndrome. In the short-term trials, the frequencies of TEAEs in the AXS-05 group were similar to the frequencies in the bupropion group and were not notably higher than the frequencies in the placebo group. Bupropion is not known to increase the risk of serotonin syndrome. The similarity between AXS-05 and bupropion in frequencies of TEAEs related to serotonin syndrome suggests that the risk of serotonin syndrome from treatment with AXS-05 is likely to be low. This analysis did not reveal a pattern of TEAEs suggestive of unrecognized occurrence of serotonin syndrome in subjects treated with AXS-05 during the clinical trials.

Adverse Events of Special Interest: Seizure

One subject (0.1%) in the AXS-05 overall group had an AE of seizure. At the time of screening, this subject had not disclosed a previous history of head trauma and seizure. No AEs of seizure occurred in the bupropion overall group or the placebo overall group.

Adverse Events of Special Interest: Hypertension

In the AXS-05 controlled clinical trials, 1.9% of subjects treated with AXS-05, 1.5% of subjects treated with bupropion, and 0.0% of subjects treated with placebo had adverse events coded with one of the following preferred terms: *hypertension*, *diastolic hypertension*, or *blood pressure increased*.

In the AXS-05 overall exposure group, 20 subjects (1.8%) treated with AXS-05 and 3 subjects (1.5%) treated with bupropion reported AESIs coded with one of the following preferred terms: *hypertension*, *blood pressure increased*, *blood pressure systolic increased*, *diastolic hypertension*, and *essential hypertension*. No subjects in the placebo group reported AESIs related to hypertension.

Clinical Reviewer's Comment: The percentage of patients with AESIs related to hypertension was minimally higher in the AXS-05 group than in the bupropion group in both the controlled trials and in the overall exposure population. It is not clear whether the difference in percentages is clinically meaningful. Dextromethorphan alone is not known to cause elevation of blood pressure, but it is unclear whether dextromethorphan could cause an increase in blood pressure when its exposure level is prolonged by coadministration with a CYP2D6 inhibitor. This issue is explored further in the Vital Signs section.

Adverse Events of Special Interest: Psychosis and Other Neuropsychiatric Reactions

A total of 19 subjects (1.7%) in the overall AXS-05 group, 3 subjects (1.5%) in the bupropion pooled group, and 2 subjects (1.2%) in the placebo group reported an AESI of psychosis and other neuropsychiatric reactions. Agitation was the most frequently reported neuropsychiatric reaction in the overall AXS-05 and pooled bupropion treatment groups. See Table 44.

Clinical Reviewer's Comment: Although there was a greater variety of neuropsychiatric reactions reported in the overall AXS-05 group than in the pooled bupropion group, the frequency of neuropsychiatric reactions was comparable in the two drug-treated groups. The frequency of neuropsychiatric reactions was higher in both drug-treated groups than in the placebo group. The occurrences of visual hallucinations and paranoia in only the AXS-05 group may raise concerns about whether these AEs could be related to the dextromethorphan component of AXS-05. However, the comparison of AE rates is somewhat confounded by differences both in population sizes and in durations of exposure for the three treatment groups in the pooled dataset. The pooled dataset includes 1114 subjects exposed to AXS-05 for up to 1 year, compared to 204 subjects exposed to bupropion for 6 weeks and 164 subjects exposed to placebo for 6 weeks. Because we do not have data on frequencies of visual hallucinations or paranoia for subjects treated with bupropion or placebo for up to 1 year, we do not know whether the frequencies of these AEs in the AXS-05 treatment group is notably different from

the base rates in the general population of patients with MDD who are either untreated or being treated with bupropion.

Table 44. Psychosis and Other Neuropsychiatric Reaction AESIs, Overall Safety Population

AESI Preferred Term	No. of Subjects (%)		
	AXS-05 Overall (N=1114)	Bupropion Pooled (N=204)	Placebo (N=164)
Psychosis and other neuropsychiatric reactions	19 (1.7)	3 (1.5)	2 (1.2)
Agitation	6 (0.5)	2 (1.0)	1 (0.6)
Hallucination, visual	3 (0.3)	0	0
Disorientation	3 (0.3)		
Autoscopy	2 (0.2)		
Paranoia	2 (0.2)	0	0
Derealization / depersonalization disorder	1 (0.6)		
Derealization			1 (0.6)
Homicidal ideation	1 (0.1)	0	0
Psychotic disorder	0	1 (0.5)	0
Impulsive behavior	1 (0.1)		

Source: NDA 215430 Summary of Clinical Safety, Table 35, page 59.
Abbreviations: AESI, adverse event of special interest; No., number

Adverse Events of Special Interest: Hypersensitivity Reactions

Six subjects (0.5%) in the AXS-05 overall group and one subject (0.5%) in the bupropion pooled group reported eight and one AESIs of hypersensitivity reaction, respectively. Urticaria was reported 6 times by four subjects (0.4%) in the AXS-05 overall group and once by one subject (0.5%) in the bupropion pooled group. In the AXS-05 overall group, angioedema and drug hypersensitivity were reported by one subject each (0.1%). The AE of drug hypersensitivity referred to an allergic reaction to Augmentin. For the angioedema AESI, the time to the AESI was 3 days, the duration was 3 days, and the reported severity was mild. No hypersensitivity reaction AESIs were reported in the placebo group. See Table 45.

Table 45. Summary of Hypersensitivity Reaction AESIs, Overall Safety Population

AESI Preferred Term	No. of Subjects (%)		
	AXS-05 Overall (N=1114)	Bupropion Pooled (N=204)	Placebo (N=164)
Hypersensitivity reactions	6 (0.5)	1 (0.5)	0
Urticaria	4 (0.4)	1 (0.5)	0
Angioedema[a]	1 (0.1)	0	0
Drug hypersensitivity[b]	1 (0.1)	0	0

Source: NDA 215430 Summary of Clinical Safety, Table 38, page 63.
[a] Angioedema was of mild severity
[b] Reported term was "allergic reaction to augmentin"
Abbreviations: AESI, adverse event of special interest; No., number

Clinical Reviewer's Comment: The frequency of hypersensitivity reaction AESIs was low in both the overall AXS-05 group and the pooled bupropion group. Because hypersensitivity reactions were observed in the development program, a contraindication for patients with a known hypersensitivity to dextromethorphan and/or bupropion will be included in future product labeling.

Adverse Events of Special Interest: Suicidality and Worsening of Suicidality

Thirteen subjects (1.2%) in the AXS-05 overall group and two subjects (1.0%) in the bupropion pooled group reported one AESI of suicidality and worsening of suicidality each. No AESIs of suicidality or worsening of suicidality were reported in the placebo group. See Table 46.

Table 46. Suicidality and Worsening of Suicidality AESIs, Overall Safety Population

AESI Preferred Term	No. of Subjects (%)		
	AXS-05 Overall (N=1114)	Bupropion Pooled (N=204)	Placebo (N=164)
Suicidality and worsening of suicidality	13 (1.2)	2 (1.0)	0
Suicidal ideation	10 (0.9)	2 (1.0)	0
Self-injurious ideation	2 (0.2)	0	0
Suicide attempt[a]	1 (0.1)	0	0

Source: NDA 215430 Summary of Clinical Safety, Table 41, page 64.
[a] Reported term was "aborted suicide attempt"
Abbreviations: AESI, adverse event of special interest; No., number

Minimal details are available about the AESI coded with the PT "suicide attempt" and reported term "aborted suicide attempt." Based in the entry in the AE database, the incident occurred in Study 303 and involved a 19-year-old male who had not participated in a previous AXS-05 study. The incident occurred on Study Day 84. The severity of the incident is reported as mild and not serious. No hospitalization was required. The suicide attempt was assessed by the

Applicant as not related to the study drug. The subject continued in the study for an additional 81 days after this incident.

Clinical Reviewer's Comment: *The frequency of AESIs related to suicidality was low and comparable for the overall AXS-05 group and the pooled bupropion group.*

Adverse Events of Special Interest: Activation of Mania/Hypomania

Two subjects (0.2%) in the AXS-05 overall group reported activation of mania/hypomania with the PT of mania. No mania/hypomania AESIs were reported in the bupropion pooled or placebo groups.

Adverse Events of Special Interest: Angle-Closure Glaucoma

There were no AESIs of angle-closure glaucoma in any treatment group.

Adverse Events of Special Interest: Discontinuation Syndrome

There were no PTs of antidepressant discontinuation syndrome, withdrawal syndrome, or drug withdrawal syndrome in any treatment group.

Assessment of the Abuse Potential for AXS-05

The Applicant assessed the abuse potential of AXS-05 through the following evaluations:

1. An evaluation of abuse-related AEs, including euphoria-related AEs, in the overall pooled safety dataset. This evaluation included 1114 patients treated with AXS-05, 204 with bupropion, and 164 with placebo.
2. A prospective, controlled evaluation for dissociative symptoms via the Brief Psychiatric Rating Scale – Factor 1 items (Reality Distortion) in Study 301.
3. A prospective, controlled evaluation for withdrawal symptoms via the Physician Withdrawal Checklist (PWC-20) in Study MDD-301.

[1] Analysis of Adverse Events Related to Abuse Potential

In the combined database of phase 2 and phase 3 studies, the most commonly observed abuse-related AEs were dizziness (13.8% AXS-05, 1.0% bupropion, 6.1% placebo) and somnolence (4.4% AXS-05, 1.0% bupropion, 3.0% placebo). The frequencies of all other abuse-related TEAEs in subjects treated with AXS-05 were 1.0% or lower. There were no PTs of antidepressant discontinuation syndrome, withdrawal syndrome, or drug withdrawal syndrome in any treatment group. See Table 47.

Table 47. Abuse-Related TEAEs by Term Category and Preferred Term, Overall Safety Population

Term Category Preferred Term, n (%)	AXS-05 Overall (N=1114)	Bupropion Pooled (N=204)	Placebo (N=164)
Euphoria-related terms			
Dizziness	154 (13.8)	2 (1.0)	10 (6.1)
Feeling abnormal	11 (1.0)	0	1 (0.6)
Euphoric mood	4 (0.4)	0	0
Hallucination, visual	3 (0.3)	0	0
Thinking abnormal	1 (0.1)	0	0
Feeling drunk	0	0	0
Feeling of relaxation	0	0	0
Inappropriate affect	0	0	0
Terms indicative of impaired attention, cognition, and mood			
Somnolence	49 (4.4)	2 (1.0)	5 (3.0)
Memory impairment	6 (0.5)	0	0
Mental impairment	2 (0.2)	1 (0.5)	1 (0.5)
Mood swings	1 (0.1)	0	0
Dissociative/psychotic terms			
Confusional state	4 (0.4)	0	0
Disorientation	3 (0.3)	0	0
Autoscopy	2 (0.2)	0	0
Anger	1 (0.1)	0	0
Aggression	0	0	0
Psychotic disorder	0	1 (0.5)	0
Related terms not captured elsewhere			
Drug tolerance	0	0	0
Habituation	0	0	0
Drug withdrawal	0	0	0
Substance-related disorders	0	0	0
Total of all abuse-related TEAEs	**241 (21.6)**	**6 (2.9)**	**17 (10.4)**
Total of abuse-related TEAEs, excluding dizziness and somnolence	**38 (3.4)**	**2 (1.0)**	**2 (1.2)**

Source: Generated by the Clinical Reviewer from the following Applicant submissions: NDA 215430 Summary of Clinical Safety, Table 83, page 100; NDA 215430 Integrated Summary of Safety. Table 4.1.1, page 261. The incident of psychotic disorder is not represented in either table but was identified through a query of the pooled adverse event dataset file provided by the Applicant.
Abbreviation: TEAE, treatment-emergent adverse event

Clinical Reviewer's Comment: The total frequency of abuse-related TEAEs was higher in the overall AXS-05 group (21.6%) than in either the pooled bupropion group (2.9%) or the placebo group (10.4%). The data are difficult to interpret, because it is unclear why the placebo group would have a higher frequency of abuse-related TEAEs than the bupropion group. Part of the difficulty in this analysis is that the TEAEs that occurred most frequently in all treatment groups, dizziness and somnolence, may be experienced as unpleasant to some patients, and thus would not elicit drug-seeking behavior in clinical practice. If incidences of dizziness and somnolence are excluded from the analysis, the frequencies of abuse-related TEAEs for the AXS-05, bupropion, and placebo groups are 3.4%, 1.0%, and 1.2%, respectively.

[2] Evaluation for Dissociative Symptoms

To assess for the presence of dissociative symptoms, the protocol for Study 301 included administration of the Brief Psychiatric Rating Scale – Factor 1 items (Reality Distortion). The

Factor 1 items assess for suspiciousness, hallucinatory behavior, and unusual thought content. Each item is scored from 1 (not present) to 7 (very severe). A total possible score of 21 indicates very severe reality distortion. In the study population, the mean (standard deviation [SD]) baseline scores were 2.8 (0.86) in the AXS-05 arm and 2.9 (0.68) in the bupropion arm. The mean (SD) changes from baseline at the end of the study were -0.1 (0.83) in the AXS-05 arm and 0.0 (0.97) in the bupropion arm. The Applicant concluded that the absence of significant changes from baseline over time and the lack of difference between the AXS-05 and bupropion treatment groups indicates that treatment with AXS-05 was not associated with dissociative symptoms.

Clinical Reviewer's Comment: Agree with the Applicant that the results on the Brief Psychiatric Rating Scale – Factor 1 items do not suggest a relationship between treatment with AXS-05 and the onset of dissociative symptoms.

[3] Evaluation for Withdrawal and Discontinuation Symptoms

To assess for withdrawal symptoms, the protocol for Study MDD-301 included completion of the Physician Withdrawal Checklist (PWC-20), a 20-item questionnaire designed to assess benzodiazepine-like discontinuation symptoms in non-selective serotonin reuptake inhibitor medications. The PWC-20 was completed once, during the safety follow-up visit, after the subject had been off drug for 7 days. The PWC-20 results are summarized in Table 48.

Clinical Reviewer's Comment: It is possible that this checklist may not have captured the entire spectrum of potential withdrawal or discontinuation symptoms, as it is possible that AXS-05 may induce withdrawal or discontinuation symptoms that are different from those of benzodiazepines.

Table 48. Study MDD-301: 20-Item Physician Withdrawal Checklist by Parameter, mITT Population

Parameter	No. (%) of Subjects		Difference (%)	
	AXS-05 (N=156)	Placebo (N=162)	(95% CI) (AXS-05 – Placebo)	p-value
Loss of appetite	34 (25.0)	33 (22.3)	2.7 (-7.2, 12.6)	0.592
Nausea – vomiting	16 (11.7)	7 (4.7)	6.9 (0.6, 13.3)	0.031
Diarrhea	15 (10.9)	8 (5.4)	5.5 (-0.8, 11.9)	0.086
Anxiety-nervousness	55 (40.1)	55 (37.2)	3.0 (-8.3, 14.3)	0.605
Irritability	53 (38.7)	56 (37.8)	0.8 (-10.4, 12.1)	0.883
Dysphoric mood – depression	81 (59.1)	89 (60.1)	-1.0 (-12.4, 10.4)	0.862
Insomnia	62 (45.6)	76 (51.4)	-5.8 (-17.4, 5.9)	0.332
Fatigue – lethargy – lack of energy	66 (48.2)	86 (58.1)	-9.9 (-21.5, 1.6)	0.093
Poor coordination	58 (42.3)	76 (51.4)	-9.0 (-20.6, 2.5)	0.128
Restlessness – agitation	40 (29.2)	53 (35.8)	-6.6 (-17.5, 4.2)	0.234
Diaphoresis	13 (9.5)	7 (4.7)	4.8 (-1.2, 10.7)	0.116
Tremor – tremulousness	3 (2.2)	1 (0.7)	1.5 (-1.3, 4.3)	0.278
Dizziness – lightheadedness	25 (18.2)	9 (6.1)	12.2 (4.6, 19.7)	0.002
Headaches	29 (21.2)	24 (16.2)	5.0 (-4.1, 14.0)	0.283
Muscle aches or stiffness	26 (19.0)	26 (17.6)	1.4 (-7.6, 10.4)	0.758
Weakness	15 (10.9)	14 (9.5)	1.5 (-5.6, 8.5)	0.678
Increased acuity for sound, smell, touch, pain	12 (8.8)	7 (4.7)	4.0 (-1.8, 9.9)	0.173
Paresthesias	7 (5.1)	4 (2.7)	2.4 (-2.1, 6.9)	0.292
Difficulty concentrating, remembering	52 (38.0)	63 (42.6)	-4.6 (-16.0, 6.8)	0.428
Depersonalization – derealization	7 (5.1)	7 (4.7)	0.4 (-4.6, 5.4)	0.882

Source: NDA 215430 Summary of Clinical Safety, Table 87, page 105.
Note: p-value is based on chi-squared test
Abbreviations: CI, confidence interval; mITT, modified intent-to-treat; NDA, new drug application; No., number

Results of the PWC-20 show that dizziness/lightheadedness and nausea/vomiting occurred at a nominally statistically significant higher rate in the AXS-05 arm than in the placebo arm. However, dizziness and nausea were the two most frequent TEAEs for patients treated with AXS-05 in the study, with frequencies for both greater than for placebo. For the other symptoms assessed by the PWC-20, the difference between AXS-05 and placebo was not nominally statistically significant. The Applicant concluded that the results from the PWC-20

demonstrate a lack of withdrawal symptoms for AXS-05 compared to placebo. The Applicant also noted that there were no TEAEs of antidepressant discontinuation syndrome, withdrawal syndrome, or drug withdrawal syndrome in the study.

Clinical Reviewer's Comment: *Agree with the Applicant that the frequency of dizziness/lightheadedness and nausea/vomiting on the PWC-20 would be expected to be high. These were the most frequent TEAEs in both the three controlled trials and the long-term safety trial. The similarity between the AXS-05 and placebo treatment arms on the other PWC-20 items, along with the absence of TEAEs related to withdrawal or discontinuation, suggest that AXS-05 has low potential for causing withdrawal or discontinuation symptoms.*

Applicant's Conclusions on the Abuse Potential of AXS-05

The Applicant concludes that the potential for abuse of AXS-05 is low, based on these three evaluations.

Clinical Reviewer's Comment: As noted above, the analysis of frequencies of abuse-related TEAEs is difficult to interpret. If incidences of dizziness and somnolence are excluded from the analysis, the total frequency of abuse-related TEAEs is still highest for the AXS-05 treatment group but is more comparable in magnitude across treatment groups. Additionally, if incidences of dizziness and somnolence are excluded, the frequencies of all other abuse-related TEAEs in the AXS-05 group ranged from 0.0% to no higher than 1.0%.

Overall, the Clinical Reviewer agrees with the Applicant that the evaluation for abuse potential of AXS-05 shows a low potential for abuse, based on the low rates of TEAEs indicative of abuse (excluding dizziness and somnolence), low frequency of dissociative symptoms, and low frequency of withdrawal symptoms.

Assessment of the Abuse Potential for AXS-05: Consult by Controlled Substances Staff

The Division of Psychiatry consulted the Controlled Substances Staff (CSS) for their assessment of the abuse potential of AXS-05. Following their review of published literature on dextromethorphan and of data from the AXS-05 clinical program, CSS reached the following conclusions:

- Neither component of AXS-05 (dextromethorphan or bupropion) is scheduled under the Controlled Substances Act (CSA).
- High doses of dextromethorphan produced psychedelic-like and dissociative effects that are associated with its abuse potential and recreational use.
- The bupropion component of AXS-05 inhibits CYP2D6 and the metabolism of dextromethorphan to its primary metabolite, dextrorphan. Limited data suggest that, relative to dextrorphan, dextromethorphan is less reinforcing and produces increased dysphoric effects. This may decrease the abuse potential of AXS-05 relative to single-entity dextromethorphan products.

- Relative to highly concentrated and flavored dextromethorphan products that are available over-the-counter and appear to be expressly marketed for recreational purposes, AXS-05 does not appear to present an increased abuse liability.
- CSS recommended that AXS-05 should not be controlled under the Controlled Substances Act but that the label should include a Drug Abuse and Dependence section that describes the abuse-related risks of dextromethorphan.

Assessment of the Abuse Potential for AXS-05: Additional Analyses by the Clinical Reviewer

The clinical reviewer searched the AE data from the short-term clinical trials pooled safety population and from the long-term trial safety population for occurrence of the following preferred terms potentially related to intentional abuse of the study drug: *drug abuse, drug overdose, intentional overdose, overdose,* and *substance abuse.* This search revealed a single adverse event in a short-term study, Study 301, coded with the term 'overdose.' This incident was discussed above in the section Serious Adverse Events: Controlled Clinical Trials. The incident appeared to have been related to multiple psychosocial stressors and did not appear to be an attempt at recreational use of the study drug. In the long-term safety study, there were no TEAEs coded with terms potentially related to intentional abuse of the study drug. This review of adverse events did not reveal patterns of subject behavior related to intentional abuse of the study drug in either the short-term or long-term trials.

For most of the AESIs, the frequencies were low in all studies and pooling of data from both the three short-term trials and the long-term safety trial seemed reasonable. For abuse-related TEAEs, certain TEAEs occurred frequently, particularly dizziness and somnolence. With these AEs, the differences in study durations and study population sizes made comparison of treatment groups more difficult. A separate analysis was conducted to examine TEAEs in only the pooled dataset of controlled trials. In this pooled dataset, all studies had the same 6-week duration, and the sizes of the pooled treatment arms are of comparable magnitude. See Table 49 for counts of abuse-related TEAEs in the pooled dataset of controlled trials.

Table 49. Abuse-Related TEAEs by Term Category and Preferred Term, Pooled Data from the Three Controlled Trials

Term Category Preferred Term, n (%)	AXS-05 Pooled (N=364)	Bupropion Pooled (N=204)	Placebo (N=164)
Euphoria-related terms			
Dizziness	50 (13.7)	3 (1.5)	10 (6.1)
Feeling abnormal	3 (0.8)	0	1 (0.6)
Euphoric mood	2 (0.5)	0	0
Hallucination, visual	0	0	0
Thinking abnormal	0	0	0
Feeling drunk	0	0	0
Feeling of relaxation	0	0	0
Inappropriate affect	0	0	0

Term Category Preferred Term, n (%)	AXS-05 Pooled (N=364)	Bupropion Pooled (N=204)	Placebo (N=164)
Terms indicative of impaired attention, cognition, and mood			
Somnolence	10 (5.2)	2 (1.0)	5 (3.0)
Memory impairment	0	0	0
Mental impairment	0	1 (0.5)	0
Mood swings	1 (0.3)	0	0
Dissociative / psychotic terms			
Confusional state	0	0	0
Disorientation	0	0	0
Autoscopy	0	0	0
Anger	0	0	0
Aggression	0	0	0
Psychotic disorder	0	1 (0.5)	0
Related terms not captured elsewhere			
Drug tolerance	0	0	0
Habituation	0	0	0
Drug withdrawal	0	0	0
Substance-related disorders	0	0	0
Total of all abuse-related TEAEs	**66 (18.1)**	**10 (4.9)**	**16 (9.8)**
Total of abuse-related TEAEs, excluding dizziness and somnolence	**6 (1.6)**	**5 (2.5)**	**1 (0.6)**

Source: Generated by the Clinical Reviewer. Adverse event data were pooled for only the three 6-week controlled clinical trials.
Abbreviation: TEAE, treatment-emergent adverse event

As in the pooled dataset that includes all phase 2 and phase 3 trials, the frequency of all abuse-related TEAEs is higher for AXS-05 (18.1%) than for either bupropion (4.9%) or placebo (9.8%). If we exclude dizziness and somnolence from the analysis, the frequency of abuse-related TEAEs is similar for AXS-05 (1.6%) and bupropion (2.5%), and both are higher than the frequency for placebo (0.6%). This suggests that a small number of adverse effects that occur frequently in subjects treated with AXS-05 may bias the analysis towards suggesting a higher abuse potential for AXS-05 than for bupropion, whereas the actual abuse potential may be comparable and low for both drugs.

Treatment-Emergent Adverse Events and Adverse Reactions: Controlled Clinical Trials

In the pooled dataset of controlled clinical trials, the most common treatment-emergent adverse events were dizziness, nausea, headache, dry mouth, and somnolence. Table 50 shows all TEAEs occurring at a frequency ≥2% in subjects treated with AXS-05 and more frequently with AXS-05 than with placebo.

Clinical Reviewer's Comment: It is notable that all TEAEs in Table 50 occurred more frequently with AXS-05 than with bupropion. This suggests that the dextromethorphan component of AXS-05 does not confer any safety benefit over bupropion given alone.

As mentioned in Section 8.2.1, subjects in the pooled bupropion column of Table 50 did not all receive the same dose of bupropion. In Study MDD-201, 48 subjects were treated with bupropion 105 mg twice daily. In Study 301, 156 subjects were treated with bupropion 150 mg twice daily. All subjects in the pooled AXS-05 column received the same dose of the combination

drug product (i.e., bupropion 105 mg + dextromethorphan 45 mg twice daily). Thus, 76% of subjects in the pooled bupropion group received a bupropion dose that is higher than that received by subjects in the pooled AXS-05 group. The higher frequencies in the AXS-05 group of all TEAEs in Table 50 compared to subjects most of whom received a higher dose of bupropion suggests that dextromethorphan makes a large contribution to the adverse effects of AXS-05.

Table 50. TEAEs of Frequency ≥2% and Greater than Placebo, Pooled Dataset, Controlled Trials

Preferred Term, n (%)	AXS-05 Pooled (n=364)	Bupropion Pooled (n=204)	PBO (n=164)
Dizziness	50 (13.7)	3 (1.5)	10 (6.1)
Nausea	37 (10.2)	9 (4.4)	14 (8.5)
Headache	24 (6.6)	13 (6.4)	6 (3.7)
Dry mouth	20 (5.5)	8 (3.9)	4 (2.4)
Somnolence	19 (5.2)	2 (1.0)	5 (3.0)
Diarrhoea	15 (4.1)	2 (1.0)	5 (3.0)
Insomnia	15 (4.1)	7 (3.4)	3 (1.8)
Anxiety	14 (3.8)	1 (0.5)	2 (1.2)
Decreased appetite	14 (3.8)	4 (2.0)	1 (0.6)
Constipation	13 (3.6)	7 (3.4)	3 (1.8)
Hyperhidrosis	10 (2.7)	1 (0.5)	0 (0.0)
Vision blurred	8 (2.2)	1 (0.5)	0 (0.0)

Source: Generated by the Clinical Reviewer.
Abbreviation: TEAE, treatment-emergent adverse event

Treatment-Emergent Adverse Events and Adverse Reactions: Long-Term Safety Trial

In the long-term safety trial, the most common treatment-emergent adverse events were dizziness, nausea, headache, dry mouth, and decreased appetite. Table 51 shows all TEAEs occurring at a frequency of ≥2%.

Clinical Reviewer's Comment: Decreased appetite occurred more frequently in the long-term trial (6.1%) than in the controlled trials (3.8%). However, AXS-05 in general demonstrated very similar safety profiles in the long-term and short-term trials. The four most frequent TEAEs were identical in the long-term and short-term trials.

Table 51. TEAEs With Frequency ≥2%, Long-Term Safety Trial

Preferred Term, n (%)	AXS-05 (N=876)
Dizziness	111 (12.7)
Nausea	104 (11.9)
Headache	77 (8.8)
Dry mouth	62 (7.1)
Decreased appetite	53 (6.1)
Nasopharyngitis	39 (4.5)
Upper respiratory tract infection	35 (4.0)
Anxiety	34 (3.9)
Diarrhoea	33 (3.8)
Insomnia	31 (3.5)
Somnolence	30 (3.4)
Constipation	29 (3.3)
Vision blurred	22 (2.5)
Weight increased	22 (2.5)
Gastroenteritis	19 (2.2)
Hyperhidrosis	18 (2.1)
Influenza	18 (2.1)

Source: Generated by the Clinical Reviewer.
Abbreviation: TEAE, treatment-emergent adverse event

Laboratory Findings: Controlled Clinical Trials

There were no clinically meaningful changes in chemistry, liver function, thyroid function, hematology, or urinalysis evaluations in any of the three 6-week controlled clinical trials. The laboratory evaluations conducted in the three controlled trials were similar, with the following exceptions: C-reactive protein was assessed only in Study MDD-201, and thyroid function studies were conducted only at screening in Study 301. Table 52 lists the laboratory studies conducted in the controlled clinical trials. Review of mean changes from baseline, shifts from baseline from normal to high values and from normal to low values, extreme outliers, and potentially clinically significant values did not reveal any patterns indicative of a clinically meaningful safety signal.

Table 52. Laboratory Studies Conducted in the Controlled Clinical Trials

Class of Laboratory Evaluation	Tests Conducted
Chemistry	Albumin, alkaline phosphatase, C-reactive protein, calcium, chloride, cholesterol, creatinine, glucose, potassium, protein, sodium, urea nitrogen
Liver Function	Alanine aminotransferase, aspartate aminotransferase, direct bilirubin
Thyroid Function	Thyrotropin, thyroxine, triiodothyronine
Hematology	Hemoglobin, hematocrit, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, mean corpuscular volume, platelet count, blood cell morphology
Urinalysis	Specific gravity, pH, glucose, ketones, protein, leukocyte esterase, microscopy

Source: Generated by the Clinical Reviewer.

Laboratory Findings: Long-Term Safety Trial

Chemistry, Long-Term Safety Trial: Shifts from Normal to Low

In Study 303, the chemistry parameters that demonstrated shifts from normal at baseline to low at the last visit in ≥5% of subjects were protein (13.3%), bilirubin (7.2%), calcium (7.2%), and urea nitrogen (5.6%). See Table 53.

Table 53. Clinical Chemistry Shift Changes From Normal at Postbaseline in ≥5% of Subjects, Long-Term Safety Population

Parameter (unit)	N1	Visit	AXS-05 Long-Term n (%)	
			Low	High
Bilirubin (µmol/L)	638	Any scheduled post-baseline visit	71 (11.1)	9 (1.4)
		Last visit	46 (7.2)	7 (1.1)
Calcium (mmol/L)	695	Any scheduled post-baseline visit	83 (11.9)	4 (0.6)
		Last visit	50 (7.2)	3 (0.4)
Protein (g/L)	579	Any scheduled post-baseline visit	129 (22.3)	1 (0.2)
		Last visit	77 (13.3)	1 (0.2)
Urea nitrogen (mmol/L)	660	Any scheduled post-baseline visit	65 (9.8)	24 (3.6)
		Last visit	37 (5.6)	19 (2.9)

Note: Denominators for percentages are N1=XXX, the total number of subjects who are normal at baseline but not subjects with only 1 baseline observation.
Source: NDA 215430 Summary of Clinical Safety, Table 56, page 74.

Clinical Reviewer's Comment: It is possible that decreases from normal to low in some chemistry values, particularly protein and calcium, could have some relationship to decreased appetite, which was reported as an AE in 5.7% of subjects in the long-term study.

Chemistry, Long-Term Safety Trial: Shifts from Normal to High

In Study 303, the chemistry parameters that demonstrated shifts from normal at baseline to high at the last visit in ≥5% of subjects were cholesterol, alanine aminotransferase (ALT), and alkaline phosphatase. See Table 54.

Table 54. Clinical Chemistry Result Shift Changes From Normal at Baseline to High at Postbaseline in ≥5% of Subjects, Long-Term Safety Population

Parameter (unit)	N1	Visit	AXS-05 Long-Term n (%)	
			Low	High
Cholesterol (mmol/L)	527	Any scheduled post-baseline visit	0	106 (20.1)
		Last visit	0	70 (13.3)
Alanine aminotransferase (U/L)	624	Any scheduled post-baseline visit	0	88 (14.1)
		Last Visit	0	59 (9.5)
Alkaline phosphatase (U/L)	618	Any scheduled post-baseline visit	20 (3.2)	41 (6.6)
		Last Visit	14 (2.3)	31 (5.0)

Note: Denominators for percentages are N1=XXX, the total number of subjects who are normal at baseline but not subjects with only 1 baseline observation.
Source: NDA 215430 Summary of Clinical Safety, Table 57, page 75.

The mean (SD) change in total cholesterol from baseline to last visit was 0.0 (0.63), suggesting no overall trends towards increased cholesterol for the study population.

Liver function tests were >2-fold the upper limit of normal in one subject (0.2%) for ALT and five subjects (0.7%) for aspartate aminotransferase (AST). One subject (0.1%) reported AST an AST value >3-fold the upper limit of normal. The mean (SD) changes from baseline to last visit for ALT, AST, and alkaline phosphatase were -0.8 (13.79), -2.1 (13.62), and 0.8 (10.29), respectively. The low percentage of subjects with values 2- or 3-fold the upper limit of normal for ALT and AST and low mean changes from baseline for ALT, AST, and alkaline phosphatase together suggest no overall trends towards increased values for any of these three laboratory tests for the study population.

Chemistry, Long-Term Safety Trial: Treatment-Emergent Adverse Events

In Study 303, TEAEs related to chemistry evaluations and occurring in more than one subject were ALT increased (0.3%), AST increased (0.3%), and hyperglycemia (0.3%). Hyperlipidemia, alkaline phosphatase increased, creatinine increased, hypokalemia, and cholesterol increased were reported for one subject each. None of these TEAEs was reported as an SAE.

One subject discontinued the study because of increased ALT and AST. The subject was a 23-year-old male who had AST of 23 U/L (reference range 14 to 39 U/L), ALT of 18 U/L (reference range 0 to 44 U/L), and elevated bilirubin of 29.1µmol/L (reference range 5.1 to 20.5µmol/L) at the baseline visit. Repeat labs were drawn at an unscheduled visit 1 week later because of a laboratory-related issue with the hematology panel collected at the baseline visit. At this second visit, AST was 379 U/L, ALT was 143 U/L, and bilirubin was 20.5µmol/L, with both AST and ALT significantly elevated. The subject was discontinued from the study and recommended for follow-up with his primary care provider to assess for Gilbert's disease. Repeat labs 1 week later showed AST 82 U/L, ALT 63 U/L, and bilirubin 25.7µmol/L, indicating improvement in AST and ALT but continued elevation of bilirubin. The Investigator evaluated the AST and ALT elevations as possibly related to the study drug.

Hematology, Long-Term Safety Trial: Shifts from Normal to Low

In Study 303, the hematology parameters that demonstrated shifts from normal at baseline to low at the last visit in ≥5% of subjects were erythrocyte mean corpuscular hemoglobin concentration (6.4%), hematocrit (6.2%), leukocytes (6.0%), and lymphocytes (10.6%). See Table 55.

Table 55. Clinical Hematology Result Shift Changes From Normal at Baseline to Low at Postbaseline in ≥5% of Subjects, Long-Term Safety Population

Parameter (unit)	N1	Visit	AXS-05 Long-Term n (%)	
			Low	High
Ery. mean corpuscular HGB concentration (g/L)	641	Any scheduled post-baseline visit	43 (6.7)	33 (5.1)
		Last visit	41 (6.4)	14 (2.2)
Hematocrit (L/L)	613	Any scheduled post-baseline visit	68 (11.1)	5 (0.8)
		Last visit	38 (6.2)	3 (0.5)
Leukocytes (10/L)	638	Any scheduled post-baseline visit	54 (8.5)	26 (4.1)
		Last visit	38 (6.0)	17 (2.7)
Lymphocytes (%)	592	Any scheduled post-baseline visit	94 (15.9)	38 (6.4)
		Last visit	63 (10.6)	26 (4.4)

Ery.=erythrocyte; HGB=hemoglobin
Note: Denominators for percentages are N1=XXX, the total number of subjects who are normal at baseline but not subjects with only 1 baseline observation.
Source: NDA 215430 Summary of Clinical Safety, Table 59, page 76.

Hematology, Long-Term Safety Trial: Shifts from Normal to High

In Study 303, the hematology parameters that demonstrated shifts from normal at baseline to high at the last visit in ≥5% of subjects were eosinophils (6.0%) and neutrophils (7.1%). See Table 56.

Table 56. Clinical Hematology Result Shift Changes From Normal at Baseline to High at Postbaseline in ≥5% of Subjects, Long-Term Safety Population

Parameter (unit)	N1	Visit	AXS-05 Long-Term n (%)	
			Low	High
Eosinophils (%)	664	Any scheduled post-baseline visit	0	58 (8.7)
		Last visit	0	40 (6.0)
Neutrophils (%)	650	Any scheduled post-baseline visit	31 (4.8)	62 (9.5)
		Last visit	22 (3.4)	46 (7.1)

Note: Denominators for percentages are N1=XXX, the total number of subjects who are normal at baseline but not subjects with only 1 baseline observation.
Source: NDA 215430 Summary of Clinical Safety, Table 60, page 76.

Hematology, Long-Term Safety Trial: Treatment-Emergent Adverse Events

In Study 303, the TEAEs related to hematology evaluations and occurring in more than one subject were TEAEs of anemia in three subjects (0.3%). None of these TEAEs were reported as SAEs.

Urinalysis, Long-Term Safety Trial: Changes from Baseline

In Study 303, there were no meaningful changes from baseline in urinalysis parameters.

Urinalysis, Long-Term Safety Trial: Treatment-Emergent Adverse Events

In Study 303, there were no TEAEs related to urinalysis findings.

Vital Signs

The evaluation of vital sign changes will focus on changes in blood pressure and pulse. Elevation of blood pressure is a known safety risk of bupropion. Although dextromethorphan when given alone in the therapeutic dose range is not known to cause hypertension or tachycardia, both can occur in cases of dextromethorphan toxicity. The clinical reviewer considered the possibility that dextromethorphan could contribute to increases in blood pressure and heart rate if given in combination with bupropion, which increases dextromethorphan exposure levels. The fact that elevated blood pressure may have contributed to some of the serious adverse events in the AXS-05 clinical trials provided additional motivation to evaluate the effect of AXS-05 on blood pressure and heart rate.

Vital Signs: Controlled Clinical Trials

The mean changes from baseline to Week 6 in systolic blood pressure, diastolic blood pressure, and heart rate were small and of comparable magnitude between the AXS-05 and the control arm in each of the controlled trials. See Table 57, Table 58, and Table 59.

Table 57. Study MDD-201: Mean Changes (SD) in Vital Signs, Baseline to Week 6

Parameter	AXS-05 (N=48)	Bupropion (N=45)
Systolic blood pressure, mm HG	1.6 (10.3)	2.5 (10.8)
Diastolic blood pressure, mm HG	2.9 (8.1)	2.9 (8.5)
Heart rate, bpm	2.5 (8.7)	3.1 (9.2)

Source: Generated by the Clinical Reviewer.
Abbreviations: bpm, beats per minute; SD, standard deviation

Table 58. Study MDD-301: Mean Changes (SD) in Vital Signs, Baseline to Week 6

Parameter	AXS-05 (N=162)	Placebo (N=164)
Systolic blood pressure, mm HG	2.6 (10.7)	-1.1 (10.7)
Diastolic blood pressure, mm HG	1.6 (8.0)	-0.2 (8.1)
Heart rate, bpm	3.0 (9.8)	1.2 (10.8)

Source: Generated by the Clinical Reviewer.
Abbreviations: bpm, beats per minute; SD, standard deviation

Table 59. Study 301: Mean Changes (SD) in Vital Signs, Baseline to Week 6

Parameter	AXS-05 (N=152)	Bupropion (N=156)
Systolic blood pressure, mm HG	-0.8 (11.5)	-0.5 (11.0)
Diastolic blood pressure, mm HG	-0.5 (8.2)	-0.6 (7.8)
Heart rate, bpm	1.1 (9.3)	0.8 (10.1)

Source: Generated by the Clinical Reviewer.
Abbreviations: bpm, beats per minute; SD, standard deviation

Vital Signs: Long-Term Safety Trial

The mean changes from baseline to the end of treatment in systolic blood pressure, diastolic blood pressure, and heart rate were small for subjects in Study 303. See Table 60.

Table 60. Study 303: Mean Changes (SD) in Vital Signs, Baseline to End of Treatment

Parameter	AXS-05 (N=876)
Systolic blood pressure, mm HG	0.8 (12.5)
Diastolic blood pressure, mm HG	0.1 (9.1)
Heart rate, bpm	3.1 (11.0)

Source: Generated by the Clinical Reviewer.
Abbreviations: bpm, beats per minute; SD, standard deviation

The Clinical Reviewer examined the percentages of subjects who experienced different magnitudes of change in systolic blood pressure, diastolic blood pressure, and heart rate from baseline to the end of treatment in Study 303. See Table 61.

Table 61. Study 303: Magnitude of Change in Vital Signs by Category

Change Category	SYSBP, N (%)	DIABP, N (%)	HR, N (%)
Increase from baseline >0 to <5	156 (18.2)	228 (26.6)	163 (19.0)
Increase from baseline 5 to <10	110 (12.9)	131 (15.3)	151 (17.6)
Increase from baseline 10 to <15	78 (9.1)	64 (7.5)	95 (11.1)
Increase from baseline 15 to <20	54 (6.3)	36 (4.2)	58 (6.8)
Increase from baseline 20 to <25	39 (4.6)	10 (1.2)	36 (4.2)
Increase from baseline 25 to <30	14 (1.6)	4 (0.5)	18 (2.1)
Increase from baseline ≥30	10 (1.2)	1 (0.1)	10 (1.2)

Change Category	SYSBP, N (%)	DIABP, N (%)	HR, N (%)
Decrease from baseline >0 to <5	123 (14.4)	139 (16.2)	133 (15.5)
Decrease from baseline 5 to <10	109 (12.7)	130 (15.2)	95 (11.1)
Decrease from baseline 10 to <15	78 (9.1)	67 (7.8)	55 (6.4)
Decrease from baseline 15 to <20	40 (4.7)	27 (3.2)	24 (2.8)
Decrease from baseline 20 to <25	23 (2.7)	15 (1.8)	11 (1.3)
Decrease from baseline 25 to <30	13 (1.5)	2 (0.2)	6 (0.7)
Decrease from baseline ≥30	9 (1.1)	2 (0.2)	1 (0.1)
Total Increase from baseline <10	266 (31.1)	359 (41.9)	314 (36.7)
Total Increase from baseline ≥10	195 (22.8)	115 (13.4)	217 (25.4)
Total decrease from baseline <10	232 (27.1)	269 (31.4)	228 (26.6)
Total decrease from baseline ≥10	163 (19.0)	113 (13.2)	97 (11.3)

Source: Generated by the Clinical Reviewer.
Abbreviations: DIABP, diastolic blood pressure; HR, heart rate; SYSBP, systolic blood pressure

One might expect that the number of subjects with increases in a vital sign parameter and with decreases in the same vital sign parameter would be fairly equal if the increases and decreases were randomly distributed throughout the study population. This appeared to be true for changes in blood pressure. The percentage of subjects with increases in systolic blood pressure ≥10 mm Hg and with decreases in systolic blood pressure ≥ 10 mm Hg were 22.8% and 19.0%, respectively, and the percentage of subjects with increases in diastolic blood pressure ≥10 mm Hg and with decreases in diastolic blood pressure ≥10 mm Hg were 13.4% and 13.2%, respectively. However, the percentage of subjects with increases in heart rate ≥10 beats per minute and with decreases in heart rate ≥10 beats per minute were 25.4% and 11.3%, respectively. This suggested the possibility that the distribution of changes in heart rate was skewed towards increased heart rate in the study population.

The Division of Psychiatry consulted the Division of Cardiology and Nephrology to evaluate for a possible safety signal for increased heart rate in Study 303. The Division of Cardiology and Nephrology reviewer noted that TEAEs related to tachycardia occurred in 8 (0.9%) subjects in Study 303. None were assessed as serious. One of the TEAEs resulted in discontinuation of study drug. For the other cases, AXS-05 was continued. All subjects who reported TEAEs related to tachycardia had not been treated with AXS-05 previously, and the majority had not participated in a previous AXS-05 study. No clear explanation for this observation has been identified. However, the Division of Cardiology and Nephrology reviewer found that the magnitude of heart rate increases in both the controlled trials and the long-term trial were small and did not indicate a major safety concern that would warrant a warning for tachycardia in the AXS-05 labeling.

Weight Changes: Controlled Clinical Trials

No clinically meaningful weight changes were noted in the controlled trials. Mean changes in weight from baseline to Week 6 for Study MDD-201 were -0.6 kg for AXS-05 and 0.1 kg for bupropion; for Study MDD-301 were -0.2 kg for AXS-05 and 0.4 kg for placebo; and for Study 301 were -0.3 for AXS-05 and -0.2 kg for bupropion.

Weight Changes: Long-Term Safety Trial

In the long-term trial, decreased appetite was reported as a TEAE in 5.7% of subjects and increased weight was reported as a TEAE in 3.1% of subjects. However, no clinically meaningful weight change was noted in the long-term trial. The mean change in weight from baseline to Month 12 was 1.0 kg. The mean weight was 87.9 kg at baseline, 90.0 kg at Month 3, 90.0 kg at Month 6, and 88.9 kg at Month 12, indicating no trend for increasing or decreasing weight over the course of the study.

Electrocardiograms: Controlled Clinical Trials

There were no clinically meaningful changes in ECG findings in any of the three controlled clinical trials.

ECG: Long-Term Safety Trial

There were minimal clinically meaningful changes in routine scheduled ECGs in the long-term safety trial. The percentage of subjects with any ECG abnormality was 41.2% at baseline and 45.1% at Month 12. For almost all subjects, the ECG abnormalities identified were assessed as not clinically significant. Clinically significant ECG abnormalities were identified in one subject at Month 3, in no subject at Month 6, in one subject at Month 9, and in no subject at Month 12. Thus, there was no pattern of increasing frequency of clinically significant ECG abnormalities in the long-term trial. See Table 62.

Table 62. Study 303: Interpretation of ECG Findings, Safety Population

VISIT	Value	Total (N=876)
Baseline	Normal	513 (58.7%)
	Abnormal - NCS	360 (41.2%)
	Abnormal - CS	0 (0.0%)
	Total	874
Month 3	Normal	413 (58.8%)
	Abnormal - NCS	288 (41.0%)
	Abnormal - CS	1 (0.1%)
	Total	702
Month 6	Normal	332 (59.7%)
	Abnormal - NCS	224 (40.3%)
	Abnormal - CS	0 (0.0%)
	Total	556
Month 9	Normal	261 (58.8%)
	Abnormal - NCS	182 (41.0%)
	Abnormal - CS	1 (0.2%)
	Total	444
Month 12	Normal	73 (54.9%)
	Abnormal - NCS	60 (45.1%)
	Abnormal - CS	0 (0.0%)
	Total	133

Source: AXS-05-303 Clinical Study Report, Table 46, page 104.
Abbreviations: CS, clinically significant; ECG, electrocardiogram; NCS, not clinically significant

Three ECG findings reported as TEAEs occurred during Study 303: T-wave abnormal, atrial fibrillation, and ventricular extrasystoles, each occurring in a different subject. The TEAE of T-wave abnormality occurred in a subject previously discussed regarding the SAE of acute myocardial infarction. The TEAE of atrial fibrillation resulted in discontinuation from the study and was assessed by the Investigator as possibly related to the study drug. The TEAE of ventricular extrasystoles was not discussed in detail in the CSR. Based on data in the AE dataset, the TEAE was assessed as possibly related to the study drug, but the severity of the TEAE was assessed as mild, the TEAE resolved, the subject continued in the study, and the dose of the study drug was not changed.

QT: Thorough QT Study

The Applicant has completed a thorough QT interval study (Study AXS-05-109) to characterize the effects of AXS-05 treatment on the corrected QT interval. AXS-05 was administered to healthy subjects at therapeutic and supratherapeutic doses. The change in corrected QT interval was compared to subjects treated with the positive control drug moxifloxacin. Analysis by the FDA QT Interdisciplinary Review Team (QT-IRT) resulted in a calculated placebo-

corrected change from baseline Fridericia corrected QT interval of 4.7 msec for the therapeutic dose and 6.6 msec for the supratherapeutic dose. The FDA QT Interdisciplinary Review Team concluded that the results indicated no significant corrected QT interval prolongation effect of AXS-05 at the therapeutic or supratherapeutic dose. The FDA QT Interdisciplinary Review Team also concluded that no dose adjustment would be required for subjects with hepatic impairment.

8.2.5. Analysis of Submission-Specific Safety Issues

Potential safety issues that warranted detailed evaluation have been described above under Adverse Events of Special Interest and Vital Signs.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

The labeling for all approved antidepressants includes a warning about the possible risk of the onset or exacerbation of suicidal ideation and behavior during treatment. The Applicant included the C-SSRS as part of the safety assessment in all three controlled trials and the long-term safety trial (refer to Section 7.3 for details on the C-SSRS instrument). The clinical reviewer analyzed the C-SSRS results for these studies to determine whether there was any observable pattern of increased suicidal ideation or behavior for subjects treated with AXS-05.

There were no subjects in either the controlled trials or the long-term safety trial who answered "Yes" to any of the six C-SSRS questions about suicidal behavior at any study visit. As discussed above under Serious Adverse Events: Long-Term Safety Trial, there was a single subject in Study 303 who had an SAE that was coded as an aborted suicide attempt. The subject was not hospitalized and continued in the study. The subject answered "No" to all six C-SSRS questions about suicidal behavior at all study visits.

The remainder of this analysis will focus on the five C-SSRS questions that elicit information about suicidal ideation.

C-SSRS: Controlled Trials, Pooled Dataset

Subjects with answers of "Yes" to either C-SSRS Question 4 or Question 5 at screening were excluded from each of the controlled trials. The dataset of C-SSRS scores shows very few subjects answering "Yes" at any time to C-SSRS Question 3 (active suicidal ideation without intent to act). Thus, the analysis for the controlled trials consisted of determining the percentage of subjects treated with AXS-05, bupropion, or placebo who answered "Yes" to Questions 1 (wish to be dead) and 2 (nonspecific active suicidal thoughts) from baseline to the end of treatment (Week 6).

C-SSRS results were available for all three trials for study visits at baseline, Week 1, Week 2, Week 4, and Week 6. For Question 1, the percentage of subjects answering "Yes" generally decreased over the course of the study for all three treatment groups. There was a slight increase in the percentage of "Yes" responses at Week 4, but this was followed by a decrease in "Yes" responses at Week 6.

For Question 2, it is difficult to discern whether there is a clear temporal pattern because the percentage of subjects answering "Yes" is small for all three treatment groups. The results for the AXS-05 group suggest a possible decrease in frequency of "Yes" answers for Question 2 from baseline to Week 2 followed by a rise in frequency of "Yes" answers from Week 2 to Week 6 (Table 63). This could represent random noise and should be considered in the context of the large percentage of subjects (96% or greater) who answered "No" to this question over the entire course of the study. Although this analysis could raise possible concerns about an initial improvement in suicidal ideation followed by worsening, the following analysis of data from the long-term safety trial does not indicate a pattern of worsening suicidal ideation over time for subjects treated with AXS-05.

Table 63. Percentage of Subjects Answering "Yes" to C-SSRS Question 1 or Question 2 From Baseline to Week 6, Pooled Dataset of Controlled Trials

C-SSRS Questions and Responses, n (%)	AXS-05 (N=292)	BUP (N=177)	PBO (N=148)
Q1: Wish to be dead="Yes"			
Baseline	47 (16.1)	36 (20.3)	17 (11.5)
Week 1	33 (11.3)	29 (16.4)	9 (6.1)
Week 2	23 (7.9)	29 (16.4)	10 (6.8)
Week 4	26 (8.9)	27 (15.3)	9 (6.1)
Week 6	24 (8.2)	23 (13.0)	6 (4.1)
Q2: Nonspecific active suicidal thoughts="Yes"			
Baseline	12 (4.1)	5 (2.8)	3 (2.0)
Week 1	7 (2.4)	7 (4.0)	2 (1.4)
Week 2	3 (1.0)	5 (2.8)	2 (1.4)
Week 4	6 (2.1)	4 (2.3)	3 (2.0)
Week 6	11 (3.8)	5 (2.8)	2 (1.4)

Source: Generated by the Clinical Reviewer.
Abbreviations: C-SSRS, Columbia-Suicide Severity Rating Scale; Q, question

C-SSRS: Long-Term Safety Trial

The long-term safety trial did not explicitly restrict subjects from entering the study on the basis of baseline C-SSRS scores. However, the number of subjects in the trial who had C-SSRS scores ≥3 at baseline was very small. Review of the percentages of subjects who answered "Yes" to Questions 1 and 2 at baseline and at Month 3, Month 6, and Month 12 did not reveal any pattern of increased frequency of suicidal ideation (Table 64, Table 65, and Table 66).

Table 64. Study 303: Percentage of Subjects Answering "Yes" to C-SSRS Question 1 or Question 2 at Baseline or at Month 3

C-SSRS Questions and Responses, n (%)	AXS-05 (N=657)
Q1: Wish to be dead='Yes'	
Baseline	118 (18.0)
Month 3	13 (2.0)

C-SSRS Questions and Responses, n (%)	AXS-05 (N=657)
Q2: Nonspecific active suicidal thoughts='Yes"	
Baseline	32 (4.9)
Month 3	5 (0.8)

Source: Generated by the Clinical Reviewer.
Abbreviations: C-SSRS, Columbia-Suicide Severity Rating Scale; Q, question

Table 65. Study 303: Percentage of Subjects Answering "Yes" to C-SSRS Question 1 or Question 2 at Baseline or at Month 6

C-SSRS Questions and Responses, n (%)	AXS-05 (N=582)
Q1: Wish to be dead='Yes'	
Baseline	96 (16.5)
Month 6	6 (1.0)
Q2: Nonspecific active suicidal thoughts='Yes'	
Baseline	26 (4.5)
Month 6	1 (0.2)

Source: Generated by the Clinical Reviewer.
Abbreviations: C-SSRS, Columbia-Suicide Severity Rating Scale; Q, question

Table 66. Study 303: Percentage of Subjects Answering "Yes" to C-SSRS Question 1 or Question 2 at Baseline or at Month 12

C-SSRS Questions and Responses, n (%)	AXS-05 (N=59)
Q1: Wish to be dead='Yes'	
Baseline	10 (16.9)
Month 12	1 (1.7)
Q2: Nonspecific active suicidal thoughts='Yes'	
Baseline	2 (3.4)
Month 12	2 (3.4)

Source: Generated by the Clinical Reviewer.
Abbreviations: C-SSRS, Columbia-Suicide Severity Rating Scale; Q, question

Clinical Reviewer's Comment: These analyses were exploratory. Patterns of change in C-SSRS question responses in the short-term trials are difficult to interpret but may represent noise. Analysis of C-SSRS question responses in the long-term trial did not reveal any pattern of increasing suicidal ideation over time.

8.2.7. Safety Analyses by Demographic Subgroups

The Clinical Reviewer analyzed the data on TEAEs from the short-term controlled trials and the long-term open-label trial by sex, age, race, and ethnicity to identify any differences in frequency of AEs for subgroups of subjects. For each subject demographic, the analysis examined only two subgroups, even if subjects could potentially be separated into more than two subgroups. The measure of difference in frequency of adverse events between Subgroup 1 and Subgroup 2 was simply the difference between the percentage of subjects experiencing the adverse event in each of the subgroups.

For the three controlled trials, the pooled dataset of AEs was used for the analysis. Only data for subjects exposed to AXS-05 were analyzed, because the treatment comparators differed between the studies (i.e., placebo, bupropion 105 mg twice daily, or bupropion 150 mg twice

daily). For the long-term open-label trial, all subjects were included, because all subjects were exposed to AXS-05. The tables display only TEAEs for which the difference in frequency between demographic groups was 2% or higher.

Sex

In the short-term controlled trials, the TEAEs with the largest difference in frequency between males and females were dizziness (difference=5.8%) and nausea (difference=4.7%), both occurring more frequently in females. In the long-term safety trial, the TEAEs with the largest difference in frequency between males and females were nausea (difference=5.3%) and headache (difference=3.4%), both occurring more frequently in females. See Table 67 and Table 68.

Clinical Reviewer's Comment: *Interpretation of the differences in AE frequencies requires caution because the sex subgroups are not balanced in size in either the pooled dataset of controlled trials or the long-term safety trial. Additionally, two of the short-term trials and the long-term trial did not include a placebo arm that could be used to estimate the base rates of AEs in the general population.*

Table 67. TEAE Frequency by Sex, With Difference in Frequency ≥2%, Pooled Controlled Trials

Preferred Term, n (%)	Male (N=138)	Female (N=226)	Difference in Frequency (%)
Dizziness	14 (10.1)	36 (15.9)	5.8
Nausea	10 (7.2)	27 (11.9)	4.7
Erectile dysfunction	6 (4.3)	0 (0.0)	4.3
Constipation	8 (5.8)	5 (2.2)	3.6
Vision blurred	0 (0.0)	8 (3.5)	3.5
Anxiety	8 (5.8)	6 (2.7)	3.1
Dry mouth	5 (3.6)	15 (6.6)	3.0
Somnolence	5 (3.6)	14 (6.2)	2.6
Yawning	4 (2.9)	1 (0.4)	2.5
Headache	7 (5.1)	17 (7.5)	2.4
Abdominal discomfort	3 (2.2)	0 (0.0)	2.2
Hyperhidrosis	2 (1.4)	8 (3.5)	2.1
Diarrhoea	4 (2.9)	11 (4.9)	2.0
Nasopharyngitis	4 (2.9)	2 (0.9)	2.0

Source: Generated by the Clinical Reviewer.
Abbreviation: TEAE, treatment-emergent adverse event

Table 68. TEAE Frequency by Sex, With Difference in Frequency ≥2%, Long-Term Safety Trial

Preferred Term, n (%)	Male (N=316)	Female (N=560)	Difference in Frequency (%)
Nausea	27 (8.5)	77 (13.8)	5.3
Headache	21 (6.6)	56 (10.0)	3.4
Urinary tract infection	0 (0.0)	17 (3.0)	3.0
Libido decreased	12 (3.8)	5 (0.9)	2.9
Dizziness	35 (11.1)	76 (13.6)	2.5
Influenza	2 (0.6)	16 (2.9)	2.3
Upper respiratory tract infection	8 (2.5)	27 (4.8)	2.3

Preferred Term, n (%)	Male (N=316)	Female (N=560)	Difference in Frequency (%)
Nasopharyngitis	10 (3.2)	29 (5.2)	2.0

Source: Generated by the Clinical Reviewer.
Abbreviation: TEAE, treatment-emergent adverse event

Age

The inclusion criteria for all studies in the clinical development program specified that eligible subjects would be in the age range from 18 to 65 years, inclusive. Thus, no subjects over the age of 65 years were included in the studies. For this analysis, subjects were divided into two subgroups: those below the median age of the study population and those at or above the median age. For the pooled dataset of controlled trials, the median age of subjects exposed to AXS-05 was 42 years. For the long-term open-label trial, the median age of subjects exposed to AXS-05 was 43 years.

In the short-term controlled trials, the TEAEs with the largest difference in frequency between younger subjects and older subjects were dizziness (difference=6.9%) and nausea (difference=6.2%), both occurring more frequently in younger subjects. In the long-term safety trial, the TEAEs with the largest difference in frequency between younger subjects and older subjects were nausea (difference=5.5%) and dry mouth (difference=3.0%), both occurring more frequently in younger patients.

Clinical Reviewer's Comment: It is notable that, of the TEAEs with a difference in frequency of 2% or higher, almost all occurred more frequently in younger patients, with the exceptions of increased blood pressure in the short-term controlled trials and constipation in the long-term safety trial. See Table 69 and Table 70.

Table 69. TEAE Frequency by Age With a Difference in Frequency of ≥2%, Pooled Controlled Trials

Preferred Term, n (%)	Age <42 Years (N=180)	Age ≥ 42 Years (N=184)	Difference in Frequency (%)
Dizziness	31 (17.2)	19 (10.3)	6.9
Nausea	24 (13.3)	13 (7.1)	6.2
Decreased appetite	10 (5.6)	4 (2.2)	3.4
Diarrhoea	10 (5.6)	5 (2.7)	2.9
Fatigue	6 (3.3)	1 (0.5)	2.8
Dry mouth	12 (6.7)	8 (4.3)	2.4
Blood pressure increased	0 (0.0)	4 (2.2)	2.2

Source: Generated by the Clinical Reviewer.
Abbreviation: TEAE, treatment-emergent adverse event

Table 70. TEAE Frequency by Age With a Difference in Frequency of ≥2%, Long-Term Safety Trial

Preferred Term, n (%)	Age <43 Years (N=430)	Age ≥43 Years (N=446)	Difference in Frequency (%)
Nausea	63 (14.7)	41 (9.2)	5.5
Dry mouth	37 (8.6)	25 (5.6)	3.0
Decreased appetite	32 (7.4)	21 (4.7)	2.7
Nasopharyngitis	25 (5.8)	14 (3.1)	2.7
Dizziness	60 (14.0)	51 (11.4)	2.6
Cough	11 (2.6)	2 (0.4)	2.2
Libido decreased	13 (3.0)	4 (0.9)	2.1

Preferred Term, n (%)	Age <43 Years (N=430)	Age ≥43 Years (N=446)	Difference in Frequency (%)
Constipation	10 (2.3)	19 (4.3)	2.0

Source: Generated by the Clinical Reviewer.
Abbreviation: TEAE, treatment-emergent adverse event

To further explore differences in AE frequencies among age subgroups, the Clinical Reviewer analyzed the AE data from Study MDD-301, which was the only study that included a placebo arm. AE frequencies for the AXS-05 arm and placebo arm were calculated for subjects below and above the study population's median age of 41 years. The differences between AE frequencies for the AXS-05 and placebo arms were calculated to assess how much the AE frequencies in the AXS-05 group differed from the frequencies in the general population (represented by the placebo group). See Table 71 and Table 72. For each age group, the AEs shown are those that occurred in both the AXS-05 arm and the placebo arm and for which the difference between frequencies of occurrence was ≥2%.

Table 71. Study MDD-301: TEAE Frequencies for Subjects < Median Age (41 Years)

Preferred Term, n (%)	AXS-05 Age < Median (N=79)	Placebo Age < Median (N=83)	% Difference (AXS-05 Minus Placebo)
Dizziness	15 (19.0)	7 (8.4)	10.6
Diarrhoea	7 (8.9)	0 (0.0)	8.9
Headache	6 (7.6)	1 (1.2)	6.4
Dry mouth	6 (7.6)	2 (2.4)	5.2
Somnolence	6 (7.6)	2 (2.4)	5.2
Nausea	10 (12.7)	7 (8.4)	4.3
Decreased appetite	4 (5.1)	1 (1.2)	3.9
Fatigue	3 (3.8)	0 (0.0)	3.8
Upper respiratory tract infection	4 (5.1)	2 (2.4)	2.7

Source: Generated by the Clinical Reviewer.
Abbreviation: TEAE, treatment-emergent adverse event

Table 72. Study MDD-301: TEAE Frequencies for Subjects ≥ Median Age (41 Years)

Preferred Term, n (%)	AXS-05 Age ≥ Median (n=83)	Placebo Age ≥ Median (n=81)	% Difference (AXS-05 Minus Placebo)
Dizziness	11 (13.3)	3 (3.7)	9.6
Insomnia	4 (4.8)	0 (0.0)	4.8
Anxiety	5 (6.0)	1 (1.2)	4.8
Nausea	11 (13.3)	7 (8.6)	4.7
Constipation	3 (3.6)	1 (1.2)	2.4
Urinary tract infection	2 (2.4)	0 (0.0)	2.4
Decreased appetite	2 (2.4)	0 (0.0)	2.4
Feeling abnormal	3 (3.6)	1 (1.2)	2.4
Somnolence	5 (6.0)	3 (3.7)	2.3
Headache	7 (8.4)	5 (6.2)	2.2

Source: Generated by the Clinical Reviewer.
Abbreviation: TEAE, treatment-emergent adverse event

For the AE of dizziness, which was the most frequent AE in both age groups in the study, the difference between frequencies in the AXS-05 arm and the placebo arm was similar in both age groups; 10.6% for age < median and 9.6% for age ≥ median. This suggests that the increased

incidence of dizziness in younger subjects treated with AXS-05 could be attributed to higher baseline rates of dizziness in this age group. It is notable that the AEs that ranked next-highest in frequency above the placebo rate were different in the two age groups; diarrhea, headache, and dry mouth for age < median; insomnia, anxiety, and nausea for age ≥ median.

Race

For the pooled population of subjects in the controlled studies who were treated with AXS-05, most subjects have a recorded race designated as either white (n=219) or as black or African American (n=117). The subjects of other racial designations were few: Asian (n=12), other (n=7), Native Hawaiian or Other Pacific Islander (n=33), multiple (n=3), not reported (n=1). For this analysis, the two racial groups compared were white and black or African American.

For the long-term open-label study, as in the pooled dataset of controlled trials, most subjects have a recorded race designated as either white (n=509) or as black or African American (n=301). The subjects of other racial designations were few: Asian (n=29), other (n=15), multiple (n=10), not reported (n=5), Native Hawaiian or Other Pacific Islander (n=4), American Indian or Alaska Native (n=3). As in the previous analysis, the two racial groups compared were white and black or African American.

In the short-term controlled trials, the TEAEs with the largest difference in frequency between white and African American subjects were diarrhea (difference=5.4%) and dry mouth (difference=4.2%), with diarrhea occurring more frequently in African American subjects and dry mouth occurring more frequently in white subjects. In the long-term safety trial, the TEAEs with the largest difference in frequency between white and African American subjects were dizziness (difference=8.5%) and nausea (difference=6.3%), with both occurring more frequently in white subjects. See Table 73 and Table 74.

Clinical Reviewer's Comment: Interpretation of the differences in AE frequencies requires caution because the racial subgroups are not balanced in size in either the pooled dataset of controlled trials or the long-term safety trial. The somewhat large difference between white and African American subjects in frequency of dizziness in the long-term safety trial is difficult to evaluate without a placebo arm in that study that could be used to estimate the base rates of AEs in the general population.

Table 73. TEAE Frequency by Race, With Difference in Frequency ≥2%, Pooled Controlled Trials

Preferred Term, n (%)	Black or African American (N=117)	White (N=219)	Difference in Frequency (%)
Diarrhoea	9 (7.7)	5 (2.3)	5.4
Dry mouth	3 (2.6)	15 (6.8)	4.2
Insomnia	2 (1.7)	12 (5.5)	3.8
Anxiety	2 (1.7)	11 (5.0)	3.3
Decreased appetite	2 (1.7)	11 (5.0)	3.3
Upper respiratory tract infection	0 (0.0)	7 (3.2)	3.2
Nasopharyngitis	0 (0.0)	6 (2.7)	2.7
Vision blurred	4 (3.4)	3 (1.4)	2.0

Source: Generated by the Clinical Reviewer.
Abbreviation: TEAE, treatment-emergent adverse event

Table 74. TEAE Frequency by Race, With Difference in Frequency ≥2%, Long-Term Safety Trial

Preferred Term, n (%)	Black or African American (N=301)	White (N=509)	Difference in Frequency (%)
Dizziness	23 (7.6)	82 (16.1)	8.5
Nausea	26 (8.6)	71 (13.9)	5.3
Upper respiratory tract infection	5 (1.7)	28 (5.5)	3.8
Insomnia	3 (1.0)	23 (4.5)	3.5
Decreased appetite	14 (4.7)	35 (6.9)	2.2
Hyperhidrosis	2 (0.7)	15 (2.9)	2.2
Headache	21 (7.0)	47 (9.2)	2.2
Increased appetite	7 (2.3)	1 (0.2)	2.1

Source: Generated by the Clinical Reviewer.
Abbreviation: TEAE, treatment-emergent adverse event

Ethnicity

In the pooled population of subjects in the controlled studies who were treated with AXS-05, the number of subjects with ethnicity recorded as Hispanic or Latino was very small (n=35 of 364 subjects). The small number is partly because the dataset for Study 301 includes a field for recording race but does not include a field for recording ethnicity. Comparison of frequency of AEs by ethnicity was conducted only for the long-term open-label study. For that study, the sizes of subgroups were as follows: Not Hispanic or Latino (n=724), Hispanic or Latino (n=151), not reported (n=1). The one subject with ethnicity not recorded was excluded from the analysis.

In the long-term safety trial, the TEAEs with the largest difference in frequency between Hispanic or Latino and non-Hispanic or Latino subjects were nausea (difference=7.3%) and headache (difference=7.0%), with both occurring more frequently in Hispanic or Latino subjects. See Table 75.

Clinical Reviewer's Comment: *Interpretation of the differences in AE frequencies by ethnicity requires caution because the ethnic subgroups are not balanced in size in either the pooled dataset of controlled trials or the long-term safety trial. Additionally, the long-term trial does not include a placebo arm that could be used to estimate the base rates of AEs in the general population.*

Table 75. TEAE Frequency by Ethnicity, With Difference in Frequency ≥2%, Long-Term Safety Trial

Preferred Term, n (%)	Hispanic or Latino (n=151)	Not Hispanic or Latino (n=724)	Difference in Frequency (%)
Nausea	27 (17.9)	77 (10.6)	7.3
Headache	22 (14.6)	55 (7.6)	7.0
Dry mouth	15 (9.9)	47 (6.5)	3.4
Vision blurred	8 (5.3)	14 (1.9)	3.4
Decreased appetite	13 (8.6)	40 (5.5)	3.1
Abdominal pain upper	5 (3.3)	5 (0.7)	2.6
Tinnitus	0 (0.0)	16 (2.2)	2.2
Abdominal pain	4 (2.6)	4 (0.6)	2.0

Source: Generated by the Clinical Reviewer.
Abbreviation: TEAE, treatment-emergent adverse event

Conclusions on Safety Analyses by Demographic Subgroup

Interpretation of the safety analyses for demographic subgroups age, race, and ethnicity requires caution because the subgroups are not balanced in size in either the pooled dataset of controlled trials or the long-term safety trial. The one analysis that involved subgroups of fairly equal size is the analysis by age, for which the median age was chosen as the threshold for separating the study populations into subgroups. These analyses suggest somewhat higher frequencies of several TEAEs in younger subjects than in older subjects, with differences in frequency during the short-term trials of 6.9% and 6.2% for dizziness and nausea, respectively. Examination of placebo-controlled differences in AE frequencies between younger and older subjects suggests the possibility of a slightly different adverse event profile in younger subjects than in older subjects. However, this analysis must be considered exploratory only, as it is based on just a single short-term trial.

None of the subgroup analyses revealed differences in frequency of any TEAE that were large enough to warrant a label warning or adjustments in the recommended therapeutic regimen. However, the analyses suggesting the possibility of higher frequency of some TEAEs in younger than in older subjects will be an issue for consideration in the future when the Applicant begins developing plans for studies of AXS-05 in the pediatric population.

8.2.8. Specific Safety Studies/Clinical Trials

The only specific safety study conducted was the thorough QT interval study discussed above.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No human carcinogenicity or tumor development studies were submitted with the application.

Human Reproduction and Pregnancy

No human reproduction or pregnancy studies were submitted with the application.

Pediatrics and Assessment of Effects on Growth

No pediatric studies were submitted with the application. See Section 10 for additional discussion of pediatric regulatory issues.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

These issues were discussed in the section of the review on AESIs.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

AXS-05 is currently not marketed in any country.

Expectations on Safety in the Postmarket Setting

The Agency expects that the safety risks with AXS-05 could be adequately managed by appropriate labeling (including a Drug Abuse and Dependence section that describes the abuse-related risks of dextromethorphan) and routine pharmacovigilance.

8.2.11. Integrated Assessment of Safety

Because AXS-05 is composed of bupropion and dextromethorphan, it is reasonable to expect that the combination drug would be susceptible to the safety risks of each component. It does not appear that either of the component's safety risks is amplified by the combination. The risk of abuse potential was of particular concern because the combination increases exposure to dextromethorphan. However, the evaluation of substance abuse potential does not show evidence of a notable risk of abuse or withdrawal for AXS-05. The possibility that AXS-05 might cause greater increases in blood pressure and pulse than bupropion alone was explored. The safety review did not reveal evidence for greater increases in blood pressure and pulse during treatment with AXS-05 than when bupropion is given alone. Based on the safety review conducted, it does not appear that the product labeling for AXS-05 will require any safety warnings that are not included in the labeling for either of its components.

8.3. Statistical Issues

As discussed in Section 8.1, the Biostatistics reviewer identified four subjects who the Applicant had erroneously included in the prespecified efficacy analysis population (mITT) in Study MDD-201: one who had never received the study drug and three who had only baseline efficacy assessments and no postbaseline efficacy assessments. All of these subjects were in the bupropion (comparator) arm of the study. Including these subjects in the efficacy analysis created a relative disadvantage for bupropion to be able to demonstrate a treatment effect in the study. If these four subjects are removed from the efficacy analysis set, Study MDD-201 would not be a positive study if the change in MADRS score from baseline to Week 6 without averaging at intermediate time points were used as the primary efficacy endpoint. However, if the Applicant's pre-specified primary efficacy endpoint is used, a statistically significant separation of AXS-05 from placebo is observed even after these four subjects are removed from the efficacy analysis set.

In the same Study MDD-201, the primary efficacy analysis was based on MMRM with *variance-components* covariance matrix, but missing data were imputed by the LOCF method prior to the MMRM analysis. The single-value-imputation approaches such as the LOCF have been discouraged by National Research Council[9]. In addition, the proposed covariance matrix, which assumes zero correlations in efficacy outcomes among visits, is not supported by the study data, either. An unstructured covariance matrix should be used to avoid substantial

[9] National Research Council, N. R. (2010). The Prevention and Treatment of Missing Data in Clinical Trials. Washington, DC, The National Academies Press. https://www.nap.edu/catalog/12955/the-prevention-and-treatment-of-missing-data-in-clinical-trials

underestimation of the standard error of the estimated treatment effect estimate, due to potential mis-specification of the covariance matrix. If a structured covariance matrix is used, it should be used with a sandwich estimator to address the potential mis-specification. FDA's re-analyses using MMRM and dropping the LOCF method (that is, without imputing missing outcomes) did not support the Applicant's primary analysis results, particularly when an unstructured covariance matrix was used.

8.4. Conclusions and Recommendations

Based on the evidence of efficacy of AXS-05 provided by Study MDD-301, the supportive evidence provided by Study MDD-201 and by the previous approval of bupropion SR to fulfill the FDA Combination Rule, and the absence of any safety risks that would preclude approval of AXS-05, the Agency recommends approval of AXS-05 for the treatment of MDD.

9. Advisory Committee Meeting and Other External Consultations

This application was not presented to an Advisory Committee.

On June 30, 2021, the Division of Psychiatry presented this application to the FDA Medical Policy and Program Review Council (MPPRC) to get input from leadership of the Center for Drug Evaluation and Research on whether the Applicant's submitted study results were adequate to fulfill the Combination Rule and provide substantial evidence of effectiveness for AXS-05.

To contextualize the discussion at this first MPPRC meeting, it is important to note that when the Division presented the results from Study MDD-201, the primary efficacy endpoint was described as the change from baseline to end of treatment in MADRS total score rather than the Applicant's pre-specified primary efficacy endpoint (mean change in MADRS total score from baseline to each time point from Week 1 to Week 6). The Division's decision to present this endpoint was because the Division had advised the Applicant at the Pre-NDA meeting that the change from baseline to end of treatment was more typically used to support the approval of antidepressants, and the Applicant used this endpoint to describe the results of Study MDD-201 in draft labeling submitted with the application.

Regarding Study MDD-201, the MPPRC agreed with the Division's assertion that the subjects who did not have any postbaseline efficacy assessments and the subject who never took the study drug should not have been included in the mITT population, which was the population prespecified by the Applicant for the efficacy analysis. MPPRC agreed with the analyses completed by Biometrics which omitted these four subjects from the mITT population; these analyses indicated that Study AXS-05-MDD-201 should be considered a negative study. In the absence of any other studies demonstrating that dextromethorphan has an antidepressant effect that is independent of the antidepressant effect of bupropion, and in light of the AE data indicating that the combination of dextromethorphan and bupropion does not provide a safety advantage over bupropion alone, MPPRC agreed that the FDA Combination Rule was not

fulfilled by the data submitted by the Applicant. In addition, the one positive study (AXS-05-MDD-301), which compared AXS-05 to placebo, would not be sufficient on its own to support a single-study NDA. The MPPRC agreed unanimously with the Division's decision at the time of this first meeting to move forward with a CR action.

The Division of Psychiatry requested a second meeting with MPPRC to discuss two issues: first, whether Study MDD-201 or Study 301 provided adequate evidence of a contribution of dextromethorphan to fulfill the combination rule; and second, whether a study that compared AXS-05 to a dose of bupropion SR that is lower than the labeled effective dose could still be used to satisfy the FDA Combination Rule.

The second MPPRC meeting was held on September 8, 2021. The Division noted that the averaged MADRS endpoint (pre-specified as the primary endpoint in the Study MDD-201 SAP) could potentially be skewed by large improvements early in treatment. One MPPRC member asserted that all antidepressants tend to show a greater treatment effect early in a clinical trial and that there is expected to be some week-to-week variability, supporting the use of the averaged MADRS endpoint. MPPRC also noted that the contribution of each component must be to a therapeutically relevant endpoint and that this does not have to be the registration endpoint. MPPRC opined that the averaged MADRS endpoint could be used to establish contribution of components, even if it was not used for registration. Regarding the bupropion dose used in Study MDD-201, the Division noted that the dose of bupropion used in the combination drug was supported by the Applicant's previous phase 1 studies demonstrating that this dose of bupropion would increase dextromethorphan exposure to a level that the Applicant believed would allow dextromethorphan to manifest an antidepressant effect. MPPRC opined that it was justified not to compare AXS-05 to a higher bupropion dose to demonstrate contribution of components.

Regarding Study 301, MPPRC noted that although the study was not positive on the primary endpoint at Week 6, the comparison between AXS-05 and bupropion did have nominal significance on the secondary endpoints, including change in MADRS at most weeks prior to Week 6, and the average change in MADRS over the course of treatment. MPPRC noted that this provides further support for the DXM contribution to the antidepressant effect. It was commented that the evidence that can support contribution of components may be considered as a weight of evidence type approach—a standard not appropriate for supporting approval. Hence, Study MDD-201 and Study 301 together provide sufficient support for contribution of components.

MPPRC felt that it was unclear whether the AXS-05 program demonstrates substantial evidence of effectiveness to support approval. MPPRC noted that, although pre-specification is important for controlling type 1 error, the lack of statistical significance in Study MDD-201 for the Division's preferred efficacy endpoint was an issue. MPPRC proposed that the Division consult an Advisory Committee for feedback on endpoints in depression trials, including whether the MADRS averaged over time should be an acceptable endpoint.

After the second MPPRC meeting, the Division of Psychiatry re-evaluated whether the results of the AXS-05 clinical trials were sufficient to support approval. An important element in our re-

assessment was the opinion of MPPRC that a clinical trial that succeeded on a therapeutically relevant endpoint could be used to demonstrate contribution of components, even if the trial did not succeed on an endpoint that would be used for registration. The results of Study MDD-201 provide supportive evidence of efficacy of AXS-05 by demonstrating contribution of the dextromethorphan component to the antidepressant effect of the drug. The previous approval of bupropion SR for the treatment of MDD provides prior evidence that the bupropion component of AXS-05 contributes to the antidepressant effect of the drug. The success of Study MDD-301 on the primary efficacy endpoint that the Division has previously used for labeling, combined with supportive evidence of the contribution of components provided by the results of Study MDD-201 and the previous approval of bupropion SR, provides substantial evidence of the efficacy of AXS-05 to support approval. Therefore, the Division of Psychiatry and the Office of Neuroscience agreed that it would not be necessary to convene an Advisory Committee to assess whether the AXS-05 program has demonstrated substantial evidence of effectiveness to support approval. Whether an averaging endpoint is acceptable as a registrational endpoint for antidepressant studies was determined to be non-critical for informing the current regulatory decision but may warrant further study in the future.

10. Pediatrics

The Applicant submitted an Agreed Initial Pediatric Study Plan to evaluate the use of AXS-05 for treatment of MDD in children and adolescents to the Agency on October 13, 2020. The Agency communicated agreement with the Agreed Initial Pediatric Study Plan to the Applicant on October 22, 2020.

The Applicant requested a waiver for studies in children aged ≤6 years old because studies would be impossible or highly impractical. The Agency agreed that this waiver is justified. A study in this age group would be impractical because of the rarity of the diagnosis of MDD in this patient population.

The Applicant requested a deferral for studies in children aged 7 to 12 years and adolescents aged 13 to 17 years until confirmation of safety and efficacy in adults and completion of a juvenile animal study. The Agency agrees with this plan.

The Agency will issue the following post-marketing requirements (PMRs) to fulfill the requirements of the Pediatric Research Equity Act (PREA):

- PMR #4233-1. Conduct a juvenile animal study to assess the safety of AXS-05 in animals of an age range and stage of development that are comparable to the population of children aged 7 to 12 years.
- PMR #4233-2. Evaluate the pharmacokinetics, efficacy, and safety of AXS-05 in pediatric patients aged 7 to 17 years with MDD.
- PMR #4233-3. Conduct a 1-year, open-label safety study in pediatric patients aged 7 to 17 years with MDD.

All post-marketing requirements and post-marketing commitments are presented in detail in Section 13, "Postmarketing Requirements and Commitments."

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The regulatory pathway for AXS-05 is 505(b)(2). The Applicant relied, in part, on safety date from two approved drugs—Nuedexta (dextromethorphan HBr / quinidine sulfate) and Wellbutrin SR (bupropion HCl extended release). Below, presented in sequential order by label section, is a discussion of pertinent aspects of the product label.

BOXED WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

The antidepressant class boxed warning is included in the AXS-05 label as it is for all antidepressant labels. The warning notes that AXS-05 is not approved for use in pediatric patients.

1. INDICATIONS AND USAGE

The labeled indication will be for the treatment of major depressive disorder (MDD) in adults.

2. DOSAGE AND ADMINISTRATION

2.1. Important Recommendations Prior to Initiating and During Therapy

This section will include recommendations to assess for hypertension, which can be exacerbated by bupropion, and for a personal or family history of bipolar disorder, mania, or hypomania, because antidepressants can precipitate a manic, mixed, or hypomanic episode. Language was added to instruct prescribers to assess whether patients are receiving other medications that contain bupropion or dextromethorphan, referencing sections in Warnings and Precautions that describe significant dose-dependent safety risks.

2.2. Recommended Dosage

The recommended starting dosage in the label is one tablet once daily in the morning. After 3 days, the dosage is to be increased to one tablet twice daily, given at least 8 hours apart. Patients should not receive more than two doses within the same day.

The recommended timing of doses is based on several factors. Pharmacokinetic data suggests that a dosing interval of less than 8 hours can result in dextromethorphan exposures that are higher than optimal, potentially precipitating adverse events related to dextromethorphan. In addition, the recommended dosage is compatible with recommendations from the Wellbutrin

SR label for reducing the risk of seizure (e.g., the total daily dose of Wellbutrin SR tablets should not exceed 400 mg; the daily dose should be administered twice daily; the rate of incrementation of dose should be gradual; and no single dose should exceed 200 mg to avoid high peak concentrations of bupropion and/or its metabolites).

3. DOSAGE FORMS AND STRENGTHS

AXS-05 extended-release tablets contain 45 mg dextromethorphan hydrobromide and 105 mg bupropion hydrochloride. This will be the only commercially-available formulation of AXS-05.

4. CONTRAINDICATIONS

AXS-05 is contraindicated in patients:

- with a seizure disorder;
- with a current or prior diagnosis of bulimia or anorexia nervosa as a higher incidence of seizures was observed in such patients treated with the immediate release formulation of bupropion;
- undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs;
- taking monoamine oxidate inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days, due to the risk of serious and possibly fatal drug interactions, including hypertensive crisis and serotonin syndrome. Allow at least 14 days after stopping AXS-05 before starting an MAOI. Starting AXS-05 in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is contraindicated;
- with known hypersensitivity to AXS-05, bupropion, or dextromethorphan. Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported with bupropion. Arthralgia, myalgia, fever with rash, and other serum sickness-like symptoms, suggestive of delayed hypersensitivity, have also been reported with bupropion.

These contraindications were derived from the Wellbutrin SR label.

5. WARNINGS AND PRECAUTIONS

The label will include warnings about the risk for suicidal thoughts and behaviors in adolescents and young adults, seizure, increased blood pressure and hypertension, activation of mania or hypomania, psychosis and other neuropsychiatric reactions, angle-closure glaucoma, dizziness, serotonin syndrome, and embryo-fetal toxicity.

A warning entitled "Neuropsychiatric Adverse Events and Suicide Risk in Smoking Cessation Treatment" is included in the labels for other products containing bupropion. This warning indicated that the other bupropion-containing products are not approved for the treatment of smoking cessation and described serious neuropsychiatric adverse reactions that have been reported in patients taking bupropion for smoking cessation. The original rationale for including this warning was because patients prescribed bupropion-containing products other than Zyban for the treatment of smoking cessation would otherwise not receive important safety information related to smoking cessation. Since the approval of Zyban for the treatment of smoking cessation, an additional product containing bupropion in combination with naltrexone (trade name: Contrave) has been approved as a weight-loss treatment; its label also includes the neuropsychiatric AE warning language.

Because AXS-05 contains dextromethorphan in addition to bupropion, it is unlikely to be prescribed for the treatment of smoking cessation in place of Zyban (or as a weight-loss treatment in place of Contrave). The team determined that (b) (4) (b) (4) any pertinent safety information from the smoking cessation warning will be presented in the appropriate sections (e.g., 5.1 – Suicidal Thoughts and Behaviors in Adolescents and Young Adults, 5.5 – Psychosis and Other Neuropsychiatric Reactions, and 6.2 – Postmarketing Experience). In addition to the label specifying that AXS-05 is indicated only for the treatment of MDD, the label instructs prescribers to screen patients for the use of other bupropion- or dextromethorphan-containing products prior to initiating treatment with AXS-05, emphasizing the potential for dose-related safety risks including seizure, hypertension, psychosis and other neuropsychiatric reactions, and serotonin syndrome.

The warning "Embryo-fetal Toxicity" was added because of uncertainties related to the safety of using AXS-05 during pregnancy. This warning specifies that patients should be advised about the potential risk to a fetus, that AXS-05 treatment should be discontinued in pregnant females, and that an alternative treatment be used in females who are planning to become pregnant. The toxicity findings described in this warning are from the Nuedexta label, derived from nonclinical studies of dextromethorphan/quinidine. Because the specific contributions of quinidine to the observed toxicities are unknown, the Agency will issue post-marketing requirements to conduct additional nonclinical studies using AXS-05. This warning may be updated in the future based on the results of forthcoming nonclinical studies.

6. ADVERSE REACTIONS

6.1. Clinical Trials Experience

The presentation of total patient exposure in the label includes patients participating in two 6-week studies in MDD (Study MDD-201 and Study MDD-301), one 6-week study in TRD (Study 301), and one long-term study enrolling patients with either MDD or TRD (Study 303). The safety data comparing subjects treated with AXS-05 to subjects treated with placebo is taken

from Study MDD-301; its placebo arm provided a better comparator for interpreting safety findings than the active comparator bupropion as used in Study MDD-201.

Under the heading "Most Common Adverse Reactions," the label will present the adverse reactions with an incidence ≥5% for AXS-05 and occurring twice as frequently as for placebo in the 6-week placebo-controlled clinical trial (i.e., dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis).

6.2. Postmarketing Experience

This section of the label will list adverse reactions reported with the use of the individual components of AXS-05, dextromethorphan and bupropion, from post-marketing experience. The adverse reactions listed for dextromethorphan are from the Nuedexta label. In addition to including adverse reactions for bupropion derived from the Wellbutrin SR label, several adverse reactions were added (b) (4) These added adverse reactions include depression, psychosis, homicidal ideation, hostility, agitation, panic, and suicidal ideation.

7. DRUG INTERACTIONS

7.1. Drugs Having Clinically Important Interaction with AXS-05

A table in the label will present drug interactions that may be anticipated with AXS-05 based on potential interactions with either of its components, bupropion hydrochloride and dextromethorphan hydrobromide. Text in the table will be based on text from the labels of the approved drugs Wellbutrin SR and Nuedexta (a combination of dextromethorphan hydrobromide and quinidine).

8. USE IN SPECIAL POPULATIONS

8.1. Pregnancy

The label will present a risk summary based largely on data from the Wellbutrin SR and Nuedexta nonclinical studies. However, these studies involved a drug containing only one component of AXS-05 (bupropion) and a drug that includes a component that is not present in AXS-05 (quinidine). Nonclinical embryo-fetal development studies in the AXS-05 development program were conducted in mice. However, studies in rabbits may provide more accurate assessments of the level of risk in humans. PMR #4233-7 (described below in Section 13, Postmarketing Requirements and Commitments) requires an embryo-fetal toxicity study of AXS-05 in rabbits. PMR #4233-8 requires a fertility and early embryonic developmental study to address the effect of AXS-05 on fertility. PMR #4233-9 requires a pre- and post-natal developmental study to assess the effect of AXS-05 on embryonic and post-natal development. PMR #4233-11 requires a study to address the neurotoxic potential of dextromethorphan during gestation and early development. The results of these postmarketing studies will inform updates to this section of the AXS-05 label.

8.2. Lactation

The risk summary notes that data from the published literature indicates that bupropion and its metabolites are present in human milk. It is not known whether dextromethorphan is present in human milk. To support the recommendation that breastfeeding is not recommended during treatment with AXS-05, the risk summary describes neurotoxicity findings observed in a nonclinical study of dextromethorphan/quinidine conducted in juvenile rats. PMR #4233-6 (described below in Chapter 13, Postmarketing Requirements and Commitments) requires a study to provide data on the presence of dextromethorphan and its metabolites in the milk of lactating women treated with AXS-05. Results from this study will inform updates to this section of the label.

8.3. Females and Males of Reproductive Potential

The label will recommend use of treatments other than AXS-05 for females who are planning to become pregnant. This recommendation is supported by developmental toxicity findings observed in nonclinical studies of dextromethorphan/quinidine conducted in juvenile rats. This section will be updated following the completion of PMRs #4233-7, #4233-8, and #4233-9.

8.4. Pediatric Use

This section indicates that the safety and effectiveness of AXS-05 has not been established in pediatric patients. The completion of PMRs #4233-1, #4233-2, and #4233-3 (described below in Chapter 13, Postmarketing Requirements and Commitments) will provide information to support updates to this section of the label.

8.5. Geriatric Use

The label will indicate that the AXS-05 clinical trials did not include patients 65 years of age and older to determine whether they respond differently than younger adult patients.

8.6. Renal Impairment

The Dosage and Administration section of the label will recommend a dosage of one tablet once daily in the morning for patients with moderate renal impairment. PMR #4233-4 (described below in Chapter 13, Postmarketing Requirements and Commitments) requires a study to evaluate AXS-05 in patients with severe renal impairment. Completion of this study will support an update to this section of the label.

8.7. Hepatic Impairment

The label will not recommend any dosage adjustment for patients with mild or moderate hepatic impairment. PMR #4233-5 (described below in Chapter 13, Postmarketing Requirements and Commitments) requires a study to evaluate AXS-05 in patients with severe hepatic impairment. Completion of this study will support an update to this section of the label.

8.8. CYP2D6 Poor Metabolizers

The label will recommend a dosage of one tablet once daily in the morning for patients known to be poor CYP2D6 metabolizers because these patients have higher dextromethorphan concentrations than extensive CYP2D6 metabolizers.

9. DRUG ABUSE AND DEPENDENCE

The label will indicate that AXS-05 is not a controlled substance but that cases of dextromethorphan abuse have been reported.

10. OVERDOSAGE

Text on overdosage will be based on the labeling text for the listed drugs Wellbutrin SR and Nuedexta.

11. DESCRIPTION

AXS-05 will be described as a combination of dextromethorphan hydrobromide, an uncompetitive NMDA receptor antagonist and sigma-1 receptor agonist, and bupropion hydrochloride, an aminoketone and CYP450 2D6 inhibitor.

12. CLINICAL PHARMACOLOGY

This section of the label will note that the mechanism of dextromethorphan in the treatment of MDD is unclear. The mechanism of action of bupropion in the treatment of MDD is also unclear; however, it may be related to noradrenergic and/or dopaminergic mechanisms. The label will note that bupropion increases plasma levels of dextromethorphan by inhibiting the metabolism of dextromethorphan by cytochrome P450 2D6. Based on the results of a thorough QT study conducted by the Applicant, the label will note that AXS-05 does not prolong the QT interval to any clinically relevant extent.

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

The label will present the results from rodent studies regarding the carcinogenic potential of dextromethorphan, from bacterial studies regarding the mutagenic potential of dextromethorphan and of bupropion, and from rat studies regarding the impairment of fertility in studies of dextromethorphan and bupropion given alone. PMR #4233-10 (described below in Chapter 13, Postmarketing Requirements and Commitments) requires a study to evaluate the carcinogenic potential of AXS-05 and will support an update to this section of the label.

14. CLINICAL STUDIES

This section of the label will present details of the design and efficacy results from Study MDD-301. In Study MDD-031, AXS-05 was statistically significantly superior to placebo on the primary

efficacy endpoint of change from baseline to the end of treatment in MADRS total score. AXS-05 was also statistically superior to placebo on the pre-specified secondary efficacy endpoints of change in MADRS total score from baseline to Week 1 and from baseline to Week 2. The efficacy results are presented in a table and in a time course figure. The time course of symptom improvement is relevant to both clinicians and patients.

Study MDD-201, which demonstrated the contribution of dextromethorphan to the antidepressant effect of AXS-05 and was a source of confirmatory evidence of efficacy, will be is described only briefly in this section of the label.

MEDICATION GUIDE

The proposed Medication Guide submitted by the Applicant was revised for consistency with the revised sections of the Prescribing Information. The Medication Guide includes the recommendation that AXS-05 should not be used during pregnancy or breastfeeding, and that the ingredients in AXS-05, bupropion and dextromethorphan, are also in medicines approved for other uses.

12. Risk Evaluation and Mitigation Strategies

Both of the components of AXS-05, bupropion HCl and dextromethorphan HBr, are approved in other drugs that do not have risk evaluation and mitigation strategies. Dextromethorphan has not required DEA scheduling and is available over the counter. Although the increased exposure to dextromethorphan caused by concurrent administration with bupropion raised concerns about the abuse potential of the combination, the safety evaluation conducted by the Division and the consultation provided by the Controlled Substances Staff did not reveal evidence of abuse in either the short-term or long-term clinical trials. Thus, there is no safety issue that warrants consideration of a risk evaluation and mitigation strategy, and a risk evaluation and mitigation strategy has not been proposed for AXS-05.

13. Postmarketing Requirements and Commitment

The following post-marketing requirements will be issued in accordance with the Pediatric Research Equity Act:

- PMR #4233-1: Conduct a juvenile animal study to assess the safety of AXS-05 in animals of an age range and stage of development that are comparable to the population of children aged 7 to 12 years.

  - Purpose: to assess potential risks, particularly risks related to early development, using an animal model prior to exposing children to the drug.

  - Acceptable to assess post-approval following establishment of safety and efficacy in adults.

- PMR #4233-2: Evaluate the pharmacokinetics, efficacy, and safety of AXS-05 in pediatric patients aged 7 to 17 years with MDD.

  - Purpose: to characterize the pharmacokinetics, safety, and efficacy of AXS-05 in children and adolescents.

  - Acceptable to assess post-approval following completion of a juvenile animal study and following establishment of safety and efficacy in adults.

- PMR #4233-3: Conduct a 1-year, open-label safety study in pediatric patients aged 7 to 17 years with MDD.

  - Purpose: to assess the long-term safety of AXS-05 for the treatment of MDD in children and adolescents.

  - Acceptable to assess post-approval following establishment of safety and efficacy in adults.

The following post-marketing requirement will be issued in accordance with the FDA Amendments Act of 2007:

- PMR #4233-4: Evaluate the effect of severe renal impairment on the pharmacokinetics of AXS-05.

  - Purpose: A clinical pharmacokinetic (PK) study is required to compare the PK of AXS-05 in subjects with severe renal impairment and subjects with normal renal function in order to provide appropriate recommendations for dosing of AXS-05 in patients with severe renal impairment and to adequately inform product labeling.

  - Acceptable to assess post-approval following establishment of safety and efficacy in adults and because the initial label will state that the drug is not recommended in patients with severe renal impairment. A PK study in adults with moderate renal impairment was conducted pre-approval.

- PMR #4233-5: Evaluate the effect of severe hepatic impairment on the pharmacokinetics of AXS-05.

  - Purpose: A clinical pharmacokinetic (PK) study is required to compare the PK of AXS-05 in subjects with severe hepatic impairment and subjects with normal hepatic function in order to provide appropriate recommendations for dosing of AXS-05 in patients with severe hepatic impairment and to adequately inform product labeling.

  - Acceptable to assess post-approval following establishment of safety and efficacy in adults and because the initial label will state that the drug is not recommended in patients with severe hepatic impairment. A PK study in adults with moderate hepatic impairment was conducted pre-approval.

- PMR #4233-6: Perform a lactation study (milk only) in lactating women who have received AXS-05 to assess concentrations of dextromethorphan and its metabolites in breast milk using a validated assay. A mother-infant pair study may be required in the future depending on the results of this milk-only study.

  - Purpose: To provide data on the presence of dextromethorphan and its metabolites in the milk of lactating women treated with AXS-05.

  - Acceptable to assess post-approval because only a small subpopulation (lactating women) is affected and it is only feasible to conduct the study post-approval.

- PMR #4233-7: Conduct an embryofetal toxicity study of AXS-05 in rabbits.

  - Purpose: To address the lack of information on the combined effect/s of dextromethorphan and bupropion in the product labeling in order to assist clinicians in proper decision making.

  - Acceptable to assess post-approval because AXS-05 will not be recommended for use in pregnant or lactating women in the initial labeling. Results of the requested study will help to inform decisions about future proposed labeling changes regarding safety in pregnancy and lactation.

- PMR #4233-8: Conduct a fertility and early embryonic developmental study to address the effect of AXS-05 on fertility.

  - Purpose: To address the lack of information on the combined effect/s of dextromethorphan and bupropion in the product labeling in order to assist clinicians in proper decision making.

  - Acceptable to assess post-approval because AXS-05 will not be recommended for use in pregnant women in the initial labeling. Results of the requested study will help to inform decisions about future proposed labeling changes regarding safety in pregnancy.

- PMR #4233-9: Conduct a pre- and post-natal developmental study to address the effect of AXS-05 on embryonic and post-natal development.

    - Purpose: To address the lack of information on the combined effect/s of dextromethorphan and bupropion in the product labeling in order to assist clinicians in proper decision making.

    - Acceptable to assess post-approval because AXS-05 will not be recommended for use in pregnant or lactating women in the initial labeling. Results of the requested study will help to inform decisions about future proposed labeling changes regarding safety in pregnancy and lactation.

- PMR #4233-10: Conduct carcinogenicity studies to address the carcinogenic potential of AXS-05.

    - Purpose: To address the lack of information on the combined effect/s of dextromethorphan and bupropion in product labeling in order to assist clinicians in proper decision making.

    - Acceptable to assess post-approval because the benefit of the drug was deemed appropriate for approval at this time and, although not ideal, the existing referenced nonclinical data could permit labeling of risk for Section 13 of the product label.

- PMR #4233-11: Conduct a study to address the neurotoxic potential of dextromethorphan using animals of an age range and stage of development that are comparable to the third trimester of gestation through the first several months of life but possibly extend to approximately three years of age in humans.

    - Purpose: To address the lack of information on the combined effect/s of dextromethorphan and bupropion in product labeling in order to assist clinicians in proper decision making.

    - Acceptable to assess post-approval because AXS-05 will not be recommended for use in pregnant or lactating women in the initial labeling. Results of the requested study will help to inform decisions about future proposed labeling changes regarding safety in pregnancy and lactation.

The following post-marketing commitment will be issued:

- PMC #4233-12: Conduct a bupropion-controlled, randomized withdrawal study to demonstrate whether the dextromethorphan component of AXS-05 contributes to the long-term efficacy of AXS-05 for the treatment of MDD.

- Purpose: To investigate whether AXS-05 is superior to bupropion alone for the long-term treatment of MDD. The study will help to establish whether the long-term added benefit of the dextromethorphan component of AXS-05 outweighs any potential long-term safety risks added by this component.

- Acceptable to assess post-approval following the establishment of safety and efficacy in short-term clinical trials and following the establishment of safety in a 1-year open-label trial.

14. Division Director Comments

The above review reflects my edits and feedback. I agree with the findings as described by the review team and concur with the approval decision.

15. Appendices

15.1. References

Not applicable; referenced in footnotes.

15.2. Financial Disclosure

Covered Clinical Studies (Names and/or Numbers)

- AXS-05-MDD-201
- AXS-05-MDD-301
- AXS-05-301
- AXS-05-303

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 127		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided?	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason?	Yes ☐ **N/A**	No ☐ (Request explanation from Applicant)

Investigators with Reportable Financial Disclosures

1. (b) (6) was a (b) (6) at Site (b) (6) for Study AXS-05-301. He was hired as a (b) (6) by Axsome. He discontinued participation in Study AXS-05-301 prior to randomizing any patients.

2. (b) (6) was a subinvestigator at Site (b) (6) for Study AXS-05-301. During the 12 months following study completion he owned equity in Axsome exceeding $50,000. The site did not enroll any patients.

Neither of these financial arrangements is expected to have any impact on interpretation of the analysis of the study data or to adversely affect the approvability of the application.

15.3. Clinical Pharmacology

15.3.1. Bioanalysis

Plasma concentrations of dextromethorphan and its metabolites (dextrorphan and dextrorphan-O-glucuronide), and bupropion and its metabolites (hydroxybupropion, threohydroxybupropion and erythrohydroxybupropion) were quantified using validated liquid chromatography with tandem mass spectrometry (Validation reports: 65138AKFO-AKEG, 145053AKIK-V and 135017AHMY). The bioanalytical methods were developed and validated by in (b) (4) ((b) (4)).

- The calibration range for dextromethorphan is 100 ng/mL to 200,000 ng/mL, dextrorphan is 50 ng/mL to 25,000 ng/mL, and dextrorphan-O-glucuronide is 8 ng/mL to 8000 ng/mL. The calibration range for bupropion is 1 ng/mL to 250 ng/mL, hydroxybupropion is 5 ng/mL to 2500 ng/mL, threohydroxybupropion is 5 ng/mL to 1000 ng/mL, and erythrohydroxybupropion is 1 ng/mL to 200 ng/mL.
- The precision and accuracy values of at least two-thirds of the overall quality control samples were within ±15% (±20% at the lower limit of quantification).
- The analytes in human plasma were stable over at least 53 days when stored at -80°C. The stability of analytes in whole blood was at least 230 minutes in an ice water bath. The postpreparative stability was at least 94 hours at room temperature, at least four freeze-thaw cycles at -80°C, and autosampler stability at 4°C over 8 hours 50 minutes.
- Up to 20-fold dilution did not affect the precision and accuracy of the measurement of analytes. No significant carryover effects were observed. More than two-thirds of the incurred sample reanalysis fell within 20% deviation.

The bioanalytical methods are acceptable and satisfy the criteria for 'method validation' and 'application to routine analysis' set by the 'Guidance for Industry: Bioanalytical Method Development'.

15.3.2. In Vitro Metabolism and Transport of Dextromethorphan

Dextromethorphan is a substrate of CYP2D6 enzyme[10] and P-gp transporter (AXS05-005). Dextromethorphan does not inhibit CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4) or transporters (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, BSEP, OCT2,

[10] Lutz, JD and N Isoherranen, 2012, Prediction of relative in vivo metabolite exposure from in vitro data using two model drugs: dextromethorphan and omeprazole, Drug metabolism and disposition: the biological fate of chemicals, 40(1):159-168.

MATE1, MATE2-K, and OCT1) at clinically relevant plasma concentrations (AXS005-DDI002 and AXS005-DDI004). Dextromethorphan does not induce CYP1A2, CYP2B6 and CYP3A4 enzymes (AXS-005-DDI003).

15.3.3. Summary of Clinical Pharmacology Studies

The clinical pharmacology studies submitted in this 505(b)(2) application are listed in Table 76.

Table 76. Clinical Pharmacology Studies

Protocol Number / Type	Trial Design	Population	Duration / Dosing Regimen	Number of Subjects
AXS-05-101 Single- and multiple-dose	Phase 1; R, OL, PK, single and multiple-dose, parallel-group trial; healthy subjects fasted, 8-days	Healthy adults Non-smokers ≥18 and ≤55 years BMI >18.5 and <30.0 kg/m^2 Extensive or ultra-rapid metabolizer of CYP2D6	8 days of dosing. Bupropion dosed QD on Days 1-3 and BID on Days 4-8. Dextromethorphan dosed BID on Days 1-8. Treatments A: Bupropion + Dextromethorphan (150 mg + 30 mg) B: Bupropion + Dextromethorphan (150 mg + 45 mg) C: Bupropion + Dextromethorphan (150 mg + 60 mg) D: Dextromethorphan 60 mg	N = 32 (8 per arm)
AXS-05-102 Single- and multiple-dose	Phase 1; R, OL, PK; single- and multiple-dose, parallel-group trial; healthy subjects fasted, 8-days	Healthy adults Non-smokers ≥18 and ≤55 years BMI >18.5 and <30.0 kg/m^2 Extensive or ultra-rapid metabolizer of CYP2D6	8 days of dosing. Bupropion dosed QD on Days 1-3 and BID on Days 4-8. Dextromethorphan dosed BID on Days 1-8. Treatments A: Bupropion + Dextromethorphan (100 mg + 30 mg) B: Bupropion + Dextromethorphan (75 mg mg+45 mg) C: Bupropion + Dextromethorphan (100 mg + 45 mg) D: Bupropion + Dextromethorphan (150 mg + 45 mg) E: Bupropion 150 mg	N = 40 (8 per arm)

Protocol Number / Type	Trial Design	Population	Duration / Dosing Regimen	Number of Subjects
AXS-05-103 Single- and multiple-dose	Phase 1; R, OL, PK; single- and multiple-dose, parallel-group trial; healthy subjects fasted, 10-days	Healthy adults Non-smokers ≥18 and ≤55 years BMI >18.5 and <30.0 kg/m^2 Extensive or ultra-rapid metabolizer of CYP2D6	10 days of dosing. Dose taken QD on Days 1-3, BID on Days 4-9, QAM on Day 10 AXS-05 (45 mg dextromethorphan-105 mg bupropion) Bupropion 150 mg	N = 30 (15 per arm)
AXS-05-104 Special population / Renal impairment	Phase 1; OL, PK; single- and multiple-dose, subjects with renal impairment and matched controls, 8-days	≥18 and ≤80 years BMI >18.5 and <40.0 kg/m^2 Extensive or ultra-rapid metabolizer of CYP2D6 Moderate renal impairment and matched normal renal function controls	8 days dosing AXS-05 (45 mg dextromethorphan-105 mg bupropion) QD on Days 1-3, BID on Days 4-7, QAM on Day 8	N = 13 (7 moderate, 6 controls)
AXS-05-105 Special population / Hepatic impairment	Phase 1; OL, PK; single- and multiple-dose, subjects with hepatic impairment and matched controls, 8-days	≥18 and ≤80 years BMI >18.5 and <40.0 kg/m^2 Extensive or ultra-rapid metabolizer of CYP2D6 Moderate hepatic impairment and matched normal hepatic function controls	8 days dosing AXS-05 (45 mg dextromethorphan-105 mg bupropion) QD on Days 1-3, BID on Days 4-7, QAM on Day 8	N = 15 (8 moderate, 7 controls)
AXS-05-106 Intrinsic factors / CYP2D6 PMs	Phase 1; OL, PK; single- and multiple-dose, healthy subjects fasted, 8-days	Healthy adults Non-smokers ≥18 and ≤55 years BMI >18.5 and <30.0 kg/m^2 EMs, UMs, and PMs of CYP2D6	8 days dosing AXS-05 (30 mg dextromethorphan-105 mg bupropion) QD on Days 1-3, BID on Days 4 8 AXS-05 (45 mg dextromethorphan-105 mg bupropion) QD on Days 1-3, BID on Days 4-8 AXS-05 (45 mg dextromethorphan-105 mg bupropion) QD on Days 1-3, BID on Days 4-7, QD on Day 8	N = 26 (23 EM/UMs; 3 PMs)

Protocol Number / Type	Trial Design	Population	Duration / Dosing Regimen	Number of Subjects
AXS-05-107 BA / Food effect	Phase 1; PK; single-dose, 2-treatment (fed vs. fasting), 2-period, crossover design	Healthy adults Non-smokers ≥18 and ≤55 years BMI >18.5 and <30.0 kg/m^2 Extensive or ultra-rapid metabolizer of CYP2D6	Single dose of AXS-05 (45 mg dextromethorphan-105 mg bupropion) given with a high fat meal (800-1000 calories) Single dose of AXS-05 (45 mg dextromethorphan-105 mg bupropion) given after a 10 hour fast, with no food for 4 hours after the dose	N = 15
AXS-05-108 DDI / CYP2D6 substrate and inhibitor (paroxetine)	Phase 1; OL, PK; parallel group, multiple-dose, paroxetine drug-interaction, healthy subjects fasted, 18-days	Healthy adults Non-smokers ≥18 and ≤55 years BMI >18.5 and <30.0 kg/m^2 Extensive or ultra-rapid metabolizer of CYP2D6	Group 1 Paroxetine 20 mg Day 1-18 AXS-05 (45 mg dextromethorphan-105 mg bupropion) Day 13-18 Group 2 AXS-05 (45 mg dextromethorphan-105 mg bupropion) Day 1-18 Paroxetine 20 mg Day 7-18	N = 29 Group 1: 15 Group 2: 16
AXS-05-109 Thorough QT	Phase 1; DB, TQT study, randomized, 6-sequence, 3-period (placebo, AXS-05, moxifloxacin), cross-over.	Healthy adults Non-smokers ≥18 and ≤55 years BMI >18.5 and <30.0 kg/m^2 Extensive or ultra-rapid metabolizer of CYP2D6	AXS-05 Period AXS-05 (45 mg dextromethorphan-105 mg bupropion) QD on Days 1-2, BID on Days 3-5, QAM on Day 6, 2x QAM on Day 7 Placebo Period Placebo QD on Days 1-2, BID on Days 3-5, QAM on Day 6, 2x QAM on Day 7 Moxifloxacin Period Placebo Days 1-6, moxifloxacin 400 mg Day 7	N = 42 (7 per sequence)

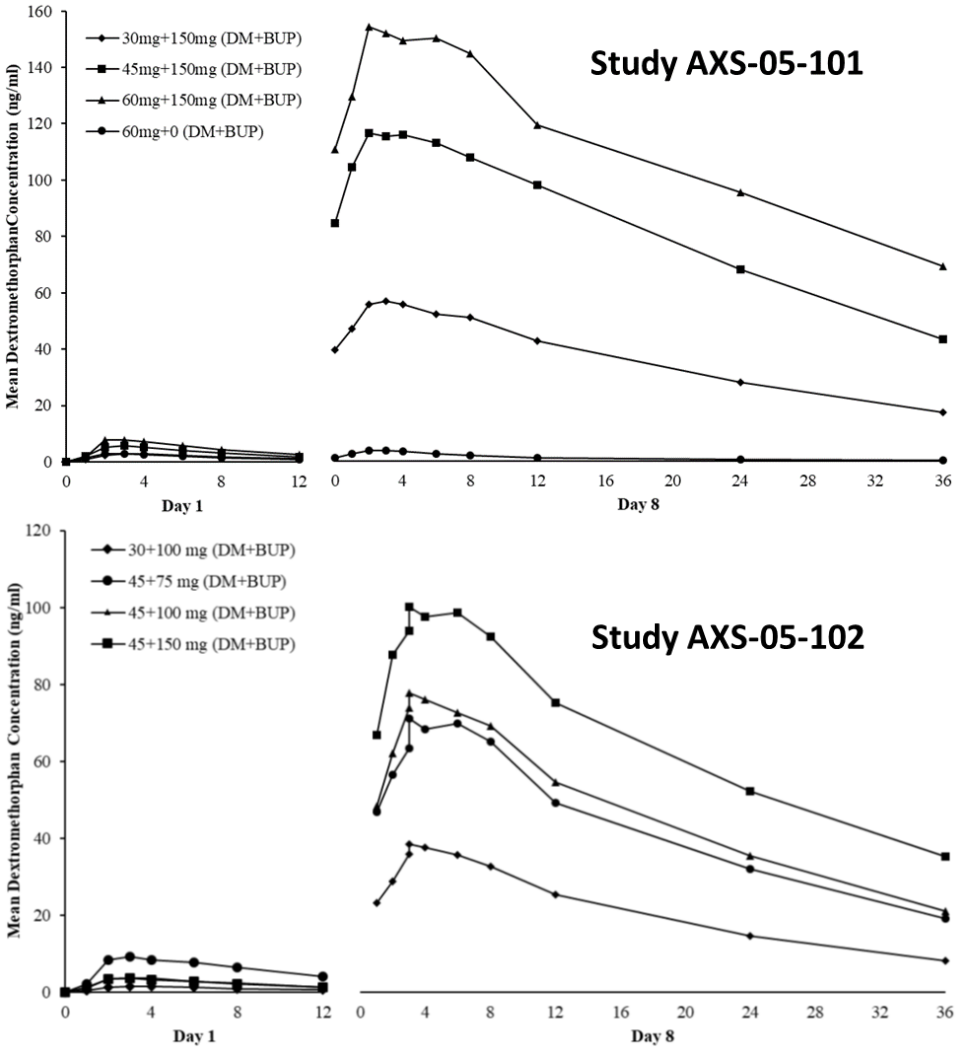
Protocol Number / Type	Trial Design	Population	Duration / Dosing Regimen	Number of Subjects
AXS-05-110 DDI / CYP2B6 inhibitor (clopidogrel)	Phase 1; OL, 2 period, 2-way crossover, PK; single- and multiple-dose, clopidogrel drug-interaction, healthy subjects fasted, 6-days	Healthy adults Non-smokers ≥18 and ≤55 years BMI >18.5 and <30.0 kg/m^2 Extensive or ultra-rapid metabolizer of CYP2D6	AXS-05 alone Period AXS-05 (45 mg dextromethorphan-105 mg bupropion) QD on Days 1-2, BID on Days 3-5, QAM on Day 6 AXS-05 + Clopidogrel Period AXS-05 (45 mg dextromethorphan-105 mg bupropion) QD on Days 1-2, BID on Days 3-5, QAM on Day 6 Clopidogrel 75 mg × 4 Day 1, 75 mg Day 2-6	N = 23
AXS-05-111 DDI / CYP2B6 inducer (carbamazepine)	Phase 1; OL, PK; multiple-dose, carbamazepine drug-interaction, healthy subjects fasted, 24-days	Healthy adults Non-smokers ≥18 and ≤55 years BMI >18.5 and <30.0 kg/m^2 Extensive or ultra-rapid metabolizer of CYP2D6	Day 1-6: AXS-05 (45 mg dextromethorphan-105 mg bupropion) Day 7-18: Carbamazepine Day 19-24: AXS-05 (45 mg dextromethorphan-105 mg bupropion) + carbamazepine	N = 24

Source: Table 1; Summary of Clinical Pharmacology.
Abbreviations: BA, bioavailability; BID, twice daily; BMI, body mass index; DB, double blind; DDI, drug-drug interaction; EM, extensive metabolizers; N, number; OL, open label; PK, pharmacokinetic; PM, poor metabolizers; QD, once daily; R, randomized; UM, ultra-rapid metabolizers

Pharmacokinetics of Dextromethorphan and Bupropion

The PK of dextromethorphan and bupropion were evaluated either alone or in combination at various dosages in healthy volunteers (Studies AXS-05-101 and AXS-05-102) (Figure 12).

Figure 12. Mean Plasma Concentration-Time Profiles of Dextromethorphan on Day 1 and Day 8 Following Administration of Dextromethorphan Either Alone or Combination With Bupropion in Healthy Subjects (Studies AXS-05-101 and AXS-05-102)



Source: Summary of clinical pharmacology, Figures 1 and 2.
Abbreviations: BUP, bupropion; DM, dextromethorphan

The PK parameters of dextromethorphan and bupropion on Day 8 in Studies AXS-05-101 and AXS-05-102 are shown in Table 77 and Table 78.

Table 77. PK Parameters of Dextromethorphan and Bupropion on Day 8 in Study AXS-05-101

Dextromethorphan PK Parameters

Treatment	Statistic	AUC_{0-12} (ng*hr/mL)	AUC_{0-24} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	C_{max} (ng/mL)	T_{max}[a] (hr)	$T_{½ el}$ (hr)
Dextromethorphan +Bupropion (30 mg + 150 mg)	N	7	7	7	7	7	7
	Mean	604.62	1,026.83	1,799.30	58.58	3.00	18.71
	SD	264.49	469.05	1,012.07	24.97	0.00-8.00	5.09
Dextromethorphan +Bupropion (45 mg + 150 mg)	N	7	7	7	7	7	7
	Mean	1,296.06	2,290.13	4,648.62	121.99	3.00	21.79
	SD	257.24	576.25	2,619.74	19.91	2.00-8.05	10.77
Dextromethorphan +Bupropion (60 mg + 150 mg)	N	7	7	7	7	7	7
	Mean	1,686.27	2,975.30	7,237.32	158.05	3.00	27.65
	SD	691.62	1,236.51	4,556.81	65.42	2.00-6.00	11.55
Dextromethorphan (60 mg)	N	8	8	8	8	8	8
	Mean	28.14	37.14	41.24	3.79	2.03	6.60
	SD	14.95	20.37	23.18	1.91	1.00-4.00	1.68

Bupropion PK Parameters

Treatment	Statistic	AUC_{0-12} (ng*hr/mL)	AUC_{0-24} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	C_{max} (ng/mL)	T_{max}[a] (hr)	$T_{½ el}$ (hr)
Dextromethorphan + Bupropion (30 mg + 150 mg)	N	7	7	7	7	7	7
	Mean	848.81	1177.26	1652.01	114.66	2.00	13.57
	SD	35.06	36.45	731.05	36.68	1.00-3.02	3.37
Dextromethorphan + Bupropion (45 mg + 150 mg)	N	7	7	7	7	7	7
	Mean	744.63	1005.99	1276.20	100.57	2.00	11.39
	SD	154.51	214.92	288.74	20.42	1.00-3.00	1.49
Dextromethorphan + Bupropion (60 mg + 150 mg)	N	7	7	7	7	7	7
	Mean	792.98	1108.07	1600.48	109.38	2.00	14.72
	SD	329.96	468.99	765.46	51.03	2.00-3.02	2.35

Source: Summary of clinical pharmacology, Tables 4 and 6.
Abbreviations: AUC_{0-12}, area under the curve to 12 hours; AUC_{0-24}, area under the curve to 24 hours; $AUC_{0-\infty}$; area under the curve; C_{max}, maximum concentration; hr, hour; N, number; PK, pharmacokinetic; SD, standard deviation; T_{max}, time to maximum concentration; $T_{½el}$, half-life of elimination

Table 78. PK Parameters of Dextromethorphan and Bupropion on Day 8 in Study AXS-05-102

Dextromethorphan PK Parameters

Treatment	Statistics	AUC_{0-12} (ng*hr/mL)	AUC_{0-24} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	C_{max} (ng/mL)	T_{max}[a] (hr)	$T_{½ el}$ (hr)
Dextromethorphan + Bupropion (30 mg + 100 mg)	N	6	6	6	6	6	6
	Mean	390.57	629.04	941.87	39.00	3.00	13.76
	SD	111.44	196.65	384.97	10.64	3.00-4.00	2.85
Dextromethorphan + Bupropion (45 mg + 75 mg)	N	8	8	8	8	8	8
	Mean	749.72	1236.41	2046.60	73.82	4.00	15.19
	SD	382.88	684.47	1390.64	36.16	3.00-8.00	4.76
Dextromethorphan + Bupropion (45 mg + 100 mg)	N	8	8	8	8	8	8
	Mean	813.82	1353.57	2235.75	80.02	3.00	15.88
	SD	354.58	624.52	1229.01	32.18	2.00-8.00	4.06
Dextromethorphan + Bupropion (45 mg + 150 mg)	N	6	6	6	6	6	6
	Mean	1086.20	1850.25	3524.61	105.77	5.01	20.19
	SD	400.79	727.31	1968.29	35.93	2.00-8.00	5.09

Bupropion PK Parameters

Treatment	Statistic	AUC_{0-12} (ng*hr/mL)	AUC_{0-24} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	C_{max} (ng/mL)	T_{max}[a] (hr)	$T_{½ el}$ (hr)
Dextromethorphan + Bupropion (30 mg + 100 mg)	N	6	6	6	6	6	6
	Mean	483.38	720.36	1076.79	60.44	3.00	15.20
	SD	182.90	284.77	465.08	22.62	2.00-4.00	2.66
Dextromethorphan + Bupropion (45 mg + 75 mg)	N	8	8	8	8	8	8
	Mean	513.66	692.94	998.80	103.15	1.50	16.38
	SD	158.22	233.11	365.63	29.15	1.00-2.03	2.58
Dextromethorphan + Bupropion (45 mg + 100 mg)	N	8	8	8	8	8	8
	Mean	629.69	908.33	1322.24	78.79	2.50	14.81
	SD	199.08	293.52	577.60	28.02	2.00-4.00	5.95
Dextromethorphan + Bupropion (45 mg + 150 mg)	N	6	6	6	6	6	6
	Mean	699.55	995.74	1442.18	92.26	2.50	15.25
	SD	150.45	208.14	307.13	23.84	1.05-4.00	2.95
Bupropion (150 mg)	N	7	7	7	7	7	7
	Mean	798.75	1122.86	1583.64	103.38	3.00	13.58
	SD	292.49	451.13	793.30	33.26	2.00-4.00	2.73

Source: Summary of clinical pharmacology, Tables 8 and 10.
Abbreviations: AUC_{0-12}, area under the curve to 12 hours; AUC_{0-24}, area under the curve to 24 hours; $AUC_{0-\infty}$; area under the curve; C_{max}, maximum concentration; hr, hour; N, number; PK, pharmacokinetic; SD, standard deviation; T_{max}, time to maximum concentration; $T_{½el}$, half-life of elimination

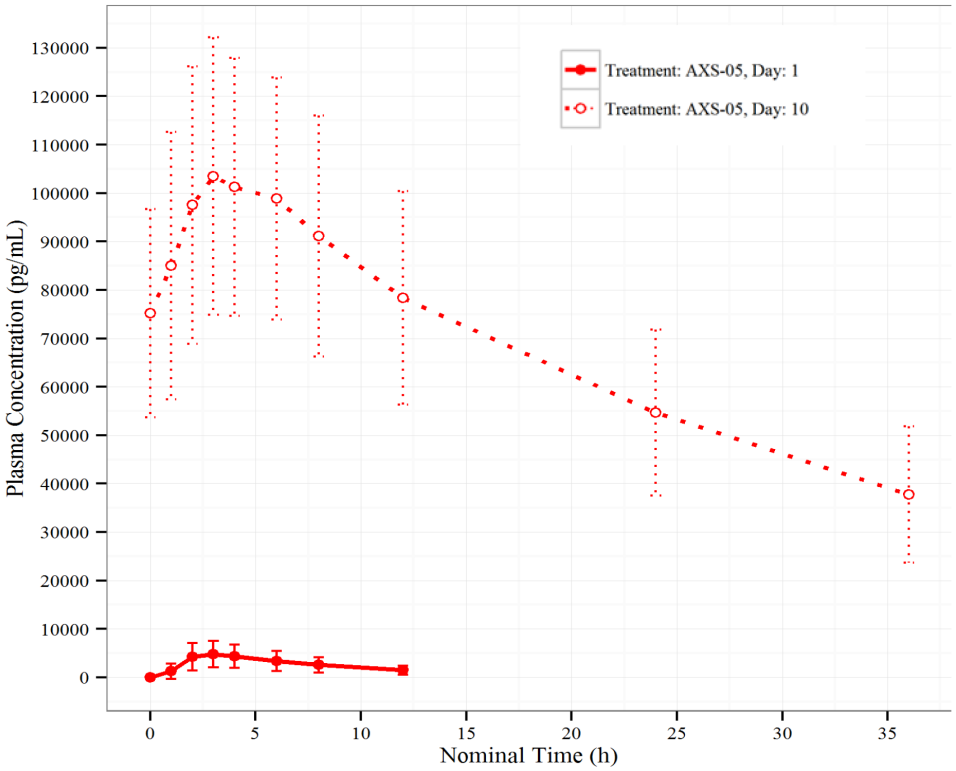
Dextromethorphan showed substantially lower systemic exposure when administered alone compared to the dextromethorphan and bupropion combination (Table 77, AXS-05-101). Coadministration of dextromethorphan did not affect the bupropion PK (Table 78, AXS-05-102).

Given the systemic exposures to dextromethorphan were relatively similar between the 45 mg dextromethorphan+100 mg bupropion combination (AXS-05-102) and those reported for the 30 mg dextromethorphan+10 mg quinidine combination (refer to Clinical Pharmacology review by Ju-Ping Lai, NDA 021879, archived on 10/27/2010), the applicant subsequently developed a bilayer tablet of a fixed-dose combination of 45 mg dextromethorphan HBr and 105 mg bupropion HCl (AXS-05).

Pharmacokinetics of a Fixed-Dose Combination of 45 mg Dextromethorphan and 105 mg Bupropion (AXS-05)

The PK of the bilayer tablet formulation (AXS-05) was evaluated in healthy subjects (Figure 13 and Table 79).

Figure 13. Mean Plasma Concentration-Time Profiles of Dextromethorphan Following Administrations of AXS-05 to Healthy Volunteers (AXS-05-103)



Source: Study report AXS-05-103, Figure 11.4.2-3-1.
Abbreviation: h, hours

Table 79. PK Parameters of Dextromethorphan and Bupropion in Study AXS-05-103

Dextromethorphan PK Parameters

Treatment	Statistic	AUC_{0-12} (ng*hr/mL)	AUC_{0-24} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	C_{max} (ng/mL)	T_{max}[a] (hr)	$T_{½ el}$ (hr)
AXS-05 (DM + BUP) (45 mg + 105 mg)	N	15	15	15	15	15	15
	Mean	1103.41	1901.42	3718.15	104.61	3.00	21.78
	SD	300.41	531.87	1314.79	28.24	3.00-6.00	4.37

Bupropion PK Parameters

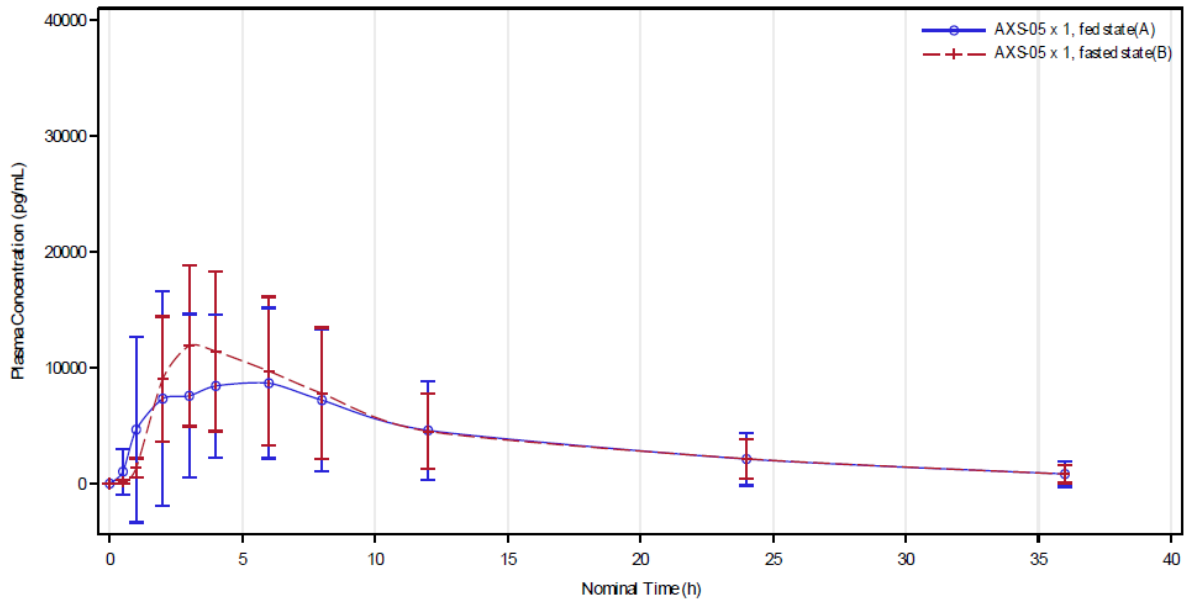
Treatment	Statistic	AUC_{0-12} (ng*hr/mL)	AUC_{0-24} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	C_{max} (ng/mL)	T_{max}[a] (hr)	$T_{½ el}$ (hr)
AXS-05 (DM + BUP) (45 mg + 105 mg)	N	15	15	15	15	15	15
	Mean	600.31	865.29	1279.07	75.92	2.00	15.45
	SD	211.79	305.44	480.84	28.12	1.00-4.02	2.83

Source: Study report AXS-05-103, Tables 11.4.2.3-1 and 11.4.2.3-2.
Abbreviations: AUC_{0-12}, area under the curve to 12 hours; AUC_{0-24}, area under the curve to 24 hours; $AUC_{0-\infty}$; area under the curve; C_{max}, maximum concentration; hr, hour; N, number; PK, pharmacokinetic; SD, standard deviation; T_{max}, time to maximum concentration; $T_{½el}$, half-life of elimination

Food Effect

In a food effect study (AXS-05-107), the effect of a high-fat (~50% of total caloric content) and a high-calorie (~800 to 1000 calories; 150 calories from protein; 250 calories from carbohydrate and 500 to 600 calories from fat) meal on the PK of AXS-05 was evaluated (Figure 14, Figure 15, and Table 80).

Figure 14. Mean Concentration-Time Profiles of Dextromethorphan Following Administration of AXS-05 Under Fasted and Fed Conditions



Source: Study report AXS-05-107, Figure 11.4.1-1.
Abbreviation: h, hours

Table 80. PK Parameters of Dextromethorphan and Bupropion in Study AXS-05-107

Dextromethorphan PK Parameters

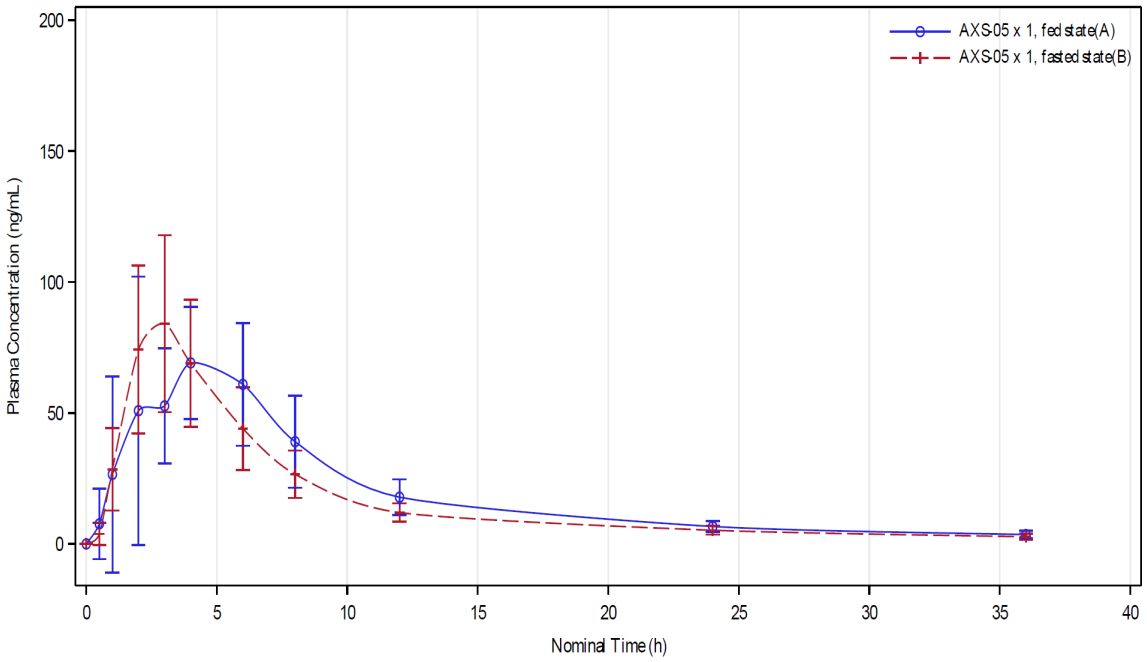
	AXS-05 (Fed)				AXS-05 (Fasted)			
Parameter (Unit)	**N**	**Mean**	**SD**	**CV%**	**N**	**Mean**	**SD**	**CV%**
$AUC_{0\text{-}inf}$ (h*ng/mL)	13	150.62	137.48	91.28	13	160.99	112.60	69.94
$AUC_{0\text{-}12}$ (h*ng/mL)	13	79.64	61.03	76.64	13	90.83	57.73	63.56
$AUC_{0\text{-}24}$ (h*ng/mL)	13	119.89	97.91	81.66	13	130.76	87.08	66.59
C_{max} (ng/mL)	13	12.37	8.66	70.00	13	12.41	7.24	58.36
$T_{1/2\ el}$ (h)	13	8.62	2.05	23.79	13	8.93	1.94	21.70
Parameter (Unit)	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**
T_{max} (h)	13	4.000	1.033	6.000	13	3.000	2.000	4.000

Bupropion PK Parameters

	AXS-05 (Fed)				AXS-05 (Fasted)			
Parameter (Unit)	**N**	**Mean**	**SD**	**CV%**	**N**	**Mean**	**SD**	**CV%**
$AUC_{0\text{-}inf}$ (h*ng/mL)	13	770.09	148.56	19.29	13	675.53	199.87	29.59
$AUC_{0\text{-}12}$ (h*ng/mL)	13	505.36	80.16	15.86	13	476.38	141.82	29.77
$AUC_{0\text{-}24}$ (h*ng/mL)	13	652.36	115.34	17.68	13	579.54	168.35	29.05
C_{max} (ng/mL)	13	95.23	36.26	38.08	13	92.04	35.27	38.32
$T_{1/2\ el}$ (h)	13	10.65	2.18	20.47	13	11.47	2.58	22.53
Parameter (Unit)	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**
T_{max} (h)	13	4.000	1.000	6.000	13	3.000	2.000	4.000

Source: Study report AXS-05-107, Tables 11.4.1-1 and 11.4.1-7.
Abbreviations: $AUC_{0\text{-}12}$, area under the curve to 12 hours; $AUC_{0\text{-}24}$, area under the curve to 24 hours; $AUC_{0\text{-}inf}$, area under the curve; C_{max}, maximum concentration; CV, coefficient of variation; h, hours; Max, maximum; Min, minimum; N, number; PK, pharmacokinetic; SD, standard deviation; T_{max}, time to maximum concentration; $T_{½el}$, half-life of elimination

Figure 15. Mean Concentration-Time Profiles of Bupropion Following Administration of AXS-05 Under Fasted and Fed Conditions



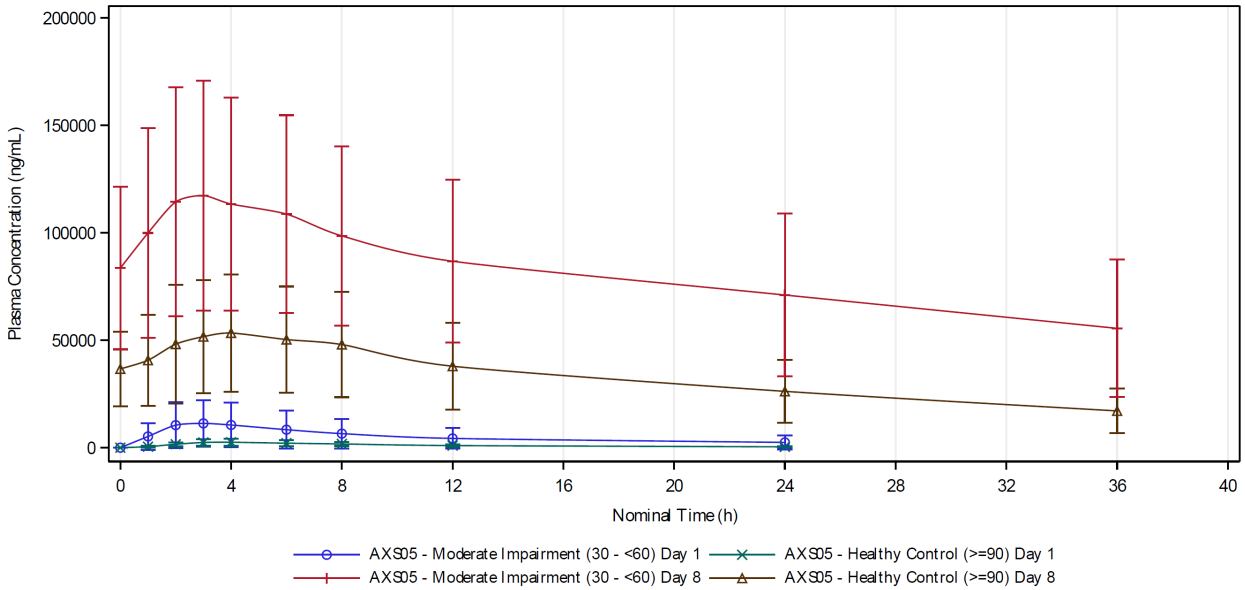
Source: Study report AXS-05-107, Figure 11.4.1-4.
Abbreviation: h, hours

Reviewer's Comment: Food did not appreciably affect the systemic exposures to dextromethorphan and bupropion compared to fasted conditions. However, food slightly delays the time to reach peak plasma concentrations from 3 hours to 4 hours for both dextromethorphan and bupropion. The results from this study suggest that AXS-05 can be administered with or without food.

Renal Impairment

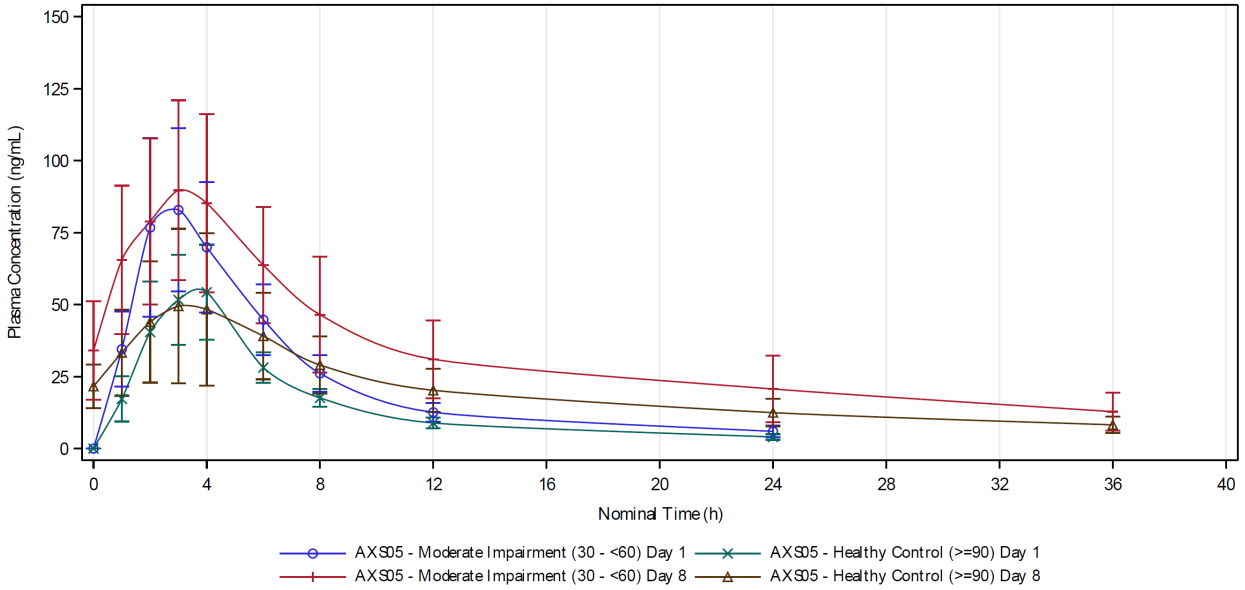
The effect of moderate renal impairment (estimated glomerular filtration rate: 30 to 60 mL/min/1.73 m^2) on the PK of AXS-05 was evaluated in Study AXS-05-104. The PK profiles and associated PK parameters of dextromethorphan and bupropion are shown in Figure 16, Figure 17, and Table 81, respectively.

Figure 16. Mean Plasma Concentration-Time Profiles of Dextromethorphan on Day 1 and Day 8 in Subjects With Moderate Renal Impairment and Subjects With Normal Renal Function



Source: Study report AXS-05-104, Figure 11.4.1-1.
Abbreviation: h, hours

Figure 17. Mean Plasma Concentration-Time Profiles of Bupropion on Day 1 and Day 8 in Subjects With Moderate Renal Impairment and Subjects With Normal Renal Function



Source: Study report AXS-05-104, Figure 11.4.1-4.
Abbreviation: h, hours

Table 81. PK Parameters of Dextromethorphan and Bupropion in Study AXS-05-104

Dextromethorphan PK Parameters

PK Parameters	Day 1			Day 8		
	Moderate	Healthy Control	Moderate/ Healthy Control[b]	Moderate	Healthy Control	Moderate/ Healthy Control
$AUC_{0\text{-}inf}$ (h*ng/mL)	166.33	32.71	5.1	5988.77	1717.81	3.5
$AUC_{0\text{-}12}$ (h*ng/mL)	87.85	19.69	4.5	1229.29	558.96	2.2
$AUC_{0\text{-}24}$ (h*ng/mL)	128.34	28.04	4.6	2175.60	943.41	2.3
C_{max} (ng/mL)	11.57	2.76	4.2	118.91	56.52	2.1
T_{max} (h)[c]	3.00	4.00	-1.00[a]	3.00	3.542	-0.542 [a]
$T_{1/2\ el}$ (h)	8.70	8.03	1.1	32.41	19.98	1.6

Bupropion PK Parameters

PK Parameters	Day 1			Day 8		
	Moderate	Healthy Control	Moderate/ Healthy Control[b]	Moderate	Healthy Control	Moderate/ Healthy Control[b]
$AUC_{0\text{-}inf}$ (h*ng/mL)	664.51	441.69	1.5	1552.58	976.82	1.6
$AUC_{0\text{-}12}$ (h*ng/mL)	491.76	321.18	1.5	707.77	415.58	1.7
$AUC_{0\text{-}24}$ (h*ng/mL)	602.92	398.44	1.5	1017.94	611.85	1.7
C_{max} (ng/mL)	91.11	57.27	1.6	91.77	55.29	1.7
T_{max} (h)[c]	3.000	3.500	-0.500 [a]	3.000	3.542	-0.542 [a]
$T_{1/2\ el}$ (h)	7.23	7.47	0.97	17.58	20.31	0.87

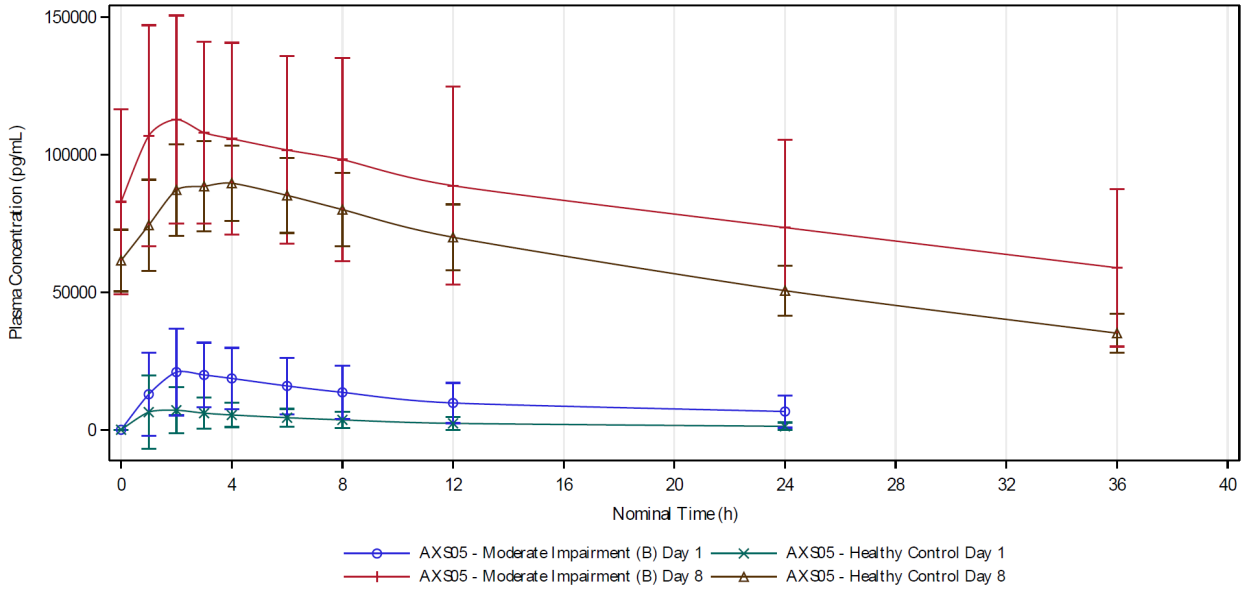
Source: Study report AXS-05-104, Table 11.4.1-8.
The values represent arithmetic means
[a]: T_{max} difference
[b]: ratio of values
[c]: median values
Abbreviations: $AUC_{0\text{-}12}$, area under the curve to 12 hours; $AUC_{0\text{-}24}$, area under the curve to 24 hours; $AUC_{0\text{-}inf}$; area under the curve; C_{max}, maximum concentration; h, hours; PK, pharmacokinetic; T_{max}, time to maximum concentration; $T_{½el}$, half-life of elimination

Reviewer's Comments: The systemic exposures (C_{max} and $AUC_{0\text{-}12h}$) to dextromethorphan and bupropion were increased by approximately 2-fold and 1.7-fold, respectively in subjects with moderate renal impairment compared to subjects with normal renal function. The systemic exposures to bupropion metabolites (hydroxybupropion, threohydroxybupropion and erythrohydroxybupropion) were not appreciably changed following correction for their potency (based on the antidepressant effects in mice, hydroxybupropion is approximately one-half as potent as bupropion; threohydroxybupropion and erythrohydroxybupropion are 5-fold less potent than bupropion; refer to the Wellbutrin SR label) in subjects with renal impairment compared to subjects with normal renal function. Given that a 2-fold increase in exposures to dextromethorphan was observed, once-daily dosing of AXS-05 is recommended in patients with moderate renal impairment.

Hepatic Impairment

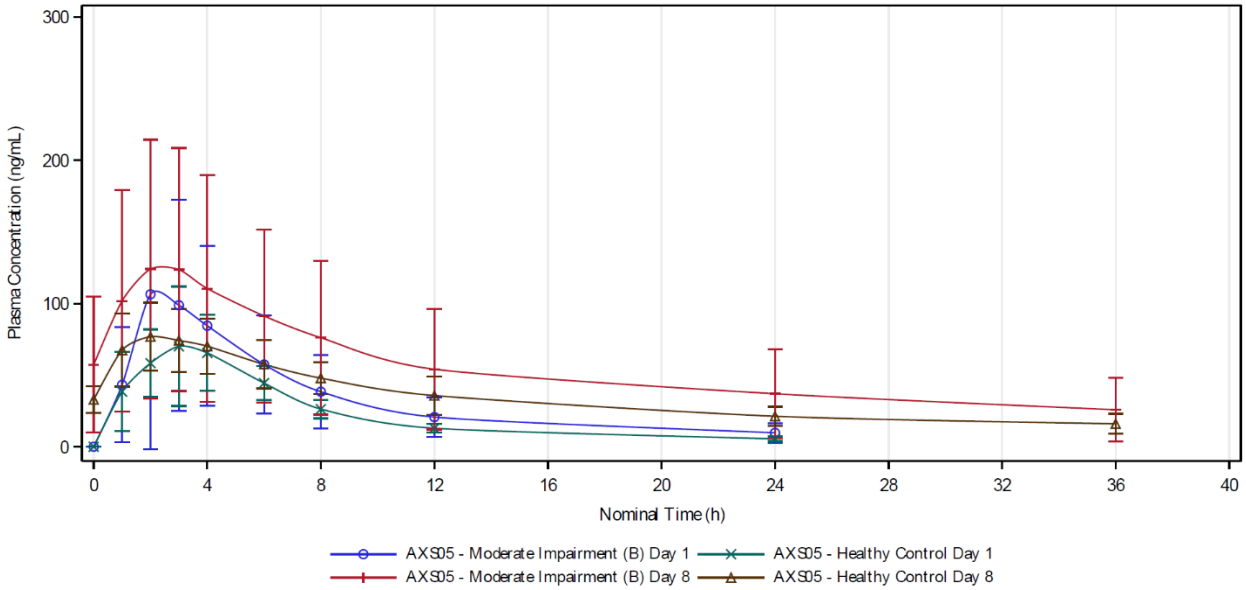
The effect of moderate hepatic impairment (Child-Pugh Class B) on the PK of AXS-05 was evaluated in Study AXS-05-105. The PK profiles and associated PK parameters of dextromethorphan and bupropion are shown in Figure 18, Figure 19, and Table 82, respectively.

Figure 18. Mean Plasma Concentration-Time Profiles of Dextromethorphan on Day 1 and Day 8 in Subjects With Moderate Hepatic Impairment and Subjects With Normal Hepatic Function



Source: Study report AXS-05-105, Figure 11.4.1-1.
Abbreviation: h, hours

Figure 19. Mean Plasma Concentration-Time Profiles of Bupropion on Day 1 and Day 8 in Subjects With Moderate Hepatic Impairment and Subjects With Normal Hepatic Function



Source: Study report AXS-05-105, Figure 11.4.1-4.
Abbreviation: h, hours

Table 82. PK Parameters of Dextromethorphan and Bupropion in Study AXS-05-105

Dextromethorphan PK Parameters

	Day 1			Day 8		
PK Parameters	**Moderate**	**Healthy Control**	**Moderate/ Healthy Control[b]**	**Moderate**	**Healthy Control**	**Moderate/ Healthy Control[b]**
$AUC_{0\text{-}inf}$ (h*ng/mL)	458.52	93.59	4.9	6618.68	3461.23	1.9
$AUC_{0\text{-}12}$ (h*ng/mL)	173.76	51.76	3.4	1202.50	965.19	1.2
$AUC_{0\text{-}24}$ (h*ng/mL)	283.52	73.12	3.9	2175.20	1688.02	1.3
C_{max} (ng/mL)	23.06	9.1	2.5	118.62	92.79	1.3
T_{max} (h)[c]	2.500	3.000	-0.500 [a]	2.500	3.000	-0.500 [a]
$T_{1/2\ el}$ (h)	13.80	8.79	1.6	37.98	24.40	1.6

Bupropion PK Parameters

	Day 1			Day 8		
PK Parameters	**Moderate**	**Healthy Control**	**Moderate/ Healthy Control[b]**	**Moderate**	**Healthy Control**	**Moderate/ Healthy Control[b]**
$AUC_{0\text{-}inf}$ (h*ng/mL)	937.63	628.70	1.5	2836.15	1709.36	1.7
$AUC_{0\text{-}12}$ (h*ng/mL)	646.52	458.72	1.4	1062.84	670.23	1.6
$AUC_{0\text{-}24}$ (h*ng/mL)	828.47	568.59	1.5	1609.14	1012.06	1.6
C_{max} (ng/mL)	120.40	79.95	1.5	138.89	82.42	1.7
T_{max} (h)[c]	2.500	3.00	-0.500 [a]	2.000	2.000	0 [a]
$T_{1/2\ el}$ (h)	7.67	7.39	1.0	21.39	19.83	1.1

Source: Study report AXS-05-105, Table 11.4.1-8.
The values represent arithmetic mean; a: T_{max} difference; b: ratio of values; c: median values
Abbreviations: $AUC_{0\text{-}12}$, area under the curve to 12 hours; $AUC_{0\text{-}24}$, area under the curve to 24 hours; $AUC_{0\text{-}inf}$; area under the curve; C_{max}, maximum concentration; h, hours; PK, pharmacokinetic; T_{max}, time to maximum concentration; $T_{½el}$, half-life of elimination

Reviewer's Comments: The systemic exposures (C_{max} and $AUC_{0\text{-}12h}$) to dextromethorphan, bupropion, and the major metabolites of bupropion (hydroxybupropion, threohydroxybupropion and erythrohydroxybupropion) were not appreciably increased in subjects with moderate hepatic impairment compared to subjects with normal hepatic function. Therefore, no dose adjustment is recommended in patients with moderate hepatic impairment.

CYP2D6 Poor Metabolizers

In Study AXS-05-106, the PK of AXS-05 in subjects with CYP2D6 poor metabolizer phenotype was compared to subjects with non-poor metabolizer phenotype (extensive/ultra-rapid CYP2D6 metabolizers). See Table 83.

Table 83. Dextromethorphan PK Parameters in CYP2D6 Poor Metabolizers and Non-Poor Metabolizers (Extensive Metabolizer/Ultra-Rapid Metabolizers) [AXS-05-106]

	Mean (%CV)					
	Day 1			Day 8		
	PMs (n = 3)	EM or UM (n =11)	Ratio[a]	PMs (n = 3)	EM or UM (n =11)	Ratio[a]
AUC_{0-12} (ng*hr/mL)	319.21 (10.11)	27.34 (83.14)	11.7	2378.16 (12.22)	755.13 (40.69)	3.1
C_{max} (ng/mL)	35.16 (5.32)	3.78 (78.11)	9.3	217.59 (13.65)	76.65 (35.48)	2.8

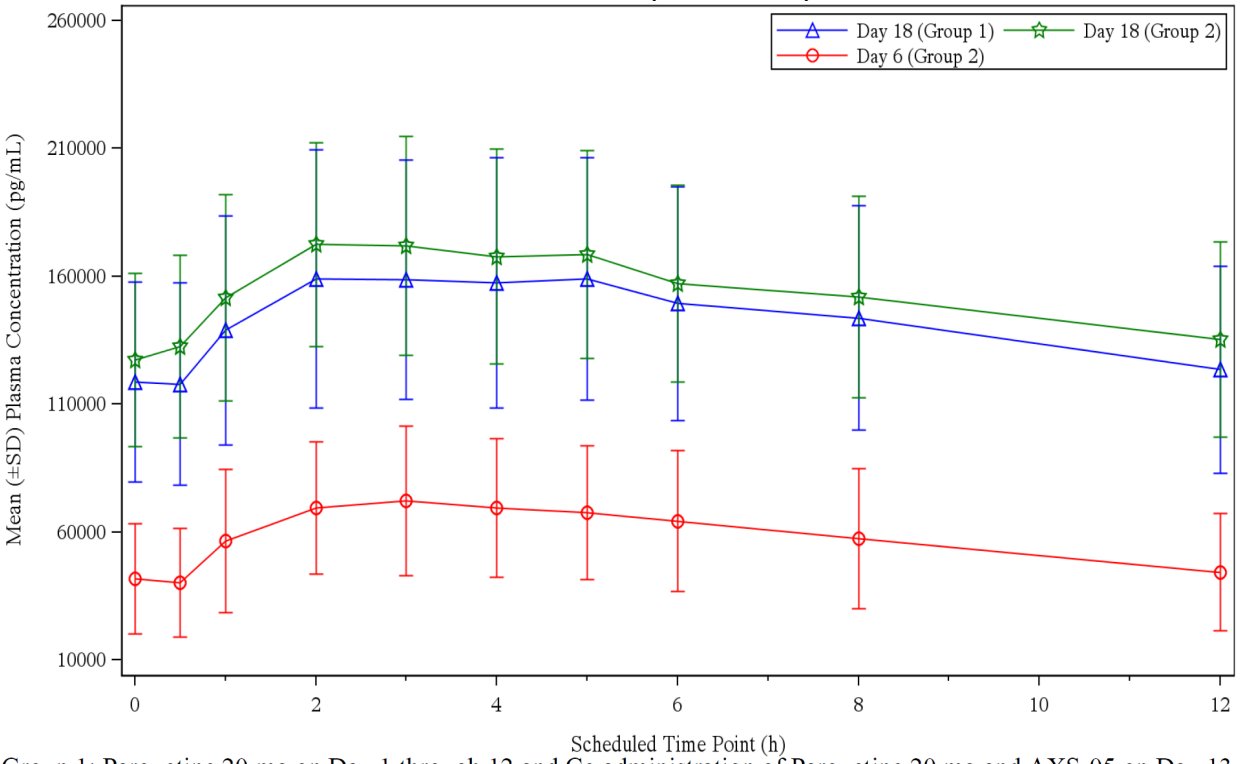
Source: Study report AXS-05-106; Table 11.4.1-1.
[a] ratio of PM:EM or UM
Abbreviations: AUC_{0-12}, area under the curve to 12 hours; C_{max}, maximum concentration; CV, coefficient of variation; EM, extensive metabolizer; PK, pharmacokinetic; PM, poor metabolizer; UM, ultra-rapid metabolizer;

Reviewer's Comments: Subjects with CYP2D6 poor metabolizer phenotype showed an approximately 3-fold increase in plasma exposures (maximum concentration [C_{max}]: 2.8-fold and area under the plasma concentration-time curve [AUC_{0-12h}]: 3.1-fold) to dextromethorphan compared to subjects who were non-poor CYP2D6 metabolizers (extensive/ultra-rapid CYP2D6 metabolizers). Given that bupropion is mainly metabolized by CYP2B6, the exposures to bupropion and its major metabolites were not appreciably altered in CYP2D6 poor metabolizers compared to CYP2D6 extensive/ultra-rapid metabolizers. Furthermore, in an open-label, long-term safety study (AXS-05-303), average steady-state plasma concentrations of dextromethorphan were approximately 2.6-fold higher in patients with CYP2D6 poor metabolizer phenotype compared to non-poor metabolizers (extensive/ultra-rapid CYP2D6 metabolizers). Therefore, once-daily dosing of AXS-05 is recommended in patients who are CYP2D6 poor metabolizers.

Strong CYP2D6 Inhibitors

In Study AXS-05-108, the effect of the strong CYP2D6 inhibitor paroxetine on the PK of AXS-05 was evaluated in healthy subjects. Plasma concentration-time profiles and PK parameters for dextromethorphan and bupropion are shown in Figure 20, Figure 21, Table 84, and Table 85.

Figure 20. Mean Plasma Concentration-Time Profiles of Dextromethorphan Following Administration of AXS-05 + Paroxetine and AXS-05 (AXS-05-108)



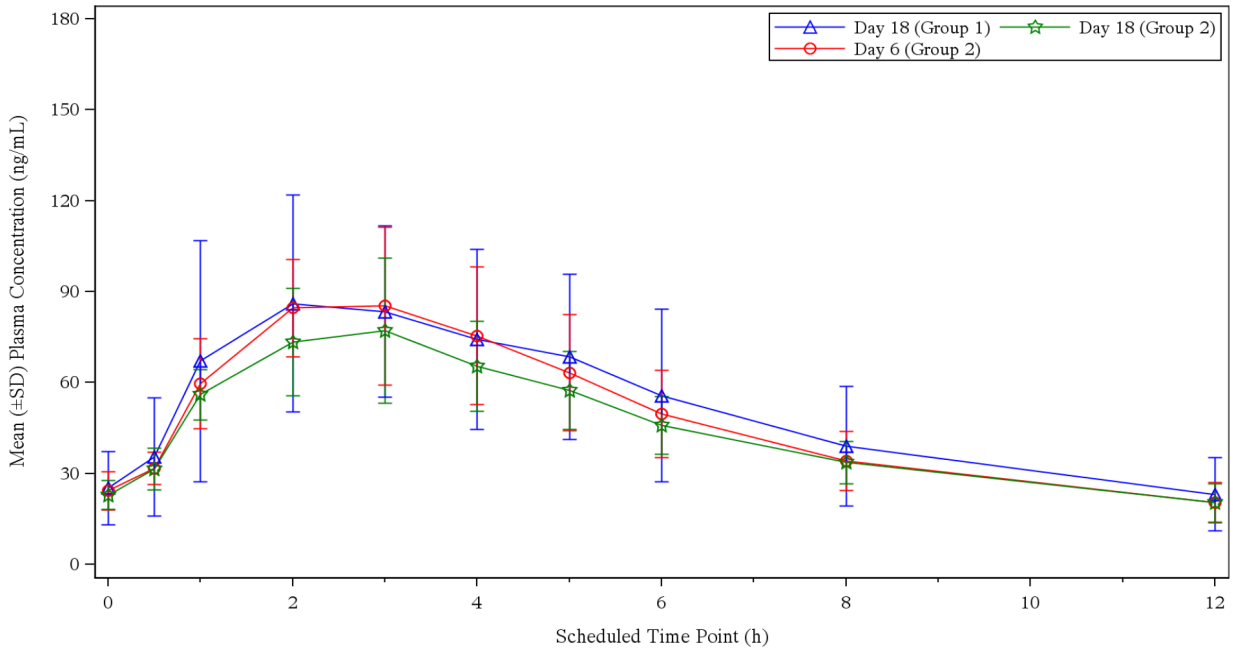
Group 1: Paroxetine 20 mg on Day 1 through 12 and Co administration of Paroxetine 20 mg and AXS-05 on Day 13 through 18; Group 2: AXS-05 on Day 1 through 6 and Co-administration of AXS-05 and paroxetine 20 mg on Day 7 through Day 18.
Source: Study report AXS-05-108; Figure 11.4.1-1.
Abbreviations: h, hours; SD, standard deviation

Table 84.Geometric Mean Ratio [Day 18 (AXS-05 + Paroxetine)/Day 6 (AXS-05); Group 2] and 90% CI for Dextromethorphan

Parameter (Unit)	Comparisons	Geometric LSM		Ratio[1] (%)	90% Geometric CI[2]	
		Day 18	Day 6		Lower (%)	Upper (%)
AUC_{0-12} (hr*pg/mL)	Day 18 - Day 6	1743101.68	647742.14	269.10	241.61	299.73
AUC_{0-24} (hr*pg/mL)	Day 18 - Day 6	3024503.69	969763.97	311.88	274.24	354.69
AUC_{0-t} (hr*pg/mL)	Day 18 - Day 6	1742956.10	645433.24	270.04	242.44	300.79
C_{max} (pg/mL)	Day 18 - Day 6	168484.30	70721.34	238.24	215.73	263.09

[1] Calculated using least-squares means according to the formula: $e^{Difference}$ X 100.
[2] 90% Geometric confidence interval using ln-transformed data.
Source: Study report AXS-05-108; Table 11.4.1-2.
Abbreviations: AUC_{0-12}, area under the curve to 12 hours; AUC_{0-24}, area under the curve to 24 hours; AUC_{0-t}; area under the curve to last measurable time; CI, confidence interval; C_{max}, maximum concentration; LSM, least-squares mean

Figure 21. Mean Plasma Concentration-Time Profiles of Bupropion Following Administration of AXS-05 + Paroxetine and AXS-05 (AXS-05-108)



Source: Study report AXS-05-108; Figure 11.4.1-4.
Abbreviations: h, hours; SD, standard deviation

Table 85. Geometric Mean Ratio [Day 18 (AXS-05 + Paroxetine)/Day 6 (AXS-05); Group 2] and 90% CI for Bupropion

Parameter (Unit)	Comparisons	Geometric LSM		Ratio[1] (%)	90% Geometric CI[2]	
		Day 18	Day 6		Lower (%)	Upper (%)
AUC_{0-12} (hr*ng/mL)	Day 18 - Day 6	543.48	577.26	94.15	87.96	100.77
AUC_{0-24} (hr*ng/mL)	Day 18 - Day 6	663.08	683.77	96.97	91.36	102.93
AUC_{0-t} (hr*ng/mL)	Day 18 - Day 6	543.44	576.08	94.33	88.12	100.98
C_{max} (ng/mL)	Day 18 - Day 6	81.37	94.09	86.48	76.57	97.68

[1] Calculated using least-squares means according to the formula: $e^{Difference}$ X 100.
[2] 90% Geometric confidence interval using ln-transformed data.
Source: Study report AXS-05-108; Table 11.4.1-8.
Abbreviations: AUC_{0-12}, area under the curve to 12 hours; AUC_{0-24}, area under the curve to 24 hours; AUC_{0-t}; area under the curve to last measurable time; CI, confidence interval; C_{max}, maximum concentration; LSM, least-squares mean

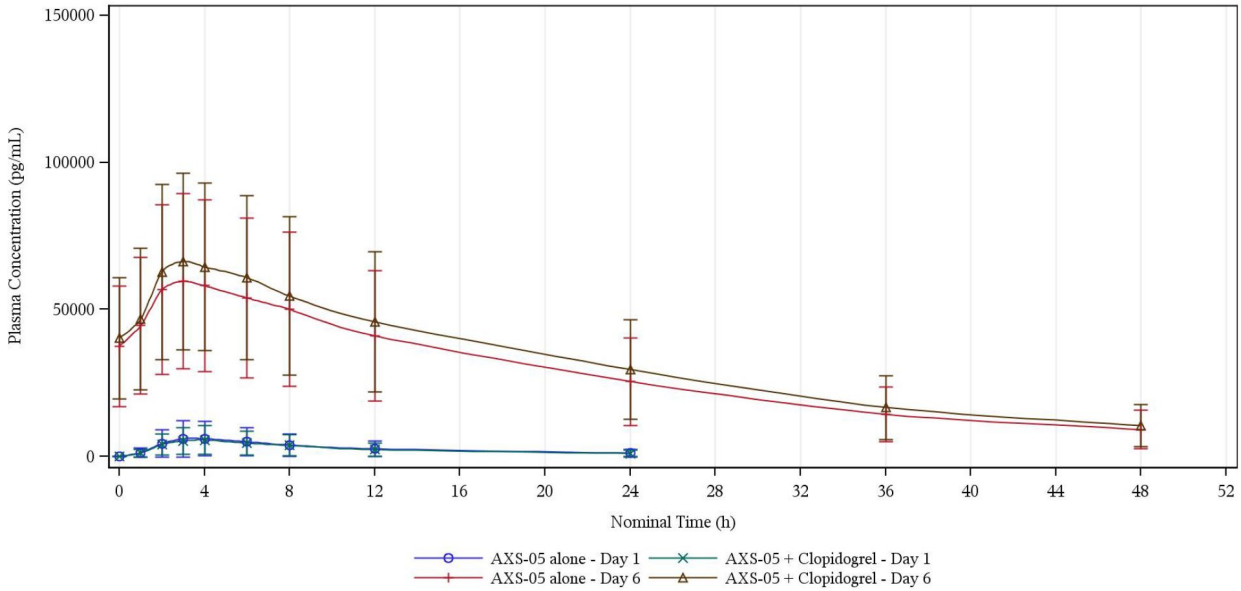
Reviewer's Comments: Following administration of AXS-05 in the presence of a strong CYP2D6 inhibitor, paroxetine, an approximately 2.4-fold increase in C_{max} and 2.7-fold increase in AUC_{0-12h} to dextromethorphan were observed compared to AXS-05 treatment alone (AXS-05-108). However, plasma exposures to bupropion and its metabolites were not appreciably altered.

Therefore, once-daily dosing of AXS-05 is recommended when AXS-05 is coadministered with strong CYP2D6 inhibitors.

Weak CYP2B6 Inhibitors

In Study AXS-05-110, the effect of a weak CYP2B6 inhibitor, clopidogrel, on the PK of AXS-05 was evaluated in healthy subjects. Plasma concentration-time profiles and PK parameters for dextromethorphan and bupropion are shown in Figure 22, Figure 23, Table 86, and Table 87.

Figure 22. Mean Plasma Concentration-Time Profiles of Dextromethorphan Following Administration of AXS-05 + Clopidogrel and AXS-05 (AXS-05-110)



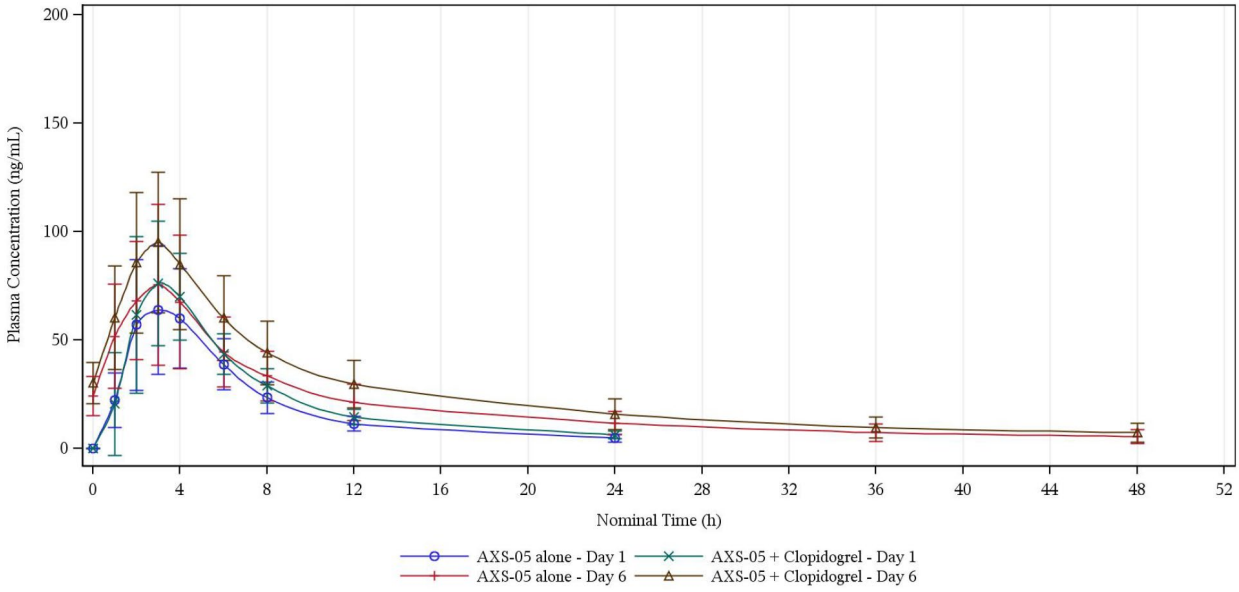
Source: Study report AXS-05-110; Figure 11.4.1-1.
Abbreviation: h, hours

Table 86. Geometric Mean Ratio [Day 6 (AXS-05 + Clopidogrel)/Day 6 (AXS-05)] and 90% CI for Dextromethorphan

Parameter (Unit)	Geometric LSM		Ratio[1] (%)	90% Geometric C.I.[2]	
	AXS-05 + Clopidogrel	AXS-05 alone		Lower (%)	Upper (%)
$AUC_{0\text{-}inf}$ (hr*pg/mL)	1464013.75	1132348.65	129.29	108.93	153.45
$AUC_{0\text{-}12}$ (hr*pg/mL)	572385.48	454359.00	125.98	107.73	147.31
$AUC_{0\text{-}24}$ (hr*pg/mL)	941471.51	738890.30	127.42	108.65	149.42
$AUC_{0\text{-}t}$ (hr*pg/mL)	1281526.85	995488.29	128.73	109.46	151.41
C_{max} (pg/mL)	59245.95	46664.06	126.96	107.92	149.37

[1] Calculated using least-squares means according to the formula: $e^{Difference}$ X 100.
[2] 90% Geometric confidence interval using ln-transformed data.
Source: Study report AXS-05-110; Table 11.4.1-3.
Abbreviations: $AUC_{0\text{-}12}$, area under the curve to 12 hours; $AUC_{0\text{-}24}$, area under the curve to 24 hours; $AUC_{0\text{-}inf}$, area under the curve; $AUC_{0\text{-}t}$; area under the curve to last measurable time; CI, confidence interval; C_{max}, maximum concentration; LSM, least-squares mean

Figure 23. Mean Plasma Concentration-Time Profiles of Bupropion Following Administration of AXS-05 + Paroxetine and AXS-05 (AXS-05-110)



Source: Study report AXS-05-110; Figure 11.4.1-4.
Abbreviation: h, hours

Table 87. Geometric Mean Ratio [Day 6 (AXS-05 + Clopidogrel)/Day 6 (AXS-05)] and 90% CI for Bupropion

Parameter (Unit)	Geometric LSM		Ratio[1] (%)	90% Geometric C.I.[2]	
	AXS-05 + Clopidogrel	AXS-05 alone		Lower (%)	Upper (%)
$AUC_{0\text{-}inf}$ (hr*ng/mL)	1257.41	989.97	127.02	115.84	139.27
$AUC_{0\text{-}12}$ (hr*ng/mL)	620.75	478.31	129.78	115.50	145.83
$AUC_{0\text{-}24}$ (hr*ng/mL)	865.57	658.79	131.39	117.93	146.38
$AUC_{0\text{-}t}$ (hr*ng/mL)	1087.70	833.76	130.46	118.45	143.68
C_{max} (ng/mL)	86.66	68.46	126.58	108.01	148.33

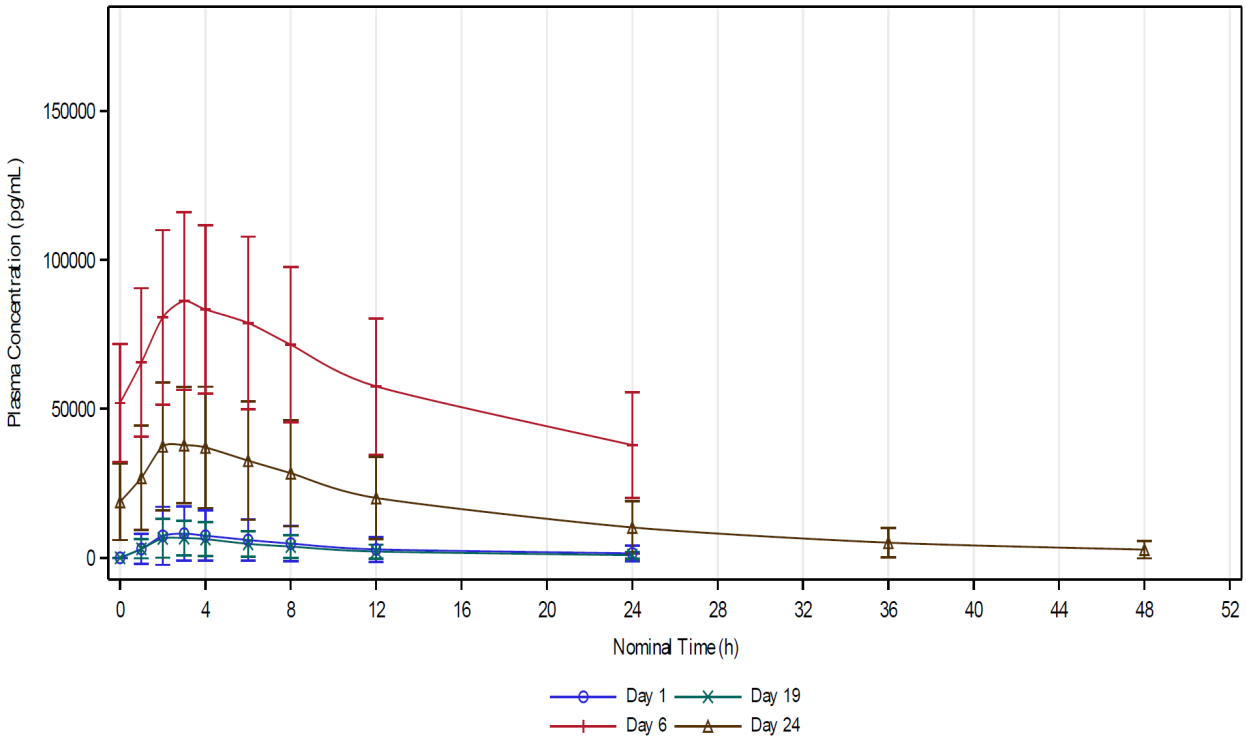
[1] Calculated using least-squares means according to the formula: $e^{Difference}$ X 100.
[2] 90% Geometric confidence interval using ln-transformed data.
Source: Study report AXS-05-110; Table 11.4.1-12.
Abbreviations: $AUC_{0\text{-}12}$, area under the curve to 12 hours; $AUC_{0\text{-}24}$, area under the curve to 24 hours; $AUC_{0\text{-}inf}$, area under the curve; $AUC_{0\text{-}t}$; area under the curve to last measurable time; CI, confidence interval; C_{max}, maximum concentration; LSM, least squares mean

Reviewer's Comments: Coadministration of the weak CYP2B6 inhibitor clopidogrel with AXS-05 resulted in minimal increase in exposures (C_{max}: 27%; $AUC_{0\text{-}12h}$: 26%) to dextromethorphan compared to AXS-05 treatment alone. The minimal increase in exposures to dextromethorphan are considered to be clinically not relevant. Furthermore, the plasma exposures to bupropion (C_{max}: 27% increase; $AUC_{0\text{-}12h}$: 30% increase) and its metabolites (hydroxybupropion: C_{max}: 42% decrease; $AUC_{0\text{-}12h}$: 41% decrease; threohydroxybupropion: C_{max}: 22% increase; $AUC_{0\text{-}12h}$: 25% increase; erythrohydroxybupropion: C_{max}: 21% increase; $AUC_{0\text{-}12h}$: 24% increase) were also minimally changed. Therefore, no dose adjustment of AXS-05 is recommended when AXS-05 is coadministered with weak CYP2B6 inhibitors.

Strong CYP2B6 Inducers

In Study AXS-05-111, the effect of a strong CYP2B6 inducer, carbamazepine, on the PK of AXS-05 was evaluated in healthy subjects. Plasma concentration-time profiles and PK parameters for dextromethorphan and bupropion are shown in Figure 24, Figure 25, Table 88, and Table 89. The PK parameters for bupropion metabolites (hydroxybupropion, threohydroxybupropion and erythrohydroxybupropion) are shown in Table 90, Table 91, and Table 92.

Figure 24. Mean Plasma Concentration-Time Profiles of Dextromethorphan Following Administration of AXS-05 + Carbamazepine and AXS-05 (AXS-05-110)



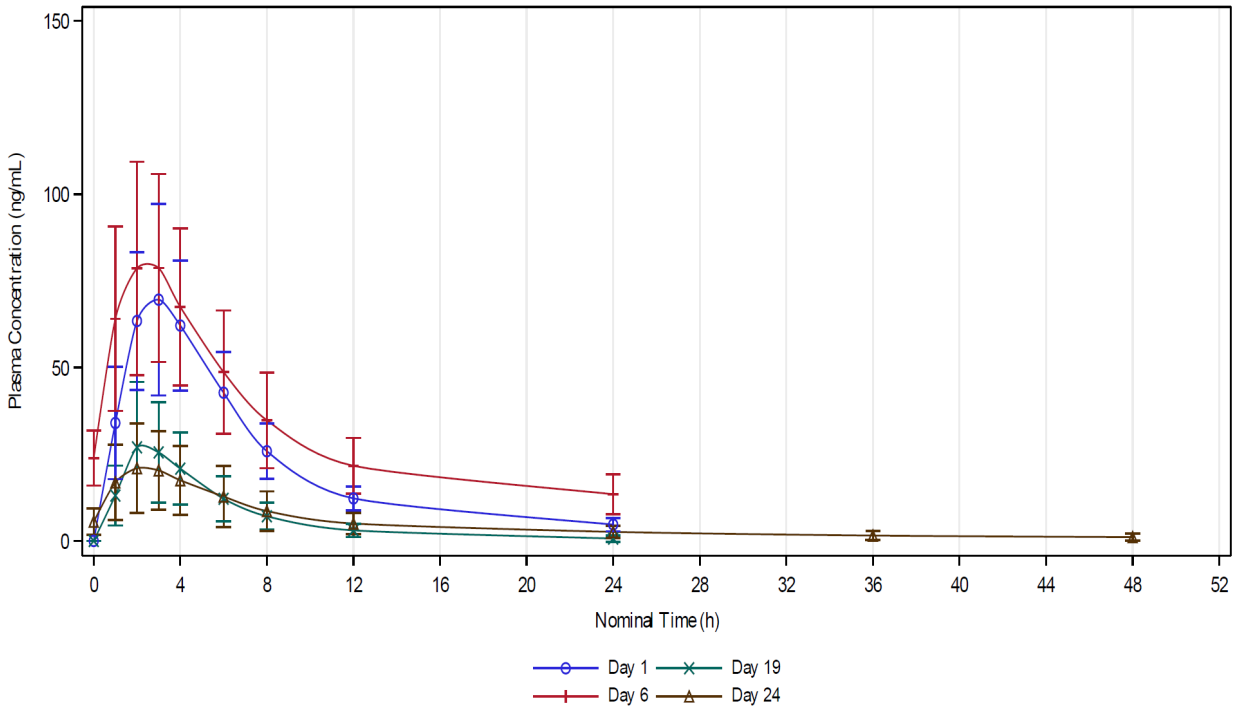
AXS-05 (Day 1-6) - Carbamazepine XR 100 mg or 200 mg (Day 7-18) - AXS-05 and Carbamazepine XR 200 mg (Day 19-24).
Source: Study report AXS-05-111; Figure 11.4.1-1.
Abbreviation: h, hours

Table 88. Geometric Mean Ratio [AXS-05 + Carbamazepine/AXS-05] and 90% CI for Dextromethorphan

Parameter (Unit)	Comparisons	Geometric LSM		Ratio[1] (%)	90% Geometric CI[2]	
		Day 24	Day 6		Lower (%)	Upper (%)
AUC_{0-12} (hr*ng/mL)	Day 24 - Day 6	281630.47	776252.84	36.28	31.18	42.21
AUC_{0-24} (hr*ng/mL)	Day 24 - Day 6	412690.84	1269727.46	32.50	27.66	38.19
C_{max} (ng/mL)	Day 24 - Day 6	32837.04	79201.07	41.46	36.19	47.50
C_{avg} (ng/mL)	Day 24 - Day 6	23469.21	64687.74	36.28	31.18	42.21

[1] Calculated using least-squares means according to the formula: $e^{Difference}$ X 100.
[2] 90% Geometric confidence interval using ln-transformed data.
Source: Study report AXS-05-111; Tables 11.4.1-3.
Abbreviations: AUC_{0-12}, area under the curve to 12 hours; AUC_{0-24}, area under the curve to 24 hours; C_{avg}, average concentration; CI, confidence interval; C_{max}, maximum concentration; LSM, least squares mean

Figure 25. Mean Plasma Concentration-Time Profiles of Bupropion Following Administration of AXS-05 + Carbamazepine and AXS-05 (AXS-05-110)



AXS-05 (Day 1-6) - Carbamazepine XR 100 mg or 200 mg (Day 7-18) - AXS-05 and Carbamazepine XR 200 mg (Day 19-24).
Source: Study report AXS-05-111; Figure 11.4.1-4.
Abbreviation: h, hours

Table 89. Geometric Mean Ratio [AXS-05 + Carbamazepine)/AXS-05)] and 90% CI for Bupropion

Parameter (Unit)	Comparisons	Geometric LSM		Ratio[1] (%)	90% Geometric CI[2]	
		Day 24	Day 6		Lower (%)	Upper (%)
AUC_{0-12} (hr*ng/mL)	Day 24 - Day 6	124.23	519.65	23.91	19.18	29.80
AUC_{0-24} (hr*ng/mL)	Day 24 - Day 6	162.48	619.92	26.21	21.13	32.51
C_{max} (ng/mL)	Day 24 - Day 6	19.64	75.67	25.95	20.49	32.87
C_{avg} (ng/mL)	Day 24 - Day 6	10.35	43.30	23.91	19.18	29.80

[1] Calculated using least-squares means according to the formula: $e^{Difference}$ X 100.
[2] 90% Geometric confidence interval using ln-transformed data.
Source: Study report AXS-05-111; Table 11.4.1-12.
Abbreviations: AUC_{0-12}, area under the curve to 12 hours; AUC_{0-24}, area under the curve to 24 hours; C_{avg}, average concentration; CI, confidence interval; C_{max}, maximum concentration; LSM, least-squares mean

Table 90. Geometric Mean Ratio [AXS-05 + Carbamazepine)/AXS-05] and 90% CI for Hydroxybupropion

Parameter (Unit)	Comparisons	Geometric LSM		Ratio[1] (%)	90% Geometric CI[2]	
		Day 24	Day 6		Lower (%)	Upper (%)
AUC_{0-12} (hr*ng/mL)	Day 24 - Day 6	14448.34	9989.20	144.64	126.82	164.96
AUC_{0-24} (hr*ng/mL)	Day 24 - Day 6	24251.17	17333.24	139.91	118.24	165.56
C_{max} (ng/mL)	Day 24 - Day 6	1421.52	945.40	150.36	132.01	171.26
C_{avg} (ng/mL)	Day 24 - Day 6	1204.03	832.43	144.64	126.82	164.96

[1] Calculated using least-squares means according to the formula: $e^{Difference}$ X 100.
[2] 90% Geometric confidence interval using ln-transformed data.
Source: Study report AXS-05-111; Table 11.4.1-15.
Abbreviations: AUC_{0-12}, area under the curve to 12 hours; AUC_{0-24}, area under the curve to 24 hours; C_{avg}, average concentration; CI, confidence interval; C_{max}, maximum concentration; LSM, least squares mean

Table 91. Geometric Mean Ratio [AXS-05 + Carbamazepine)/AXS-05] and 90% CI for Threohydroxybupropion

Parameter (Unit)	Comparisons	Geometric LSM		Ratio[1] (%)	90% Geometric CI[2]	
		Day 24	Day 6		Lower (%)	Upper (%)
AUC_{0-12} (hr*ng/mL)	Day 24 - Day 6	1077.17	3492.45	30.84	26.83	35.45
AUC_{0-24} (hr*ng/mL)	Day 24 - Day 6	1769.63	5996.89	29.51	25.04	34.78
C_{max} (ng/mL)	Day 24 - Day 6	107.78	332.13	32.45	28.88	36.47
C_{avg} (ng/mL)	Day 24 - Day 6	89.76	291.04	30.84	26.83	35.45

[1] Calculated using least-squares means according to the formula: $e^{Difference}$ X 100.
[2] 90% Geometric confidence interval using ln-transformed data.
Source: Study report AXS-05-111; Table 11.4.1-21.
Abbreviations: AUC_{0-12}, area under the curve to 12 hours; AUC_{0-24}, area under the curve to 24 hours; C_{avg}, average concentration; CI, confidence interval; C_{max}, maximum concentration; LSM, least-squares mean

Table 92. Geometric Mean Ratio [AXS-05 + Carbamazepine)/AXS-05] and 90% CI for Erythrohydroxybupropion

Parameter (Unit)	Comparisons	Geometric LSM		Ratio[1] (%)	90% Geometric CI[2]	
		Day 24	Day 6		Lower (%)	Upper (%)
AUC_{0-12} (hr*ng/mL)	Day 24 - Day 6	291.24	754.08	38.62	34.16	43.66
AUC_{0-24} (hr*ng/mL)	Day 24 - Day 6	510.36	1324.50	38.53	33.44	44.41
C_{max} (ng/mL)	Day 24 - Day 6	27.04	69.37	38.97	34.88	43.56
C_{avg} (ng/mL)	Day 24 - Day 6	24.27	62.84	38.62	34.16	43.66

[1] Calculated using least-squares means according to the formula: $e^{Difference}$ X 100.
[2] 90% Geometric confidence interval using ln-transformed data.
Source: Study report AXS-05-111; Table 11.4.1-18.
Abbreviations: AUC_{0-12}, area under the curve to 12 hours; AUC_{0-24}, area under the curve to 24 hours; C_{max}, maximum concentration; C_{avg}, average concentration; CI, confidence interval

Reviewer's Comments: Coadministration of a strong CYP2B6 inducer, carbamazepine, with AXS-05 resulted in an approximately 2-fold decrease in exposures (C_{max}: 2.4-fold; AUC_{0-12h}: 2.8-fold) to dextromethorphan compared to AXS-05 treatment alone. The plasma exposures to bupropion (C_{max}: 3.9-fold; AUC_{0-12h}: 4.2-fold), and its metabolites (threohydroxybupropion: C_{max}: 3.1-fold; AUC_{0-12h}: 3.2-fold and erythrohydroxybupropion: C_{max}: 2.6-fold; AUC_{0-12h}: 2.6-fold) were decreased, and hydroxybupropion exposures (C_{max}: 1.2-fold; AUC_{0-12h}: 1.4-fold) were increased compared to AXS-05 treatment alone. Given that the pivotal clinical efficacy and safety studies evaluated one dose level of AXS-05, a 2-fold reduction in dextromethorphan and approximately 4-fold reduction in bupropion exposures are expected to reduce the efficacy of AXS-05. Therefore, avoiding use of AXS-05 with strong CYP2B6 inducers is recommended.

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