ADASUVE (LOXAPINE) INHALATION POWDER
NDA 022549

PSYCHOPHARMACOLOGIC DRUG ADVISORY COMMITTEE
BRIEFING DOCUMENT

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ΔΔQTcI	time-matched difference from placebo in pre-dose-subtracted QTcI
A	ADASUVE
ACES	Agitation-Calmness Evaluation Scale
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AUC_{0-2h}	area under the concentration-time curve from 0 to 2 hours post-dose, also known as PK-AUC_{0-2h}
AUC_{inf}	area under the concentration-time curve from Time 0 to infinity
bpm	beats per minute
CGI-I	Clinical Global Impression - Improvement Scale
CGI-S	Clinical Global Impression - Severity Scale
CI	confidence interval
C_{max}	maximum concentration (at T_{max})
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CYP450	cytochrome P450; also known as CYP
DPI	dry powder inhaler
ECG	electrocardiogram
ED	emergency department
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IM	intramuscular
LSmean	least-squares mean
MDI	metered-dose inhaler
MMAD	mass median aerodynamic diameter
NDA	New Drug Application

P	placebo
PEC	Positive and Negative Symptom Scale, Excited Component
P-gp	P-glycoprotein
PK	pharmacokinetic
prn	as needed
QT interval	interval between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc interval	corrected QT interval
QTcI interval	individually corrected QT interval
Rx	study medication
REMS	Risk Evaluation and Mitigation Strategy
SAE	serious adverse event
SD	standard deviation
SEM	standard error of the mean
T_{max}	time to maximum concentration
US	United States
VAS	visual analog scale
VAS-AUC_{0-2h}	area under the VAS (sedation)-time curve (0 to 2 hours)

1 EXECUTIVE OVERVIEW

1.1 Agitation

Alexza Pharmaceuticals, Inc (Alexza) developed ADASUVE to improve treatment of agitation for adults with schizophrenia and bipolar disorder. Agitation is a severe, disruptive, and morbid complication of these illnesses (Osser and Sigadel, 2001). Patients who experience agitation describe feeling an inner distress (nervous, restless, overwhelmed, out of control, anguish, panic) that then progresses to an outwardly apparent dysfunctional state manifested by verbal abuse, hostility, and difficulty controlling impulses, with uncooperative behavior and increased potential for violence. While the time course for agitation to require treatment can be variable (taking minutes, hours or days), once the patient escalates to this point, urgent treatment is always required. ADASUVE, an inhaled formulation of the antipsychotic drug loxapine begins to control patients' agitation as early as 10 minutes and provides this relief in a noninvasive manner.

Currently, the standard of care in the treatment of acute agitation is pharmacological tranquilization with antipsychotics, sometimes combined with benzodiazepines (Currier and Trenton, 2002; Currier et al, 2004; Battaglia, 2005). These antipsychotic drugs are available in a variety of forms, including oral tablets, orally disintegrating tablets, oral liquids, and intramuscular (IM) injections. Intramuscular formulations of anti-agitation agents (antipsychotics and/or benzodiazepines) provide relatively faster relief compared to the oral formulations of these drugs, with marketed IM drugs taking between 15-120 minutes in patients with schizophrenia and 30-90 minutes in patients with bipolar disorder for onset of effect.

Although injections have a more rapid onset of effect than oral formulations, patients can be resistant to IM injection, which can also present risks to both patients and caregivers, such as physical injuries that occur during the containment process. Other factors limiting the use of IM injections include mental and physical trauma to the patient that compromises the patient-physician relationship, exposure to contaminated needles, and effects on long-term compliance (Allen et al, 2001).

No currently available agitation treatment meets all of the needs identified by an expert consensus panel for behavioral emergencies detailed in the Consensus Guidelines for Treatment of Behavioral Emergencies (Allen et al, 2001). Specifically, this expert panel identified requirements for an anti-agitation treatment, including speed of onset, control of aggressive behavior, patient preference, preservation of the physician-patient relationship, and reliability of delivery.

The discrepancy between the need for rapid onset of anti-agitation effects and the slow onset of the most frequently utilized treatments represents a substantial unmet medical need in patients with agitation that is addressed by ADASUVE.

1.2 ADASUVE: Loxapine Delivered with the *Staccato*® Delivery System

Loxapine, introduced more than 35 years ago in the United States (US), Canada, and Europe, has a well established efficacy and safety profile in the treatment of schizophrenia. Its antipsychotic effects are similar to those of other antipsychotics such as haloperidol, and are likely attributable to its action at dopamine D_2 receptors (Heel et al, 1978). Loxapine shares some of its clinical effects with atypical antipsychotics such as clozapine and olanzapine (Glazer, 1999), due to its antagonism of 5-HT_{2A} receptors.

ADASUVE is based on the proprietary *Staccato* delivery system developed by Alexza. Oral inhalation through the product initiates the controlled rapid heating of a thin film of excipient-free loxapine to form a thermally generated, highly pure drug vapor. The vapor condenses into aerosol particles with a particle size distribution appropriate for efficient delivery to the deep lung. The rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration.

1.3 ADASUVE Development Program

ADASUVE's clinical development program was designed similar to those of the IM formulations of the previous approved products for agitation (IM Zyprexa and IM Abilify). Because of the inhalation route of delivery and since the studies to assess the pulmonary safety of ADASUVE had not been completed, the Phase 2 and 3 trials excluded patients who had acute respiratory signs/symptoms or who were being treated for asthma or chronic obstructive pulmonary disease (COPD). Alexza completed a series of Phase 1 safety studies to assess the pulmonary safety of ADASUVE subsequent to the Phase 3 program.

The data of the overall development program demonstrated that ADASUVE reaches the systemic circulation quickly and reduces agitation rapidly. The results also helped Alexza identify a subset of the agitated patient population (ie, those with active airways disease) who are not appropriate for ADASUVE treatment due to a risk of bronchospasm.

The development program included:

- Five Phase 1 safety, tolerability, and/or pharmacokinetic studies in volunteers.
- One Phase 2 and two Phase 3 double-blind, placebo-controlled studies in agitated patients from 2 distinct patient populations (schizophrenia and bipolar I disorder, manic or mixed episode) to support the efficacy of ADASUVE in the control of agitation in different patient populations.
- Three Phase 1 pulmonary safety studies in normal healthy volunteers and in subjects with asthma or COPD.

1.4 Pharmacokinetics of ADASUVE

The main findings of the clinical pharmacology studies of ADASUVE are as follows:

- Time to maximum plasma concentration (T_{max}) within 2 minutes.
- Pharmacokinetic profile similar in healthy subjects, including smokers and nonsmokers, and subjects on stable antipsychotic regimens.
- Mean plasma loxapine concentrations consistent and linear over the clinical dose range.
- Minimal accumulation during the 4-hour dosing interval with repeat administration.
- No clinically significant effects of age, weight, body mass index, gender, and race on loxapine pharmacokinetics.
- Drug-drug interaction not anticipated based on the metabolic profile of loxapine.

The pharmacokinetics of ADASUVE is described in more detail in Section 2.2.2.3.

1.5 Efficacy of ADASUVE

The same primary efficacy endpoint was used in the 2 Phase 3 studies. The primary endpoint was the change in Positive and Negative Symptom Scale, Excited Component (PEC) score from baseline to 2 hours following Dose 1 of ADASUVE, compared with placebo, and was the same as that used in the clinical development programs of the IM formulations of two antipsychotics (Zyprexa and Abilify) marketed for the treatment of agitation. The key secondary endpoint was the Clinical Global Impression - Improvement Scale (CGI-I) score 2 hours following Dose 1 of ADASUVE, compared with placebo. Additional efficacy endpoints included the percentage of CGI-I responders ("very much improved" or "much improved" at 2 hours after dosing), the number of doses of study and rescue medication; and the time to Dose 2 of study medication (an as needed dose). To further characterize the efficacy of ADASUVE, the following post hoc analyses were performed: a PEC responder analysis and changes in individual PEC scale items.

The Phase 3 program included patients who were significantly agitated and representative of the population requiring treatment of agitation in clinical practice. The patients in these studies had, on average, a moderate level of agitation as determined by multiple rating instruments and had significant and long-standing psychiatric disease, based on years since diagnosis and previous hospitalizations, consistent with the pivotal clinical studies that supported the approval of IM Abilify and IM Zyprexa for agitation.

The findings of the Phase 3 studies demonstrate the efficacy of both the 5- and 10-mg doses of ADASUVE in the treatment of agitation in patients with schizophrenia or bipolar disorder. Across multiple endpoints, the effects of the 5- and 10-mg doses were statistically different from placebo, and typically there was a numerically larger treatment effect in the 10-mg group than the 5-mg group. These data support the administration of 1 to 3 doses of ADASUVE (up to a total of 30 mg/day) during a 24-hour period. This efficacy was

demonstrated in clinically agitated patients with significant and long-standing disease, who presented or were referred for study treatment through normal channels by which psychiatric patients obtain treatment for agitation.

Specifically, the Phase 3 studies support the following conclusions:

- Both the 5- and 10-mg doses of ADASUVE were statistically significantly superior to placebo for the primary efficacy endpoint, the change in the PEC score from baseline to 2 hours (5 and 10 mg versus placebo).

- For both doses, the treatment effect was evident 10 minutes after Dose 1 and was sustained at all assessment times through 24 hours.

- The findings for post hoc analyses of PEC (ie, the percentage of patients with ≥40% decrease from baseline in the total PEC score and mean changes in each of the individual PEC items at each assessment time from 10 minutes to 2 hours after Dose 1) also support the efficacy and clinical relevance of ADASUVE. These latter data indicate that the change in total PEC score is comprised of rapid and significant improvement in each of the 5 symptom domains assessed by the PEC scale (hostility, excitement, poor impulse control, uncooperativeness, and tension).

- Both doses of ADASUVE were statistically significantly superior to placebo for the key secondary efficacy endpoint, the CGI-I score at 2 hours (5 and 10 mg versus placebo).

- The findings for additional endpoints also support the efficacy of ADASUVE. These include the percentage of patients judged by the investigator to be very much improved or much improved 2 hours after Dose 1 (CGI-I responder analysis), the use of additional doses of study medication, and time to Dose 2 of study medication.

- There were no apparent differences in response to treatment between subgroups based on age, gender, race, baseline PEC score, or between bipolar I disorder patients with manic or mixed episodes.

- Across multiple endpoints, the magnitude of the treatment effect was larger in the 10-mg group than the 5-mg group, supporting a dose-response pattern for ADASUVE 5 and 10 mg.

- All of the agitated patients in the clinical studies were able to use the product successfully.

The efficacy of ADASUVE is described in more detail in Section 7.

A comparison of efficacy results in the ADASUVE Phase 3 studies with those from the IM Abilify and IM Zyprexa studies is provided in Appendix 1.

1.6 Safety of ADASUVE

General Safety Conclusions

In the Phase 2 and 3 studies, the safety assessment demonstrates that ADASUVE is safe and well tolerated for the treatment of agitation in patients with schizophrenia or bipolar disorder. This population includes 524 patients who received at least 1 dose of ADASUVE and 263 patients who received at least 1 dose of placebo.

Only 3 serious adverse events (AEs) in total were reported in ADASUVE patients in the Phase 2/3 agitated patient population (5 mg: 1 patient [hypertension] and 10 mg: 2 patients [exacerbation of schizophrenia and gastroenteritis, respectively]), none of which were considered related to ADASUVE by the investigator. Similarly, a very low incidence of AEs that led to premature discontinuation of study medication was reported in the Phase 2/3 agitated patient population: 1 patient experienced bronchospasm and 2 patients experienced anxiety. All 3 events were considered by the investigator to be moderate in severity, and resolved. The bronchospasm was considered by the investigator to be probably related to study medication and 1 event of anxiety was considered by the investigator to be possibly related to study medication.

The main safety findings in the Phase 2/3 agitated patient population were as follows:

- Adverse events were reported for a similar percentage of ADASUVE- and placebo-treated patients (All ADASUVE, 36.5%; placebo, 37.3%).

- Dysgeusia, sedation (including sedation combined with somnolence), fatigue, and throat irritation were identified as potential adverse reactions associated with ADASUVE (incidence rate of ≥2% and greater than placebo in either the 5-mg or 10-mg ADASUVE groups).

- ADASUVE was not associated with qualitatively excessive or adverse sedation.

- No clinically important effects of ADASUVE on mean clinical laboratory values or mean vital signs were observed. Few marked laboratory or vital sign abnormalities were identified. A thorough QT/QTc study was negative according to ICH E14 criteria.

Pulmonary Safety Conclusions

The subjects enrolled in the ADASUVE clinical development program comprise two distinct populations regarding pulmonary safety: subjects without airways disease, and subjects with currently-treated asthma or COPD who participated in spirometry-based pulmonary safety studies. Among the 1095 study subjects without airways disease, only 1 (0.09%) required treatment for post-treatment airway-related symptoms (ie, bronchospasm). The main pulmonary safety findings were as follows:

- The rate of treatment-related airway AEs was very low in the Phase 2/3 agitated patient population (0.4%). There was no evidence for additional risk of an airway AE following a second or third dose of ADASUVE.

- Respiratory function was not adversely affected in normal healthy subjects given 2 doses of ADASUVE within a day in a Phase 1 study. A thorough examination of spirometry findings determined that there was no effect on airways.

- Respiratory symptoms and/or changes in flow parameters (ie, FEV_1) were common in subjects with asthma after ADASUVE treatment, and were less common in subjects with COPD in Phase 1 studies. All airway AEs in these subjects were mild or moderate.

- All respiratory signs or symptoms requiring treatment in the Phase 1 asthma and COPD studies were readily managed with an inhaled bronchodilator.

- The susceptibility to airway AEs in subjects with active airways disease was well characterized. The AE data and FEV_1 results are consistent with an irritant effect of the inhaled drug that typically occurs shortly after dosing and responds to standard bronchodilator therapy without clinical sequelae.

- Based on results of the clinical development program, the patients at risk of bronchospasm from ADASUVE treatment can be identified; namely, patients with active airways disease. Excluding this patient population and mitigating the risk of bronchospasm in agitated patients can be addressed via risk management measures.

The general safety of ADASUVE is described in more detail in Section 8. Detailed discussion of pulmonary safety is provided in Section 9.

1.7 Risk Management

The risk management goal is to mitigate the safety risk associated with bronchospasm through labeling plus a Risk Evaluation and Mitigation Strategy (REMS) program. Alexza is proposing a contraindication to exclude these patients from those who should receive receive ADASUVE.

> *ADASUVE is contraindicated in patients with acute respiratory signs/symptoms (eg, wheezing) or who are taking medications to treat asthma or COPD.*

The REMS program will identify and exclude those patients at risk for bronchospasm from receiving ADASUVE. In the event that some patients who are at risk for bronchospasm may not be identified for exclusion from treatment with ADASUVE in clinical practice, the proposed REMS program includes components designed to mitigate the risk of bronchospasm should it occur. The REMS comprises measures to help healthcare professionals monitor for bronchospasm and treat it as quickly as possible in a setting that is appropriately equipped to treat it. Specifically, the REMS includes a Medication Guide, Communication Plan, and an Element to Assure Safe Use (ensuring that ADASUVE is only available in enrolled healthcare facilities where there is ready access to a short-acting beta-agonist bronchodilator).

The risk management program for ADASUVE is described in more detail in Section 10.

1.8 Benefits and Risks Conclusions

By the time agitated patients present at a treatment setting, their agitation is at a severity level in which emergent treatment is needed. Treatment goals in emergency psychiatric patients are to quickly calm the patient so that they can be more accurately assessed by the physician. Ideally, these patients should be treated in a non-coercive manner. Currently available products for treating agitation are lacking because they either work slowly or they are invasive and are likely to require coercive measures to deliver the medication.

ADASUVE is an important new therapeutic option for the management of agitation since it provides: 1) a rapid onset of anti-agitation effects, 2) an easily administered dosage form producing consistent and reliable pharmacokinetics, and 3) a non-invasive treatment option, which is preferred by patients, and serves to maintain the therapeutic alliance between patient and healthcare professional.

The efficacy of ADASUVE was demonstrated in agitated patients across multiple measures and across multiple time points. Starting at 10 minutes, ADASUVE showed a clinical benefit on all domains of the PEC scale (hostility, excitement, poor impulse control, uncooperativeness, and tension), total PEC scores, and PEC 40 responder analysis. Efficacy was confirmed by study investigators using the CGI-Improvement assessments at 2 hours post-dose with ADASUVE. Using the responder analyses (CGI-I and PEC 40) at the 2 hour time point, the number needed to treat (NNT) for ADASUVE is approximately 3.2 for patients with schizophrenia and 2.2 for patients with bipolar disorder.

The pulmonary safety results identified a population of patients in whom ADASUVE should not be used due to a risk of bronchospasm (ie, patients with acute respiratory signs/symptoms such as wheezing, or who are taking medications to treat asthma or COPD). This risk of bronchospasm in agitated patients can be addressed via product labeling and a REMS program that will ensure appropriate patient selection and management of bronchospasm if it occurs.

The efficacy and relatively benign general safety profile demonstrated in the clinical program for ADASUVE, along with the potential benefits for both patients and healthcare providers, and the proposed REMS to mitigate the risk of bronchospasm in a clearly defined subpopulation support a positive risk-benefit assessment for this product in the proposed indication.

2 INTRODUCTION

2.1 Agitation Associated with Psychiatric Disorders and Limitations of Current Treatment

Agitation is a severe, disruptive, and morbid complication of many chronic mental illnesses, including schizophrenia (Osser and Sigadel, 2001), mania (Alderfer and Allen, 2003), and dementia (Conn and Lieff, 2001). Schizophrenia affects approximately 2.4 million adults in the United States (US), and bipolar disease affects approximately 5.7 million adults in the US, according to National Institutes of Mental Health prevalence rates. Psychomotor agitation is defined by the Diagnostic and Statistical Manual of Mental Disorders, Edition 4 as 'excessive motor activity associated with a feeling of inner tension.' Patients who experience agitation describe feeling an inner distress (nervous, restless, overwhelmed, out of control, anguish, panic) that then progresses to an outwardly apparent dysfunctional state manifested by cursing, hostility, difficulty controlling impulses, with uncooperative behavior and increased potential for violence. The time course for agitation escalation can be minutes, hours or days, and patients can require hours to days of treatment to reduce agitation symptoms while they are being stabilized. Acute agitation associated with psychiatric diseases is one of the most important contributors to the continued stigmatization of mental illness (Buckley, 1999).

Mental health crises comprise a substantial number of urgent medical interventions, with more than 3 million mental health-related diagnosis patients seen in emergency departments (EDs) in the US annually (McCaig and Burt, 2002). Patients with these illnesses are at increased risk for agitation in the emergency setting (Marco and Vaughn, 2005). As many as 1.7 million medical emergency room visits per year may involve agitated patients (Sachs 2006). Of psychiatric emergency visits in the US, it is estimated that 20% to 50% might involve patients at risk for agitation (Allen and Currier, 2004; Marco and Vaughn, 2005).

As such, the significance of agitation cannot be overstated. At the very least, agitation disrupts psychiatric healthcare settings. In addition, in the absence of prompt intervention, agitation can lead to destruction and violence, and these can affect an institution significantly both in terms of cost and casualties. In a survey of psychiatric emergency services across the country in 1999, it was estimated that agitation led to an average of 8 patient-to-staff assaults per facility annually, with some centers reporting more than 25 assaults per year (Allen et al, 2001). Most of these assaults resulted in staff injury severe enough to miss work (Allen et al, 2001). One study determined that one-third of such assaults were apparently random, whereas two-thirds occurred during containment procedures (Carmel and Hunter, 1989). For example, in a recent cross-sectional survey by the Emergency Nurses Association, 54.8% of registered nurses reported being verbally or physically abused at work within the previous 7 days (Emergency Nurses Association Institute for Nursing Research, 2010). Because agitation also carries a high risk of injury to the patients themselves (Zeller and Rhoades, 2010), appropriate intervention in agitation is paramount in the acute care setting.

Currently, the standard of care in the treatment of acute agitation is pharmacological tranquilization with antipsychotics, sometimes combined with benzodiazepines (Currier and Trenton, 2002; Currier et al, 2004; Battaglia, 2005). These antipsychotic drugs are available in a variety of forms, including oral tablets, orally disintegrating tablets, oral liquids, and intramuscular (IM) injections. Intramuscular formulations of anti-agitation agents (antipsychotics and/or benzodiazepines) provide relatively faster relief compared to the oral formulations of these drugs, with marketed IM drugs taking between 15-120 minutes in patients with schizophrenia (see Appendix 1) and 30-90 minutes in patients with bipolar disorder for onset of effect.

From the healthcare professional's perspective, agitation, if not treated quickly and effectively, may escalate unpredictably. With the current treatment options, clinicians must either choose a treatment for agitation that is non-invasive (oral) or faster acting (injection). Waiting for an oral formulation to take effect leaves a significant period during which agitation can escalate and patients, staff, and property remain vulnerable to the deleterious behaviors associated with agitation. While injections have a more rapid onset of effect, patients may resist an IM injection, which can present risks to both patients and caregivers, such as physical injuries that occur during the containment process. Other factors limiting the use of IM injections include mental and physical trauma to the patient, an adverse effect on the patient-physician relationship, exposure to contaminated needles, and negative effects on long-term compliance (Allen et al, 2001).

No currently available agitation treatment meets all of the needs identified by an expert consensus panel for behavioral emergencies detailed in the Consensus Guidelines for Treatment of Behavioral Emergencies (Allen et al, 2001). Specifically, this expert panel identified the following requirements for an anti-agitation treatment:

- **Speed of onset**: This is considered the most important factor in selecting an agitation treatment. A treatment that is fast acting can mitigate the escalation of agitation sooner so that it does not reach a volatile point at which the patient becomes dangerous to himself or others.

- **Control of aggressive behavior**: This short-term treatment goal is critical to avoid harm to the patient and others. Agitation can lead to destruction and violence in the absence of intervention, and can affect an institution in terms of cost and injuries (Bruch and Zeller, 2008).

- **Patient preference**: The expert panel stressed the importance of determining the patient's preference for treatment before intervening with medication in a psychiatric emergency. A consumer panel indicated preference for oral anti-agitation medication and stressed the importance of staff using the least intrusive interventions possible (Allen et al, 2003).

- **Preserving the physician-patient relationship**: Patients advocate to be treated respectfully during a behavioral emergency (Allen et al, 2003; Fishkind, 2008). The panel emphasized the importance of the collaboration between patient and physician and

respecting the wishes of the patient in order to achieve a favorable long-term outcome (Allen et al, 2001).

- **Reliability of delivery**: If medication is not reliably delivered at the dose intended, the therapeutic effect may be compromised.

2.2 ADASUVE

Loxapine, which was introduced more than 35 years ago in the US, Canada, and Europe, has a well established efficacy and safety profile in the treatment of schizophrenia. Its antipsychotic effects are similar to those of other antipsychotics such as haloperidol, and are likely attributable to its action at dopamine D_2 receptors (Heel et al, 1978). There is limited evidence that loxapine shares some of its clinical effects with atypical antipsychotics, such as clozapine and olanzapine (Glazer, 1999), due to its unique binding profile, especially its action at 5-HT_{2A} receptors (Table 1).

Table 1. Comparison of Affinity of Loxapine and Other Antipsychotics for Neurotransmitter Receptors (Ki, nM)

Receptor	Loxapine	Clozapine	Olanzapine	Haloperidol
D_1	18	290	52	120
D_2	9.8	130	20	1.4
5-HT_{2A}	2	8.9	50	120
α1	28	4	54	4.7
α2	250	33	170	1200
H1	5	1.8	2.8	440

Staccato® loxapine for Inhalation (ADASUVE) is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery by inhalation of a thermally generated aerosol of loxapine. ADASUVE represents a new dosage form for loxapine. ADASUVE (5-mg and 10-mg dose levels) has been developed for the treatment of agitation in patients with schizophrenia or bipolar I disorder. Since agitation in these psychiatric populations is an acute and intermittent condition, it is expected that patients will be treated with ADASUVE on an infrequent basis.

ADASUVE is an important new therapeutic option for the management of agitation since it provides:

1. rapid onset of anti-agitation effects

2. an easily administered dosage form producing consistent and reliable pharmacokinetics

3. a non-invasive treatment option, which is preferred by patients, and serves to maintain the therapeutic alliance between patient and healthcare professional.

2.2.1 Description of Product

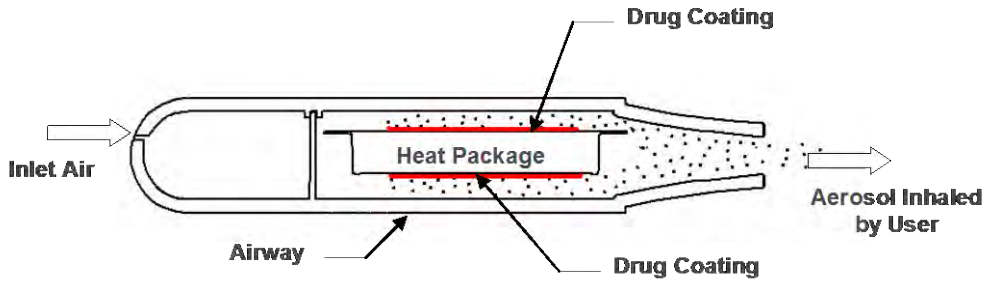
ADASUVE is based on the proprietary *Staccato* delivery system developed by Alexza Pharmaceuticals, Inc (Alexza). Oral inhalation through the product initiates the controlled rapid heating of a thin film of excipient-free loxapine to form a thermally generated, highly pure drug vapor. The vapor condenses into aerosol particles with a particle size distribution appropriate for efficient delivery to the deep lung. The rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration.

The product comprises the following four principal components (shown schematically in Figure 1):

- Heat package: The sealed assembly, composed of a reactant coating on the interior surfaces of stainless steel substrates, that generates heat to vaporize the drug and produce the aerosol.
- Drug coating: The thin film of excipient-free loxapine coated on the exterior stainless steel surface(s) of the heat package (single-sided coating for the 5-mg dose and double-sided coating for the 10-mg dose.
- Breath sensor: The breath-activation mechanism that initiates actuation of the heat package.
- Airway: The channel formed by the medical-grade plastic housings surrounding the heat package; it controls and directs the airflow over the vaporizing drug.

Staccato placebo systems used in the clinical studies were identical in size and operation to ADASUVE except that *Staccato* placebo contained no drug coating. *Staccato* placebo was used in the same manner and produced the same heat output as ADASUVE.

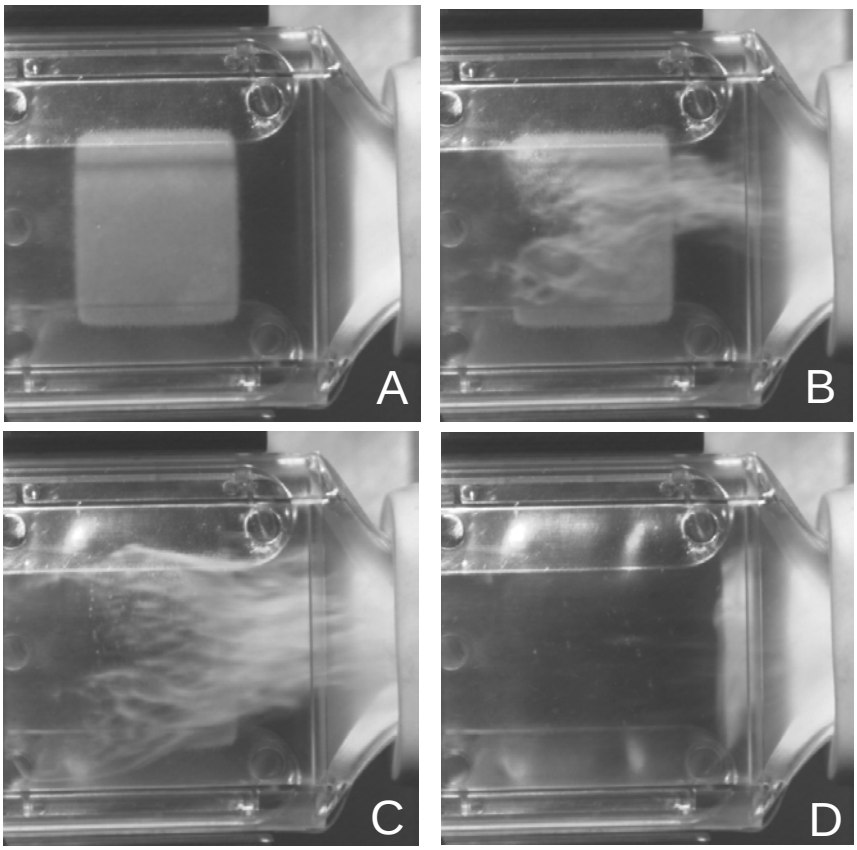
Figure 1. Schematic Side-View of ADASUVE



The interior surface of the stainless steel substrate of the heat package is coated with a reactant. When activated, this undergoes a controlled, gasless, oxidation-reduction (redox) reaction that liberates heat. The redox reaction is initiated by a battery-activated starter inserted into the heat package.

Inhalation through the product is detected by the breath sensor within the early portion of the breath. The breath detection event causes the starter to initiate the redox reaction and subsequent rapid heating of the substrate. Heat then transfers into the thin film of loxapine that is coated on the exterior surface of the substrate. The loxapine is completely vaporized in <1 second, thereby limiting thermal decomposition. The vapor cools in the airflow and condenses to form aerosol particles that are characterized by a mass median aerodynamic diameter (MMAD) in the range of 1.0 to 3.5 µm. The entrainment of the aerosol in the early portion of the inhalation helps to ensure delivery to the deep lung. Figure 2 shows frames taken from high speed photography of the vaporization process. Note that by 200 msec after actuation, the drug has completely vaporized from the heat package and the aerosol particles have been removed from the airway by the inhaled breath.

Figure 2. Images of the Vaporization Process



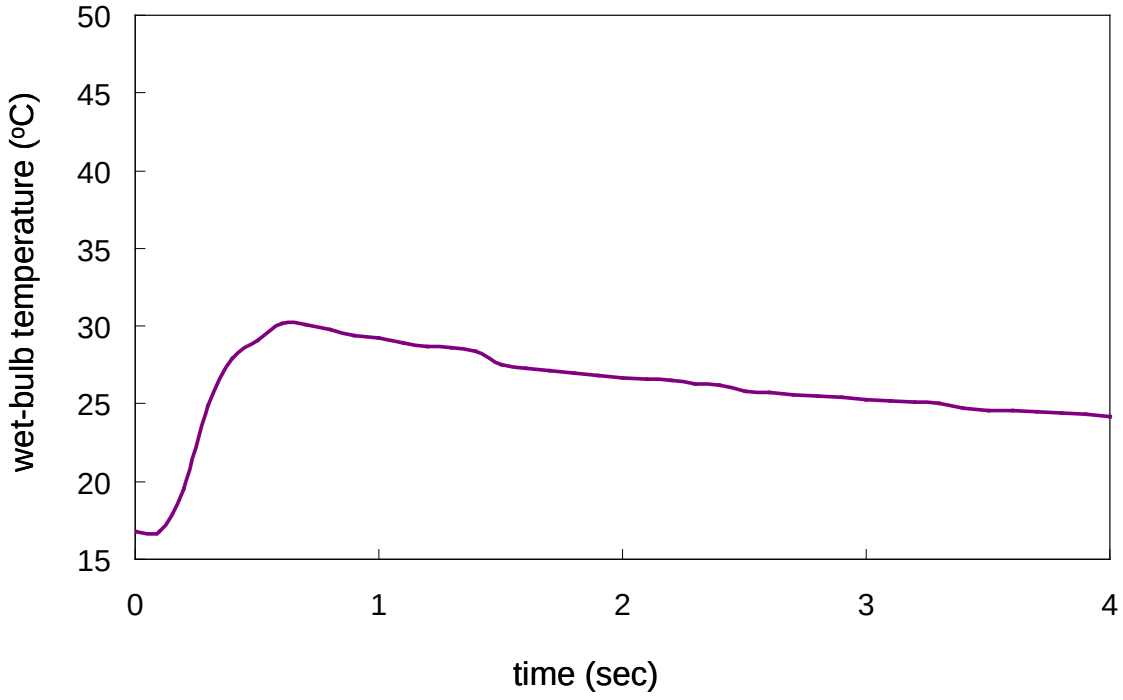
A) actuation; B) 30 ms after actuation; C) 50 ms after actuation; D) 200 ms after actuation

Each product is packaged inside a sealed foil pouch. Removal of a pull-tab from the product renders it ready for use, as indicated by illumination of a green light. Successful dosing is signaled by the green light turning off. ADASUVE is a single-use device and disposable.

The *Staccato* aerosol has been thoroughly characterized. The purity of the drug aerosol exceeds 99.6% loxapine. In assays of impurities unrelated to the drug (eg, leachables, microbial content), nothing was detected above safety thresholds. Prior research and standards for inhalation of warm air indicate that the wet-bulb temperature, which takes into

account the total energy of the air stream including moisture content, is the appropriate metric for evaluating safety. As shown in Figure 3, aerosol temperature peaks within a second after actuation and rapidly declines thereafter. The peak temperatures reached here are well within accepted safety standards and were well tolerated by the subjects in the clinical program.

Figure 3. Typical Wet-bulb Temperature Profile of ADASUVE Aerosol



ADASUVE does not rely on breath-hand coordination (like a metered-dose inhaler [MDI]) or a forceful inhalation to disperse particles (like a dry powder inhaler [DPI]). Because of the intrinsic mechanism of aerosol formation, the particle sizes tend to be smaller than those produced by MDIs or DPIs. ADASUVE has a fine particle fraction (percentage of aerosol particles <5 μm) of approximately 86-90%. Fine particle fraction is considered the content of aerosol particles likely to transit past the upper airway and potentially deposit in the lungs. The ADASUVE product has a number of other characteristics that distinguish it from other typical inhalers, including no priming, no cleaning or maintenance, and insensitivity to ambient temperature and humidity conditions.

ADASUVE has demonstrated a high degree of product reliability during the conduct of the clinical development program. For the Phase 3 studies and all subsequent clinical studies, product reliability was evaluated primarily based on a formal complaint system, consistent with how Alexza will evaluate reliability in a commercial environment.

2.2.2 Pharmacokinetics of Loxapine

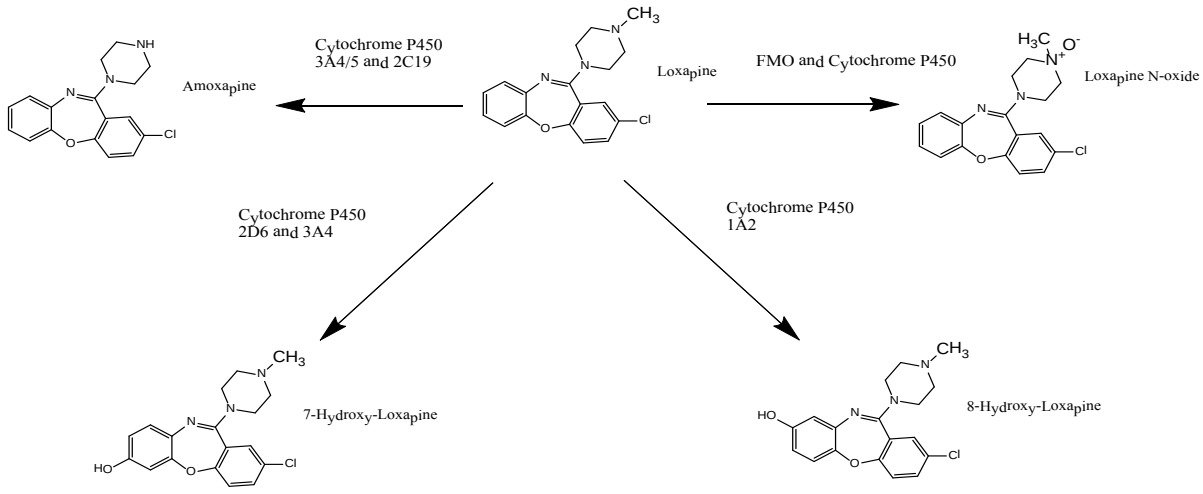
2.2.2.1 Established Clinical Pharmacology of Loxapine

The in vivo pharmacological activity of loxapine is primarily related to its affinity and antagonist activity at the various dopamine and serotonin receptor subtypes, especially dopamine D_2 and 5-HT_{2A}. The main observations reported in the literature are summarized below.

Following oral administration, loxapine is well absorbed from the gastrointestinal tract and undergoes substantial first-pass metabolism, with systemic bioavailability approximately 33%. Time to maximum concentration (T_{max}) is approximately 1 to 3 hours following both oral and IM administration. Loxapine and its metabolites are lipophilic, and they distribute widely and rapidly in the body. High loxapine concentrations are found mainly in the liver, brain, spleen, and lungs.

Loxapine is metabolized extensively in the liver following its oral administration, with multiple metabolites formed. The main metabolic pathways include hydroxylation, N-oxidation, and demethylation. The major metabolite is 8-OH-loxapine. Other metabolites include 7-OH-loxapine, N-oxides of loxapine and its metabolites, and amoxapine (N-desmethyl-loxapine) and its hydroxylated metabolites. The proposed metabolism of loxapine in humans is shown in Figure 4.

Figure 4. Proposed Loxapine Metabolism in Humans



Plasma levels of 8-OH-loxapine exceed levels of the parent compound in most studies with oral delivery of loxapine. However, 8-OH-loxapine is not pharmacologically active at the relevant dopamine receptors. 7-OH-loxapine is an active metabolite with 4 to 5 times higher affinity for the dopamine D_2 receptor compared with loxapine, but plasma levels of 7-OH-loxapine are typically less than one-half of the levels of the parent compound following oral delivery. Compared with oral delivery, IM delivery of loxapine leads to higher loxapine plasma levels but substantially lower levels of loxapine metabolites over the

24 hours after dosing. This observation is consistent with a hepatic first-pass effect following oral dosing.

The elimination half-life of oral loxapine is reported as 3 to 8 hours and appears to be slightly longer after IM administration. Loxapine and its metabolites are excreted mainly in the urine (56% to 70%; glucuronide or sulfate conjugates of the metabolites), and to a lesser extent, in the feces (15% to 22%; unconjugated metabolites). Following dosing, a substantial proportion of the drug is excreted in the first 24 hours.

2.2.2.2 In Vitro Pharmacokinetics of Loxapine

Loxapine is highly bound (>96%) to human plasma proteins. Loxapine concentrations from spiked human plasma were similar to loxapine concentrations in plasma from spiked human whole blood. Therefore, loxapine is expected to rapidly equilibrate between the plasma and the red blood cell compartments, and the pharmacokinetics and pharmacodynamics of loxapine can be predicted using plasma concentrations.

Liver microsomes metabolized loxapine more extensively than lung microsomes, with all metabolites formed in lung microsomes also formed in liver microsomes. In reaction phenotyping experiments, 8-OH-loxapine was formed from loxapine primarily via CYP1A2, 7-OH-loxapine was formed from loxapine mainly via CYP2D6 and 3A4/5, and amoxapine from loxapine via CYP3A4/5, 2C19, and 2C8. Formation of loxapine N-oxide is attributed mainly to flavin-containing monooxygenases, and partially due to cytochrome P-450 (CYP450) metabolism. Since loxapine is a substrate for multiple CYP450 enzymes in addition to flavin-containing monooxygenases, the risk of metabolic interactions caused by an effect on an individual isoform is minimized. Since CYP1A2 is induced in smokers, higher levels of 8-OH-loxapine might be expected in smokers compared with nonsmokers. However, in the sponsor-conducted clinical pharmacokinetics study, there were no significant differences in the levels of loxapine or its metabolites between smokers and nonsmokers (Section 2.2.2.3).

The potential for loxapine and its metabolites (amoxapine, 7-OH-loxapine, 8-OH-loxapine, and loxapine N-oxide) to inhibit CYP450-mediated drug metabolism has been examined in vitro for CYPs 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4. No significant inhibition was observed. In vitro studies indicated that loxapine was not a substrate for p-glycoprotein (P-gp) but does inhibit P-gp. At therapeutic concentrations, however, it is not expected to inhibit P-gp-mediated transport of other drugs in a clinically relevant manner.

2.2.2.3 Pharmacokinetics of ADASUVE

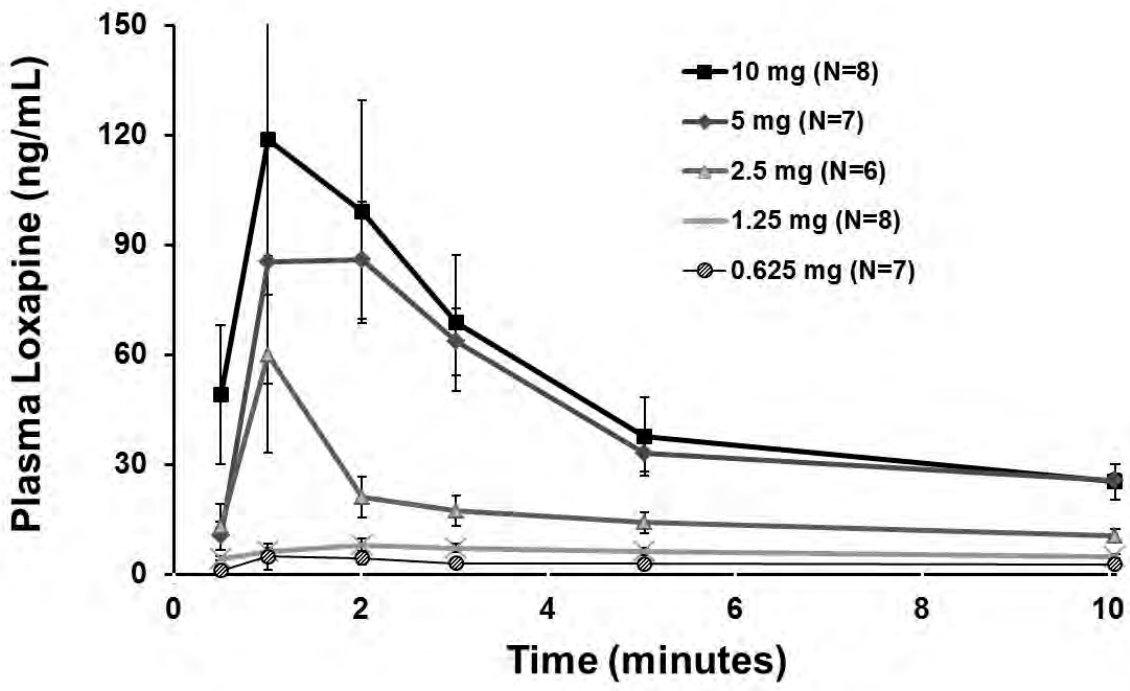
Staccato technology delivers aerosolized drug that is absorbed quickly and reliably (ie, with intravenous-like kinetics) (eg, Macleod et al, 2007 [fentanyl]; Avram et al, 2009 [prochlorperazine]; Spyker et al, 2010 [loxapine]). ADASUVE has been developed as a noninvasively delivered, rapidly acting dosage form of loxapine for use in treating agitation in patients with schizophrenia or bipolar I disorder. In clinical pharmacokinetic studies of ADASUVE, peak plasma levels in the systemic circulation are observed within 2 minutes.

The clinical development program for ADASUVE included several studies that examined the pharmacokinetics of loxapine following administration of ADASUVE in relevant populations. These studies comprise a dose-escalation pharmacokinetic study in healthy subjects, a multidose pharmacokinetic study in subjects on chronic, stable antipsychotic regimens, a pharmacokinetic study in smokers versus nonsmokers, and a thorough QT/QTc study in healthy subjects. Additionally, pharmacokinetic data are available from the clinical bioequivalence study comparing the clinical and commercial versions of ADASUVE in healthy subjects.

The individual pharmacokinetic studies in healthy nonsmoking subjects demonstrated similar loxapine pharmacokinetic parameters across individual studies and device versions following administration of either 5-mg or 10-mg doses of ADASUVE. In all studies, plasma loxapine concentrations increased rapidly with a median T_{max} within 2 minutes, followed by a rapid decrease in plasma concentrations.

Plasma concentrations of loxapine by dose group during the first 10 minutes after dosing in healthy subjects are displayed in Figure 5.

Figure 5. Plasma Concentrations of Loxapine by Dose Group (First 10 minutes) in Healthy Subjects

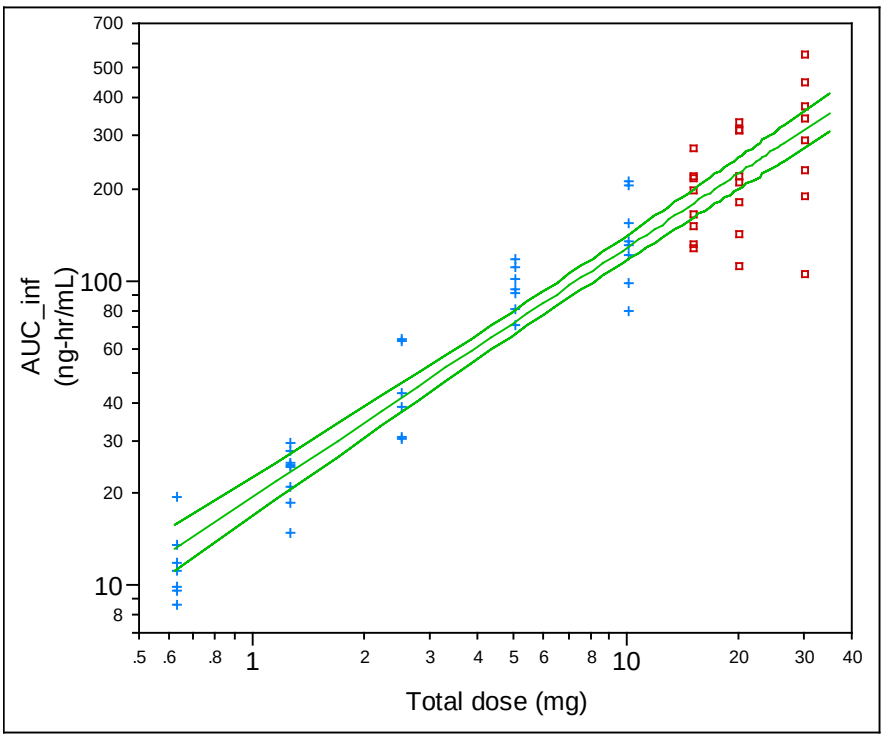


T_{max} = 2 [0.5, 60] min
Half-life = 7.1 ± 1.5 hr

The pharmacokinetic profile of loxapine following administration of ADASUVE to subjects on stable antipsychotic regimens was similar to that observed in studies of healthy subjects. In both healthy subjects and subjects on stable antipsychotic regimens, the mean plasma loxapine concentrations following administration of ADASUVE were linear over the clinical

dose range. Values for area under the concentration-time curve from 0 to 2 hours post-dose, also known as PK- $AUC_{0\text{-}2h}$ ($AUC_{0\text{-}2h}$), AUC from Time 0 to infinity (AUC_{inf}), and maximum concentration (C_{max}) increased in an expected dose-dependent manner. Mean AUC_{inf} by dose in healthy subjects and in subjects on chronic, stable antipsychotic regimens is illustrated in Figure 6.

Figure 6. Mean Loxapine AUC_{inf} after Administration of ADASUVE in Healthy Subjects and in Subjects on Chronic, Stable Antipsychotic Regimens



Note: Hatches represent subjects from Study 004-101 (N=36) and boxes represent subjects from Study 004-102 (N=24).
Slope [90% confidence interval, CI]=0.818 [0.762, 0.875]; r-squared=0.910; N=60.
The hashed lines show the 95% confidence curves on the fit (linear regression of log AUC vs log Dose)

The early exposure to loxapine ($AUC_{0\text{-}2h}$) and the total exposure to loxapine (AUC_{inf}) were similar for smokers and nonsmokers (geometric mean ratios of 91.6% and 85.3%, respectively). No dosage adjustment is recommended based on smoking status.

Based on a pooled analysis of loxapine pharmacokinetic parameters for all healthy subjects (nonsmokers and smokers) who were administered ADASUVE, loxapine exposure in the first 2 hours after administration ($AUC_{0\text{-}2h}$), a measure of early exposure that is relevant to the onset of therapeutic effect, was 25.6 ng·h/mL for the 5-mg dose and 66.7 ng·h/mL for the 10-mg dose. The mean elimination half-life ranged from 7.61 to 7.64 hours. The results are presented in Table 2.

Table 2. Summary of Loxapine Pharmacokinetic Parameters Following Administration of ADASUVE 5 or 10 mg in Healthy Subjects

Parameter	5 mg (N=31)	10 mg (N=114)
$AUC_{0\text{-}2h}$ (ng·h/mL) Mean ± SD	25.6 ± 7.31	66.7 ± 18.2
AUC_{inf} (ng·h/mL) Mean ± SD	70.1 ± 17.8	188 ± 46.6
C_{max} (ng/mL) Mean ± SD	116 ± 85.1	257 ± 219
T_{max} (min) Median (25%, 75%)	1.50 (1, 2)	1.13 (0.948, 1.98)
Half-life (h) Mean ± SD	7.64 ± 2.22	7.61 ± 1.87

$AUC_{0\text{-}2h}$=area under the concentration-time curve from 0 to 2 hours post-dose (also known as PK-$AUC_{0\text{-}2h}$); AUC_{inf}=area under the concentration-time curve from Time 0 to infinity; C_{max}=maximum concentration (at T_{max}); T_{max}=time to maximum concentration

Note: Pooled data from: Studies 004-103 (clinical version 2 and commercial version); 004-106 (commercial version); and 004-107 (commercial version).

The mean plasma concentration-time profiles for loxapine and 8-OH-loxapine were similar in the smoker and the nonsmoker groups (Figure 7 and Figure 8, respectively).

Figure 7. Mean Loxapine Concentration-Time Profiles in Smokers and Nonsmokers after Dosing with 10 mg

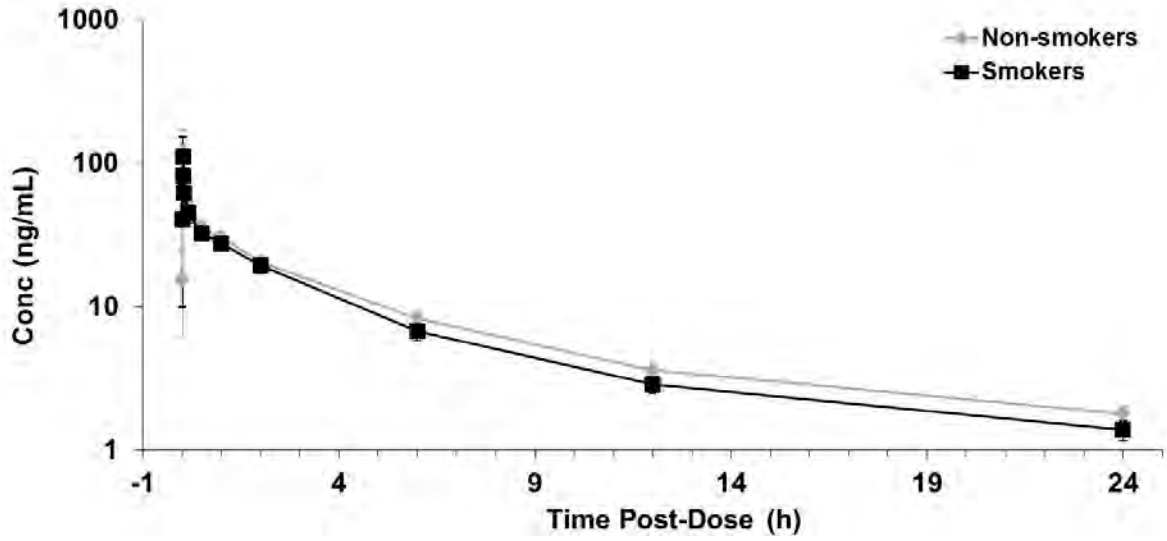
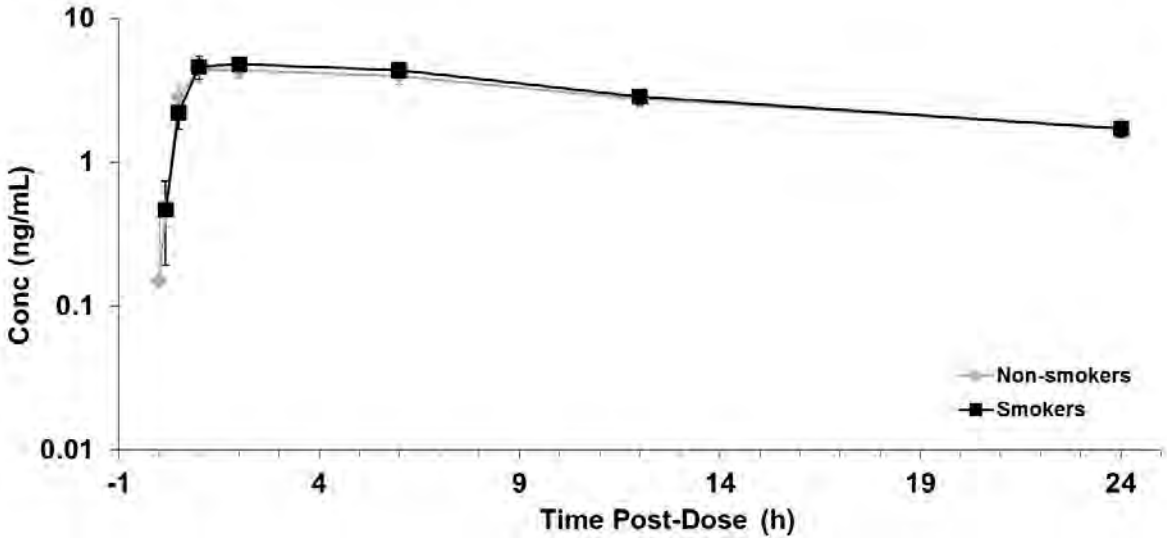


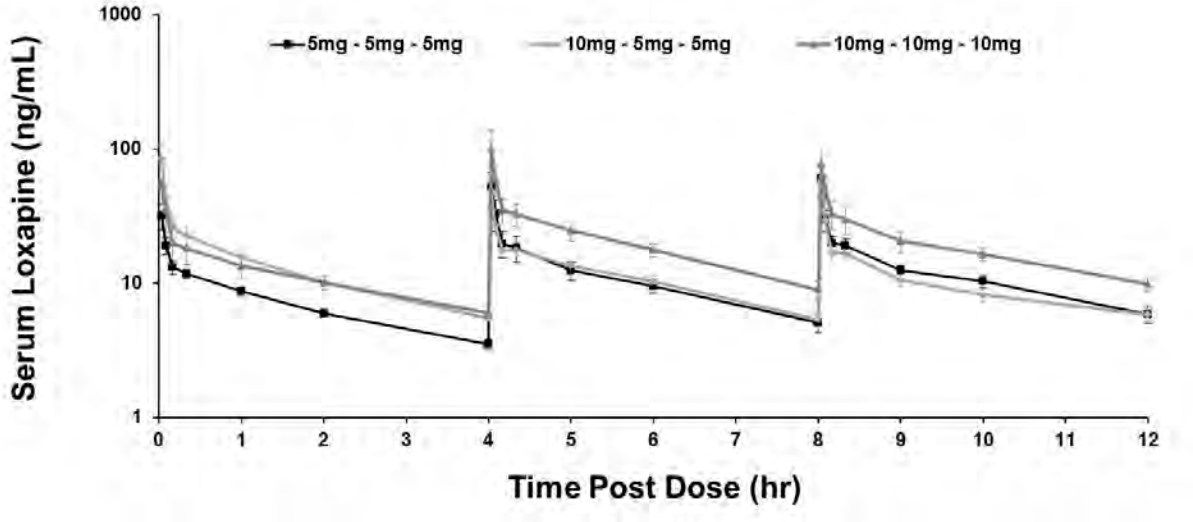
Figure 8. Mean 8-OH-Loxapine Concentration-Time Profiles in Smokers and Nonsmokers after Dosing with 10 mg



Subjects on chronic, stable antipsychotic regimens received 3 doses of ADASUVE (either 5 mg or 10 mg) every 4 hours. Mean peak plasma concentrations were similar after the first and third dose of ADASUVE, indicating minimal accumulation during the 4-hour dosing interval (Figure 9). Relative to C_{max}, there were small differences in loxapine concentration between 2 and 4 hours after dosing. Therefore, a second dose of ADASUVE could be administered as early as 2 hours following a first dose, with minimal increase in C_{max}.

ADASUVE has been shown to have linear (proportional) pharmacokinetics for single doses from 0.625 to 10 mg (Spyker et al, 2010) and for multiple doses from 15 to 30 mg (see Figure 6). Linear pharmacokinetic systems share the superposition property, ie, concentration profiles following 2 or more doses represent the sum of the responses following each dose individually). Thus, if Dose A produces response $C_A(t)$, and Dose B produces response $C_B(t)$, then $C_{A+B}(t) = C_A(t) + C_B(t)$ for any dose and for all times (Wang and Ouyang, 1998). Results of a multidose pharmacokinetic superposition simulation confirm this dosing strategy. Based on multidose superposition simulation, giving the second dose at 2 hours versus at 4 hours would result in a 4% higher loxapine peak plasma concentration. This result supports the safety of giving the second dose at 2 hours, as was carried out in the Phase 3 studies.

Figure 9. Mean Concentrations of Loxapine Following Administration of Repeat Doses of ADASUVE to Subjects on Chronic, Stable Antipsychotic Therapy



Demographic subgroup analysis did not reveal any clinically significant effects of age, weight, body mass index, gender, and race on loxapine pharmacokinetics following administration of ADASUVE.

2.2.2.4 Pharmacodynamics

Since sedation is a consistent effect of antipsychotic agents, sedation scales served as the primary pharmacodynamic measure in the non-efficacy studies of the clinical development program. Changes in sedation score from baseline were measured using either the Stanford Sleepiness Scale or a 100-mm visual analog scale (VAS).

Based on the VAS analysis, a clear sedation effect was observed in all 5 studies in which VAS was measured. As expected, sedation was more marked in the healthy subjects than in the subjects on chronic, stable antipsychotic regimens. There was a rapid onset of a measurable sedative effect as early as 2 minutes, reaching a peak effect at 30 minutes to 1 hour, and declining to near baseline by 2 hours post-dose. In 2 studies (subjects on chronic, stable oral antipsychotic medication and healthy nonsmokers and smokers) in which both

pharmacokinetics and pharmacodynamics were measured, a strong sedation-exposure relationship was seen (ie, VAS-AUC_{0-2h} was strongly related to PK-AUC_{0-2h}).

2.2.2.5 Summary of ADASUVE Pharmacokinetics

The main findings of the clinical pharmacology studies of ADASUVE are as follows:

- After administration of ADASUVE, plasma loxapine concentrations increased rapidly with a median T_{max} within 2 minutes, followed by a rapid decrease in plasma concentrations (terminal half-life ranged from 6 to 8 hours). The pharmacokinetic profile was similar in healthy subjects, including smokers and nonsmokers, and subjects on stable antipsychotic regimens.

- Mean plasma loxapine concentrations following administration of ADASUVE were linear over the clinical dose range. Values for AUC_{0-2h}, AUC_{inf}, and C_{max} increased in an expected dose-dependent manner.

- With repeat administration, mean peak plasma concentrations were similar after the first and third dose of ADASUVE, indicating minimal accumulation during the 4-hour dosing interval.

- Demographic subgroup analysis did not reveal any clinically significant effects of age, weight, body mass index, gender, and race on loxapine pharmacokinetics following administration of ADASUVE.

- Loxapine is a substrate for multiple CYP450 enzymes in addition to flavin-containing monooxygenases; therefore the risk of metabolic interactions caused by an effect on an individual isoform is minimized.

- The primary pharmacodynamic effect observed in non-efficacy trials is sedation, which is seen as early as 2 minutes, reaching a peak effect at 30 minutes to 1 hour, and declining to near-baseline by 2 hours post-dose. Sedation was more marked in healthy subjects than in subjects on chronic, stable antipsychotic regimens.

3 BACKGROUND

3.1 Regulatory History

3.1.1 Previous and Current Formulations of Loxapine

Loxapine was first approved for marketing in the US in 1975. Following the initial approval for oral tablets and capsules, an oral concentrate and an IM dosage form were approved. Details of loxapine approvals in the US are summarized in Table 3. Only loxapine capsules are currently marketed in the US. Discontinuation appears to be due to reasons other than safety or effectiveness. FDA announced recently that Loxitane (the brand drug) was not withdrawn from sales for reasons of safety or effectiveness (Federal Register notice, 23 September 2011).

Oral loxapine is indicated for the treatment of schizophrenia. For oral administration, an initial dose of 20 mg daily given in two 10-mg doses is recommended, although in severely disturbed schizophrenic patients an initial dose up to a total of 50 mg per day may be required. The usual therapeutic and maintenance range is 60 to 100 mg per day. A dosage greater than 250 mg per day is not recommended (Watson Pharmaceuticals, US Prescribing Information, 2010).

Intramuscular loxapine also was previously approved for prompt symptomatic control in acutely agitated schizophrenic patients and in patients whose symptoms rendered oral medication temporarily impractical. Intramuscular loxapine was labeled for administration in doses of 12.5 to 50 mg at intervals of 4 to 6 hours or longer, with both the dose and interval depending on the patient's response.

Table 3. Approved Formulations of Loxapine

Drug Name	Active Ingredient	Strength (loxapine base)	Dosage Form/Route	Application No. / Approval Date	Marketing Status
Loxitane	Loxapine succinate	5 mg, 10 mg, 25 mg, 50 mg	Oral Capsule	NDA 17-525 / 25 Feb 1975	Prescription
Loxitane	Loxapine succinate	10 mg, 25 mg, 50 mg	Oral Tablet	NDA 17-525 / 25 Feb 1975	Discontinued
Loxitane C	Loxapine hydrochloride	25 mg/mL	Oral Concentrate	NDA 17-658 / 4 May 1976	Discontinued
Loxitane IM	Loxapine hydrochloride	50 mg/mL	Intramuscular Dosing Solution	NDA 18-039 26 Oct 1979	Discontinued

NDA=New Drug Application

3.1.2 Regulatory History of ADASUVE

The design of the clinical development program reflects feedback from and agreements with the Food and Drug Administration (FDA), including design of the Phase 3 studies and the pulmonary safety program.

Alexza submitted the original New Drug Application (NDA) on 11 December 2009 to support the approval of ADASUVE as a prescription drug product. The Division issued a Complete Response Letter on 8 October 2010. The Complete Response Letter identified pulmonary safety as the primary clinical concern based on data from the Phase 1 pulmonary safety studies, particularly in subjects with asthma and chronic obstructive pulmonary disease (COPD).

Alexza met with FDA to discuss the issues raised in the Complete Response Letter and how they should be resolved. It was agreed that submission of a Risk Evaluation and Mitigation Strategy (REMS) program for the use of ADASUVE was a reasonable approach. Alexza received further guidance from the Division on the content of product labeling and the components of a REMS submission (see Section 10).

3.2 ADASUVE Development Program

The clinical development program for ADASUVE in agitation consists of 11 studies (Table 4): 5 Phase 1 clinical pharmacology studies, 3 Phase 1 studies evaluating pulmonary safety, 1 Phase 2 study, and 2 Phase 3 studies. The 2 Phase 3 studies evaluated 1 to 3 doses of ADASUVE in agitated patients with schizophrenia (Study 004-301) or bipolar I disorder (Study 004-302).

Supportive data were provided in the NDA from the Phase 2 study, which evaluated 1 dose in agitated patients with schizophrenia or schizoaffective disorder (Study 004-201). Efficacy results from the Phase 2 study are not discussed in this briefing document. However, safety data from this study are included, as patients from this study are part of the Phase 2/3 agitated patient population (ie, patients from the 3 Phase 2 and 3 studies - agitated patients with schizophrenia [including schizoaffective disorder] or bipolar I disorder).

The total number of patients who received at least 1 dose of ADASUVE in the agitation clinical program is 777, of whom 177 were healthy volunteers, 24 were on stable oral antipsychotic regimens, 52 had asthma or COPD, and 524 participated in the agitation studies.

In addition to the studies conducted as part of the clinical development program evaluating ADASUVE for the treatment of agitation in schizophrenia and bipolar disorder, 2 additional safety studies, also included in Table 4, evaluated ADASUVE for the treatment of migraine headache.

Table 4. Clinical Development Program for ADASUVE in Agitation

Study No.	Design	Patient Population	Study & Control Drugs, Dose, Route	No. Randomized
Biopharmaceutic, Pharmacokinetic, and Pharmacodynamic Studies				
004-101	Phase 1, single-center, randomized. double-blind, placebo-controlled, parallel-group, single-dose dose-escalation PK study	Healthy nonsmokers	ADASUVE 0.625 mg, 1.25 mg (2×0.625 mg), 2.5 mg, 5 mg, or 10 mg (2×5 mg) *Staccato* placebo Orally inhaled	N=50
004-102	Phase 1, single-center, randomized. double-blind, placebo-controlled, parallel-group, multiple-dose PK study	Subjects on chronic, stable oral antipsychotic medication (smokers and nonsmokers)	ADASUVE Total doses 15, 20, or 30 mg or *Staccato* placebo, orally inhaled 3 divided doses, 4 hours apart: 15 mg: 5/5/5 mg 20 mg: 10/5/5 mg 30 mg: 10/10/10 mg	N=32
004-103	Phase 1, single-center, randomized, double-blind, 2-treatment, 4-period, dose-stratified, replicate-design bioequivalence study of commercial and clinical product designs	Healthy nonsmokers	ADASUVE commercial and clinical versions; 5- or 10-mg doses, orally inhaled	N=32
004-106	Phase 1, single-center, single-dose, single-treatment, open-label study evaluating PK in smokers and nonsmokers	Healthy subjects (smokers and nonsmokers)	ADASUVE 10 mg, orally inhaled	N=35 (17 smokers, 18 nonsmokers)
004-107	Phase 1, single-center, randomized, double-blind, double-dummy, active- and placebo-controlled, 3-period crossover thorough QT/QTc study	Healthy nonsmokers	A: ADASUVE 10 mg + oral placebo B: *Staccato* placebo + oral placebo C: *Staccato* placebo + oral moxifloxacin Orally inhaled (*Staccato*) Subjects randomized to 1 of 6 treatment sequences containing A, B, and C	N=48

Study No.	Design	Patient Population	Study & Control Drugs, Dose, Route	No. Randomized
Safety Studies				
004-104	Phase 1, multicenter, randomized, double-blind, placebo-controlled, 2-period crossover study of the pulmonary safety of ADASUVE (2 doses/period, doses 8 hours apart)	Healthy nonsmokers	ADASUVE 10 mg or *Staccato* placebo, orally inhaled	10 mg/placebo sequence: N=15 Placebo/10 mg sequence: N=15
004-105	Phase 1, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the pulmonary safety of ADASUVE (2 doses, 10 hours apart)	Mild or moderate persistent asthma (nonsmokers)	ADASUVE 10 mg or *Staccato* placebo, orally inhaled	10 mg: N=26 Placebo: N=26
004-108	Phase 1, multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the pulmonary safety of ADASUVE (2 doses, 10 hours apart)	COPD (smokers and nonsmokers; all had history of smoking)	ADASUVE 10 mg or *Staccato* placebo, orally inhaled	10 mg: N=26 Placebo: N=27
Efficacy and Safety Studies				
004-301	Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled efficacy and safety study (1-3 doses, as required)	Schizophrenia; clinically agitated at baseline (smokers and nonsmokers)	ADASUVE 5 mg or 10 mg or *Staccato* placebo, orally inhaled	5 mg: N=116 10 mg: N=113 Placebo: N=115
004-302	Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled efficacy and safety study (1-3 doses, as required)	Bipolar I disorder; clinically agitated at baseline (smokers and nonsmokers)	ADASUVE 5 mg or 10 mg or *Staccato* placebo, orally inhaled	5 mg: N=104 10 mg: N=105 Placebo: N=105
004-201	Phase 2A, multicenter, randomized, double-blind, parallel-group, placebo-controlled, single-dose efficacy and safety study	Schizophrenia or schizoaffective disorder; clinically agitated at baseline (smokers and nonsmokers)	ADASUVE 5 mg or 10 mg or *Staccato* placebo, orally inhaled	5 mg: N=45 10 mg: N=41 Placebo: N=43

Study No.	Design	Patient Population	Study & Control Drugs, Dose, Route	No. Randomized
Additional Safety Studies				
104-201	Phase 2A, multicenter, randomized, double-blind, placebo-controlled, single-dose study	Patients with moderate to severe migraine headache with or without aura	ADASUVE 1.25, 2.5, or 5 mg, or *Staccato* placebo, orally inhaled	1.25 mg: N=43 2.5 mg: N=43 5 mg: N=43 Placebo: N=39
104-202	Phase 2B, multicenter, randomized, double-blind, placebo-controlled, parallel-group, single-dose study	Patients with moderate to severe migraine headache with or without aura	ADASUVE 1.25, or 2.5 mg, or *Staccato* placebo, orally inhaled	1.25 mg: N=121 2.5 mg: N=120 Placebo: N=125

COPD=chronic obstructive pulmonary disease; PK=pharmacokinetic

4 CLINICAL METHODOLOGY AND RATIONALE FOR THE AGITATION STUDIES

Studies 004-301 (schizophrenia) and 004-302 (bipolar I disorder) were inpatient, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety studies that evaluated ADASUVE 5 or 10 mg or matching placebo in patients with acute agitation. These 2 Phase 3 studies had the same study design but were conducted in different patient populations: Study 004-301 enrolled patients with schizophrenia, and Study 004-302 enrolled patients with bipolar I disorder (manic or mixed episodes).

The design of the ADASUVE Phase 3 studies was modeled on the design of the clinical studies that supported the registration of IM antipsychotic agents for the treatment of agitation in schizophrenia and bipolar disorder (ie, Abilify [aripiprazole] and Zyprexa [olanzapine]). The study design also incorporated guidance received from the US FDA during the End-of-Phase 2 Meeting for ADASUVE (official meeting minutes for End-of-Phase 2 Meeting, 13 September 2007).

The Phase 3 clinical study designs: (1) facilitated the collection of appropriate safety and efficacy data to support registration, and (2) included patients representative of the agitated patient population in clinical practice. This section summarizes the key considerations and rationale underlying the following key design aspects of the 2 Phase 3 clinical studies:

- efficacy measures for assessing agitation
- patient populations
- study duration

4.1 Efficacy Measures for Assessing Agitation

The same primary efficacy endpoint was used in the 2 Phase 3 studies. The primary endpoint was the change in Positive and Negative Symptom Scale, Excited Component (PEC) score from baseline to 2 hours following Dose 1 of ADASUVE, compared with placebo. The primary endpoint was the same as that used in the clinical development programs of the IM formulations of two antipsychotics (Zyprexa and Abilify) marketed for the treatment of agitation. The change in PEC score from baseline to 10, 20, 30, and 45 minutes after Dose 1 (statistical testing was only performed for 10 mg versus placebo comparison) was also determined.

The key secondary endpoint was the value of the Clinical Global Impression - Improvement Scale (CGI-I) score 2 hours following Dose 1 of ADASUVE compared with placebo and was selected based on guidance received from the FDA (Official Meeting Minutes, End-of-Phase 2 Meeting, 13 September 2007).

4.1.1 Positive and Negative Symptom Scale, Excited Component (PEC)

This scale asks the investigator to rate the following 5 symptoms associated with agitation:

- poor impulse control
- tension
- hostility
- uncooperativeness
- excitement

Each of the 5 items is rated on a scale of 1 (absent) to 7 (extreme), as shown below, and ratings for the individual items are then summed. Therefore, scores can range from 5 (all rated symptoms are absent) to 35 (all rated symptoms are extreme).

1 = absent

2 = minimal

3 = mild

4 = moderate

5 = moderate severe

6 = severe

7 = extreme

4.1.2 Clinical Global Impression(CGI) Scales

4.1.2.1 Clinical Global Impression - Severity Scale (CGI-S)

This scale (shown below) asks the investigator to make the following assessment: Considering his/her total clinical experience with this particular population, how agitated is the patient at this time? Scores range from 1 (normal, not at all agitated) to 7 (among the most extremely agitated patients). This scale (CGI-S) was used for the baseline assessment, while the CGI-I scale (below) was used for the assessment of efficacy after treatment.

0 = not assessed

1 = normal, not at all agitated

2 = borderline agitated

3 = mildly agitated

4 = moderately agitated

5 = markedly agitated

6 = severely agitated

7 = among the most extremely agitated patients

4.1.2.2 Clinical Global Impression - Improvement Scale (CGI-I)

This scale (shown below) asks the investigator to assess the change from baseline in the degree of agitation. Scores range from 1 (very much improved) to 7 (very much worse). This scale (CGI-I) was used for the assessment of efficacy after treatment, while the CGI-S scale (above) was used for the baseline assessment.

0 = not assessed

1 = very much improved

2 = much improved

3 = minimally improved

4 = no change

5 = minimally worse

6 = much worse

7 = very much worse

4.1.3 Efficacy Measures–Training

Raters were trained and certified by an independent contract research organization in the use of the PEC and CGI scales. Training included a didactic presentation; practice videos for scoring the PEC and CGI scales; and certification videos for the PEC and CGI scales. Absentee and new raters had on-line training. Each rater was required to receive written notification of certification before making any study ratings.

4.2 Patient Populations

The criteria used to select the disease states for study were:

- agitation commonly occurs in the disease state and poses a need for intervention
- agitation is frequently treated during the course of the disease

Two patient populations were chosen for study based on these criteria: schizophrenia and bipolar I disorder. These conditions represent common neuropsychiatric conditions for which

antipsychotic medications are used. Although each of these 2 patient populations presents with agitation, with a common symptom presentation and similar treatment approaches short-term, the diseases are clearly different in their long-term course and treatment.

Patients presented to study sites through normal channels by which psychiatric patients obtain treatment for agitation. Several types of patients could have been enrolled: (1) those admitted to a hospital setting or a research unit for the purpose of the study, (2) those already hospitalized for treatment who had acute agitation, and (3) those treated at a psychiatric emergency room setting that allowed extended patient stays in a secluded observation room for the period of the study.

4.2.1 Agitation Criteria

In both Phase 3 studies, consistent with the pivotal IM Zyprexa studies, patients eligible for enrollment were required to meet the following agitation criteria:

- judged to be clinically agitated at baseline, with a total score of ≥14 on the 5 items (poor impulse control, tension, hostility, uncooperativeness, and excitement) comprising the PEC scale

  and

- had a value of ≥4 (out of 7) on at least 1 of the 5 items on the PEC scale

It should be noted that a moderate severity rating for any 1 of the items comprising the PEC may be sufficient for the patients to need or seek treatment.

4.2.2 Diagnostic Criteria

In both Phase 3 studies, patients were enrolled who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for schizophrenia (Study 004-301) or bipolar I disorder, manic or mixed episodes. The latter was confirmed by administration of the Mini International Neuropsychiatric Interview, Version 5.0.0 (with or without psychotic features) (Study 004-302).

Patients with any psychiatric diagnosis other than bipolar I disorder that required pharmacotherapy were excluded from Study 004-302.

4.2.3 General Entry Criteria

In both Phase 3 studies, patients who were in good general health and 18 to 65 years of age (inclusive) were enrolled. Only patients willing and able to stay in the hospital or clinic throughout the post-treatment evaluation period and for at least 12 hours after the last dose of study medication were enrolled.

Key exclusion criteria were:

- agitation primarily due to acute intoxication

- a urine drug screen positive for psychostimulants
- a history of drug or alcohol dependence in the previous 2 months
- a serious risk of suicide
- use of benzodiazepines or other hypnotics or oral or short-acting IM antipsychotics in the 4 hours before study treatment
- use of injectable depot neuroleptics within 1 dose interval before study treatment
- laboratory or electrocardiogram (ECG) abnormalities considered significant by the investigator that would have clinical implications for the patient's participation in the study
- significant hepatic, renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease and congestive heart failure), endocrinologic, neurologic (including seizures), or hematologic disease
- clinically significant acute or chronic pulmonary disease (eg, clinically apparent asthma, chronic bronchitis, emphysema) and/or a history of chronic bronchodilator use in the past 1 year (Study 004-302 only)

Additional exclusion criteria in Study 004-302 included use of fluoxetine and other antidepressants within 7 days of randomization, and the use of anticonvulsants (except valproate) within 7 days of randomization.

Once study drug was administered, the use of additional antipsychotic medication, other than additional doses of study drug, was not allowed during the 24-hour post-treatment evaluation period. Sedative-hypnotics were not allowed, other than rescue lorazepam. Study 004-302, (bipolar I disorder) allowed continuation of ongoing and stable (unchanged for ≥7 days) doses of lithium or valproate, but not initiation or dose-adjustment of these agents, and prohibited use of antidepressant drugs and anticonvulsant drugs other than valproate.

Unless medically required, rescue medication (ie, IM lorazepam) was not to be given until after the 2-hour efficacy assessments had been completed, Dose 2 of study medication had been given, and at least 20 minutes had elapsed after administration of study medication. Patients who received lorazepam rescue medication were not eligible to receive additional doses of study medication. Anti-Parkinson's or antihistamine agents were allowed if patients developed extrapyramidal symptoms (EPS).

4.3 Study Duration

As ADASUVE is intended for short-term use, patients in the Phase 3 studies received 1 to 3 doses of study medication during the 24-hour evaluation period (with Doses 2 and 3 administered if needed). Administration of Dose 1 occurred at Time 0. If required, a maximum of 3 doses were allowed during the subsequent 24-hour post-treatment evaluation period. If agitation did not subside sufficiently after the first dose or if agitation recurred, a

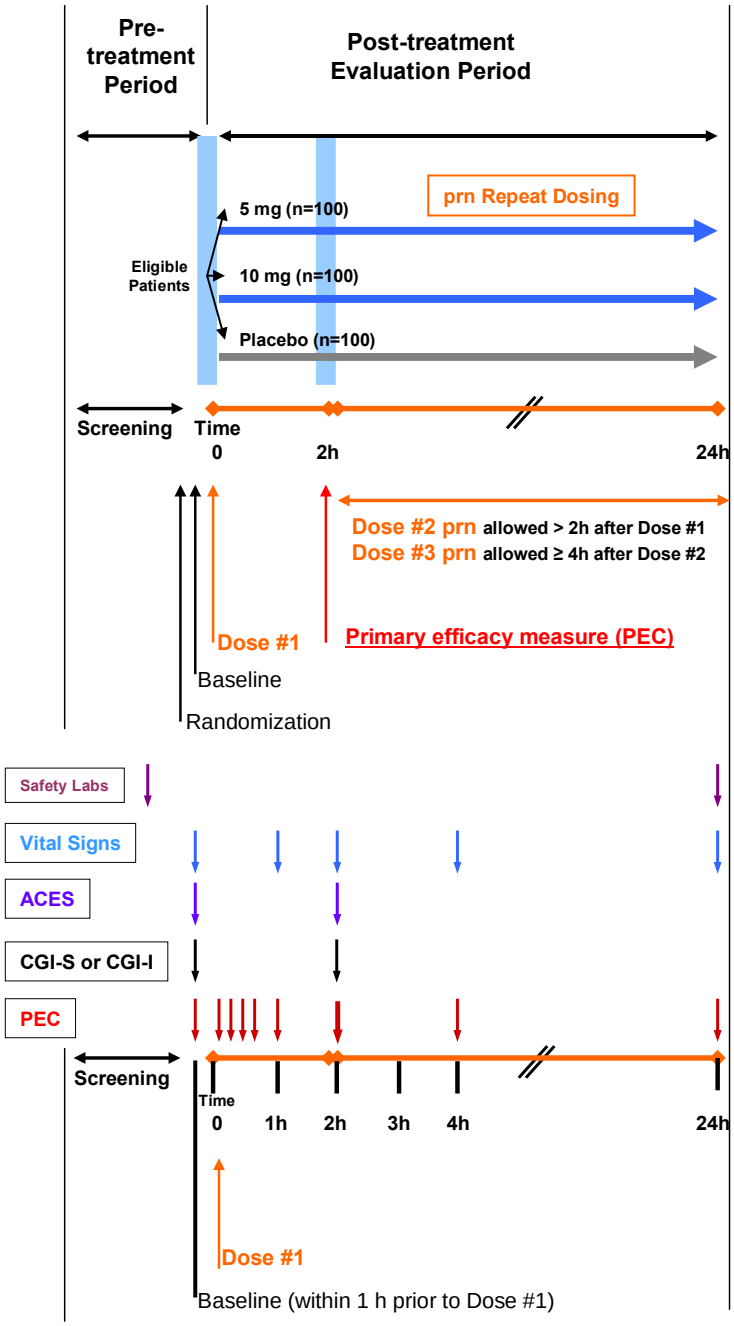
second dose could be given >2 hours after Dose 1 (and after the 2-hour assessments had been completed). If required, a third dose could be given ≥4 hours after Dose 2.

The 24-hour duration of study participation is consistent with the IM antipsychotic programs as well as the intended short-term use of ADASUVE.

5 PHASE 3 STUDY DESIGN

The study design for the 2 Phase 3 pivotal studies in agitated patients with schizophrenia and bipolar I disorder is summarized in Figure 10.

Figure 10. Design of Studies 004-301 (Schizophrenia) and 004-302 (Bipolar I Disorder)



6 PATIENT CHARACTERISTICS

This section summarizes the key entry criteria and the patient characteristics at baseline for the 2 ADASUVE Phase 3 studies.

The Phase 3 studies enrolled agitated patients with either schizophrenia or bipolar I disorder who presented to study sites through normal channels by which psychiatric patients obtain treatment for agitation. The patients had a sufficient level of agitation at baseline to warrant treatment and to assess the efficacy and safety of ADASUVE for this indication.

The patients in these studies had, on average, a moderate level of agitation, as determined by multiple rating instruments. Consistent with the pivotal clinical studies that supported the approval of IM Abilify and IM Zyprexa for agitation, the requirement for informed consent constrained the severity of agitation for patients recruited into the Phase 3 studies.

The patients had significant and long-standing psychiatric disease, based on years since diagnosis and previous hospitalizations. The majority of patients required, on average, 2 to 3 inpatient days for psychiatric stabilization following dosing.

These findings demonstrate that the Phase 3 program included patients who were significantly agitated and representative of the patient population requiring treatment of agitation in clinical practice.

6.1 Baseline Characteristics

6.1.1 Demographics

In both Phase 3 studies, the treatment groups were generally well matched with respect to demographic characteristics (Table 5).

Table 5. Patient Demographics in Studies 004-301 (Schizophrenia) and 004-302 (Bipolar I Disorder) (Safety Population)

Study 004-301 (Schizophrenia)		**Placebo (N=115)**	**ADASUVE 5 mg (N=116)**	**ADASUVE 10 mg (N=113)**	**Total (N=344)**
	Mean (SD)	43.9 (9.45)	43.2 (10.24)	42.2 (9.82)	43.1 (9.84)
	Median	45	44.5	44	45
Age (years)	Min, Max	23, 63	18, 65	21, 62	18, 65
	Caucasian	32 (27.8%)	48 (41.4%)	36 (31.9%)	116 (33.7%)
	Black	70 (60.9%)	61 (52.6%)	67 (59.3%)	198 (57.6%)
	Hispanic	9 (7.8%)	6 (5.2%)	8 (7.1%)	23 (6.7%)
	Asian	4 (3.5%)	1 (0.9%)	1 (0.9%)	6 (1.7%)
Race, n (%)	Other	0	0	1 (0.9%)[a]	1 (0.3%)[a]
	Male	80 (69.6%)	87 (75.0%)	86 (76.1%)	253 (73.5%)
Gender, n (%)	Female	35 (30.4%)	29 (25.0%)	27 (23.9%)	91 (26.5%)
Study 004-302 (Bipolar I Disorder)		**Placebo (N=105)**	**ADASUVE 5 mg (N=104)**	**ADASUVE 10 mg (N=105)**	**Total (N=314)**
	Mean (SD)	40.6 (9.82)	41.2 (9.63)	40.5 (9.80)	40.8 (9.72)
	Median	42	41.5	42	42
Age (years)	Min, max	19, 60	19, 62	19, 64	19, 64
	Caucasian	33 (31.4%)	58 (55.8%)	47 (44.8%)	138 (43.9%)
	Black	54 (51.4%)	38 (36.5%)	47 (44.8%)	139 (44.3%)
	Hispanic	14 (13.3%)	8 (7.7%)	7 (6.7%)	29 (9.2%)
	Asian	0	0	1 (1.0%)	1 (0.3%)
	Native American	1 (1.0%)	0	1 (1.0%)	2 (0.6%)
Race, n (%)	Other	3 (2.9%)[b]	0	2 (1.9%)[b]	5 (1.6%)
	Male	56 (53.3%)	47 (45.2%)	53 (50.5%)	156 (49.7%)
Gender, n (%)	Female	49 (46.7%)	57 (54.8%)	52 (49.5%)	158 (50.3%)

SD=standard deviation

a. "Other" race: African American/Caucasian

b. "Other" races: Filipino, "Filipino mix," and Caucasian-Hispanic in placebo group; Native American-Caucasian and Hispanic-Native American in 10-mg group

6.1.2 Patient Psychiatric Characteristics and Baseline Level of Agitation

The majority of the Phase 3 study sites (66.7%) were hospitals or clinics with an active clinical practice. All sites included inpatient facilities, and all sites had previously conducted inpatient psychiatric trials.

All patients either presented or were referred for treatment for agitation. More than half of the patients presented directly to the study site or were brought for treatment by family or friends, approximately one-third were referred by a medical/mental health professional, and smaller numbers were enrolled from inpatient wards or emergency rooms.

Agitation at baseline was similar in the 2 studies and across the 3 treatment groups in each study (Table 6). The Phase 3 patients had significant and long-standing psychiatric disease. Almost all patients with schizophrenia—324 (94.2%)—had a history of at least 1 previous psychiatric hospitalization, with 294 (85.5%) having had 2 or more previous hospitalizations. Similarly, almost all of the bipolar disorder patients—269 (85.7%)—had a history of at least 1 previous psychiatric hospitalization, with 218 (69.4%) of the patients having had 2 or more hospitalizations.

Table 6. Baseline Disease Characteristics in Studies 004-301 (Schizophrenia) and 004-302 (Bipolar I Disorder)

Study 004-301 (Schizophrenia)		**Placebo (N=115)**	**ADASUVE 5 mg (N=116)**	**ADASUVE 10 mg (N=112)**
Diagnosis: Schizophrenia	n (%)	115 (100%)	116 (100%)	113 (100%)
Baseline PEC score	Mean (SD)	17.4 (1.80)	17.8 (2.34)	17.6 (2.06)
	Median	17	18	17
	Min, max	14, 24	14, 28	14, 27
Baseline CGI-S score	Mean (SD)	3.9 (0.53)	4.0 (0.56)	4.1 (0.60)
	Median	4	4	4
	Min, max	2, 5	3, 6	2, 6
Time since diagnosis (years)	Mean (SD)	18.8 (10.34)	16.5 (10.80)	18.2 (10.03)
	Median	18	15.5	18
	Min, max	0, 40	0, 41	1, 49
Duration of current agitation episode at screening (days)	Mean (SD)	6.9 (9.21)	6.1 (7.50)	7.6 (11.52)
	Median	4	4	4
	Min, max	<1, 72	<1, 45	<1, 90
Study 004-302 (Bipolar I Disorder)		**Placebo (N=105)**	**ADASUVE 5 mg (N=104)**	**ADASUVE 10 mg (N=105)**
Diagnosis: Bipolar I disorder, manic episodes	n (%)	72 (68.6%)	68 (65.4%)	76 (72.4%)
Diagnosis: Bipolar I disorder, mixed episodes	n (%)	33 (31.4%)	36 (34.6%)	29 (27.6%)
Baseline PEC score	Mean (SD)	17.7 (2.80)	17.4 (2.23)	17.3 (2.25)
	Median	17	17	17
	Min, max	14, 31	14, 26	14, 25
Baseline CGI-S score	Mean (SD)	4.1 (0.57)	4.0 (0.53)	4.0 (0.49)
	Median	4	4	4
	Min, max	2, 6	3, 6	3, 5
Time since diagnosis (years)	Mean (SD)	12.0 (10.09)	12.8 (8.91)	11.7 (9.05)
	Median	10	10	9
	Min, max	0, 45	0, 38	0, 38
Duration of current agitation episode at screening (days)	Mean (SD)	14.2 (21.52)	16.0 (32.36)	9.7 (10.10)
	Median	6.2	6.2	5
	Min, max	0.25, 146	0.25, 210	0.25, 45

CGI-S=Clinical Global Impression - Severity Scale; PEC=Positive and Negative Symptom Scale, Excited Component; SD=standard deviation

Baseline PEC scores are similar to those reported in the pivotal trials for IM Zyprexa and Abilify (Appendix 1). Furthermore, the majority of patients in the ADASUVE Phase 3 studies had at least 2 PEC item scores ≥4 (*moderate*) at baseline (Table 7), and multiple assessment scales confirm that the patients were, on average, moderately agitated at baseline.

A comparison of baseline agitation characteristics of patients in the ADASUVE Phase 3 studies with those of the patients in the IM Abilify and IM Zyprexa studies is provided in Appendix 1.

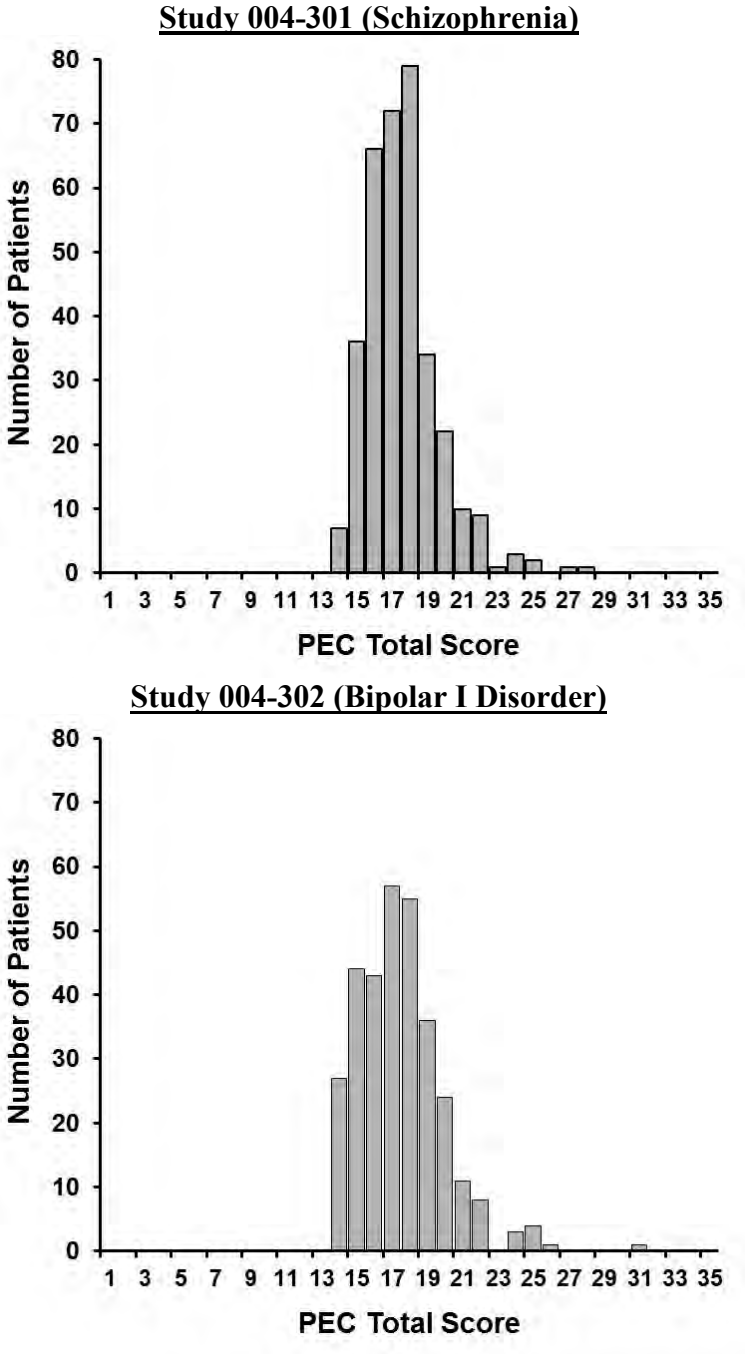
Table 7. Baseline Agitation as Assessed by PEC Scale Item Scores in Studies 004-301 (Schizophrenia) and 004-302 (Bipolar I Disorder)

PEC Item Scores at Baseline[a]	Study 004-301 (Schizophrenia)[b]	Study 004-302 (Bipolar I Disorder)[b]
At least 1 item ≥4 *(moderate)* (inclusion criterion)	343 (100%)	314 (100%)
At least 2 items ≥4 *(moderate)*	288 (84.0%)	268 (85.4%)
At least 1 item ≥5 *(moderate/severe)*	97 (28.3%)	107 (34.1%)
At least 1 item ≥6 *(severe)*	11 (3.2%)	12 (3.8%)
At least 1 item=7 *(extreme)*	0	1 (0.3%)

a. A patient can be counted in multiple rows.
b. Total number of enrolled patients: 004-301=344, 004-302=314

Baseline distributions of PEC scores in each Phase 3 study are provided in Figure 11. Baseline total PEC scores ranged from 14 to 28 in Study 004-301 (schizophrenia) and from 14 to 31 in Study 004-302 (bipolar I disorder), with a median score of approximately 17.

Figure 11. Baseline PEC Total Score Distribution in Studies 004-301 (Schizophrenia) and 004-302 (Bipolar I Disorder)

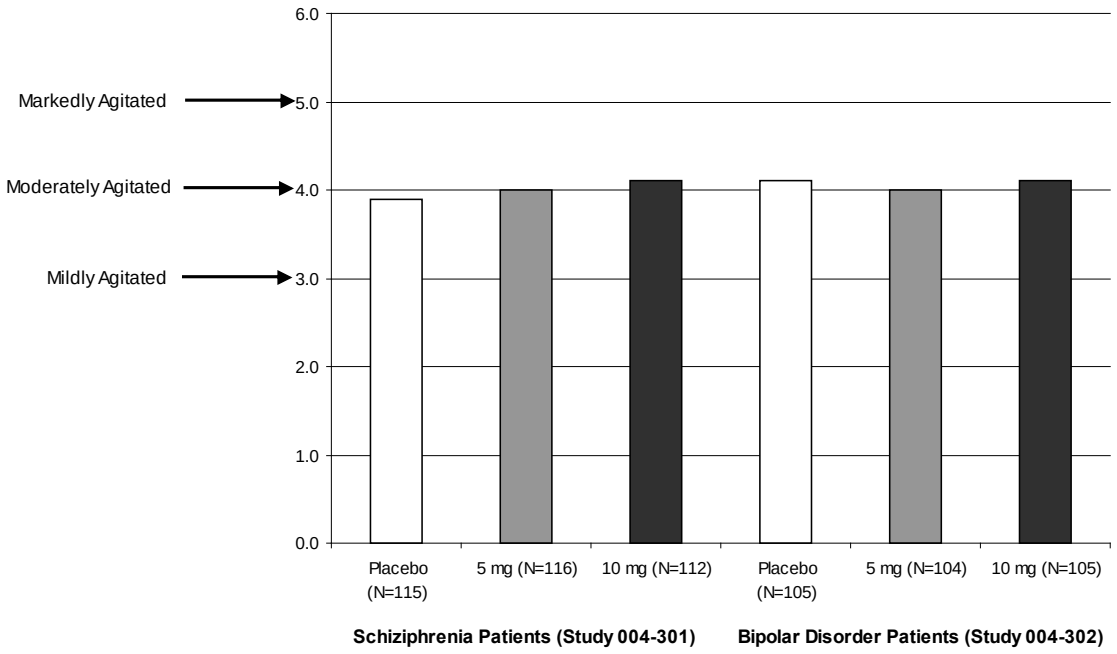


As in registration studies of other treatments for agitation, a limitation with respect to agitation severity in the ADASUVE studies was the suitability of patients for an informed consent discussion.

Baseline CGI-S mean values ranged from 3.9 to 4.1 and from 4.0 to 4.1 across treatment groups in Studies 004-301 (schizophrenia) and 004-302 (bipolar I disorder), respectively

(score of 4 indicates moderate agitation) (Figure 12). These results are similar to those reported in the pivotal trials for IM Abilify (Appendix 1).

Figure 12. Mean Baseline CGI-S Scores in Studies 004-301 (Schizophrenia) and 004-302 (Bipolar I Disorder)



6.2 Disposition and Compliance

In Study 004-301 (schizophrenia), 374 patients were screened for the study, and 344 were randomized and received at least 1 dose of study medication. Of the 344 treated patients, 338 (98.3%) completed the study. Six patients (1.7%) discontinued prematurely: 3 patients withdrew consent, 1 was withdrawn because of an investigator decision (administration of a psychotropic concomitant medication), 1 was withdrawn because of an adverse event (AE) (moderate bronchospasm), and 1 was withdrawn on discovery of her previous participation in this study at another center. The patient who was withdrawn because of an AE was excluded from all efficacy analyses because she was withdrawn prior to the first efficacy assessment (N=343).

In Study 004-302 (bipolar I disorder), 355 patients were screened for the study, and 314 were randomized and received at least 1 dose of study medication. Of the 314 treated patients, 312 (99.4%) completed the study. Two patients (0.6%) discontinued prematurely—both because of an AE of moderate anxiety that resolved with medication.

No patient refused dosing with study medication.

7 EFFICACY RESULTS

Two adequate and well-controlled Phase 3 clinical studies demonstrate the efficacy and safety of ADASUVE for the treatment of agitation—Study 004-301 in patients with schizophrenia and Study 004-302 in patients with bipolar I disorder.

The same efficacy endpoints were used in the 2 Phase 3 studies. The primary endpoint was the change in PEC score from baseline to 2 hours following Dose 1 of ADASUVE, compared with placebo, and was the same as that used in the clinical development programs of the IM formulations of 2 antipsychotics (Zyprexa and Abilify) marketed for the treatment of agitation. The key secondary endpoint was the CGI-I score 2 hours following Dose 1 of ADASUVE, compared with placebo. Additional efficacy endpoints included the percentage of CGI-I responders ("very much improved" or "much improved" at 2 hours after dosing), the number of doses of study and rescue medication; and the time to Dose 2 of study medication (an as needed [prn] dose).

To further characterize the efficacy of ADASUVE, the following post hoc analyses were performed: a PEC responder analysis and changes in individual PEC scale items.

A comparison of efficacy results in the ADASUVE Phase 3 studies with those from the IM Abilify and IM Zyprexa studies is provided in Appendix 1.

7.1 Primary Endpoint: Change in PEC Score from Baseline

In both studies, the 5- and 10-mg doses of ADASUVE were statistically significantly superior to placebo for the primary efficacy endpoint. The change in the PEC score from baseline to 2 hours after Dose 1 was significantly larger in each ADASUVE group compared with the placebo group (Figure 13 and Table 8).

Figure 13. Mean (SEM) Change in PEC Score from Baseline to 2 Hours − Studies 004-301 (Schizophrenia) and 004-302 (Bipolar I Disorder)

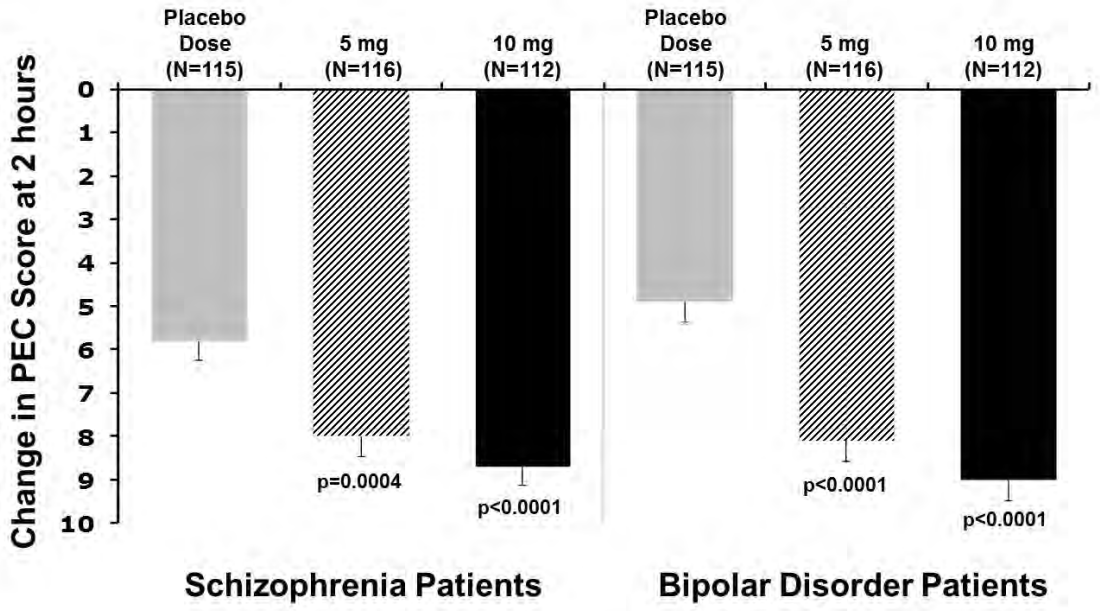


Table 8. Primary Efficacy Endpoint: Change in PEC Score 2 Hours after Dose 1 in Studies 004-301 (Schizophrenia) and 004-302 (Bipolar I Disorder)

Study 004-301 (Schizophrenia)	**Placebo (N=115)**	**ADASUVE 5 mg (N=116)**	**ADASUVE 10 mg (N=112)**
Baseline PEC Score			
Mean (SD)	17.4 (1.80)	17.8 (2.34)	17.6 (2.06)
Median	17	18	17
Min, max	14, 24	14, 28	14, 27
Change in PEC score from baseline to 2 hours after Dose 1			
LSmean[a]	-5.8	-8.0	-8.7
Mean (SD)	-5.5 (4.92)	-8.1 (5.17)	-8.6 (4.37)
Median	-5	-9	-10
Min, max	-18, 10	-19, 7	-16, 2
p-value for overall treatment effect[b]	p<0.0001	—	—
p-values for active/placebo comparisons[c]	—	p=0.0004	p<0.0001
Study 004-302 (Bipolar I Disorder)	**Placebo (N=105)**	**ADASUVE 5 mg (N=104)**	**ADASUVE 10 mg (N=105)**
Baseline PEC Score			
Mean (SD)	17.7 (2.80)	17.4 (2.23)	17.3 (2.25)
Median	17	17	17
Min, max	14, 31	14, 26	14, 25
Change in PEC score from baseline to 2 hours after Dose 1			
LSmean[a]	-4.7	-8.2	-9.2
Mean (SD)	-4.9 (4.77)	-8.1 (4.90)	-9.0 (4.67)
Median	-3	-9	-10
Min, max	-19, 5	-21, 2	-20, 4
p-value for overall treatment effect[b]	p<0.0001	—	—
p-values for active/placebo comparisons[c]	—	p<0.0001	p<0.0001

LSmean=least-squares mean; PEC=Positive and Negative Symptom Scale, Excited Component; SD=standard deviation

a. LSmean was used in the primary efficacy analysis
b. ANCOVA model with terms for baseline PEC total score, pseudocenter, and treatment
c. p-values (adjusted) using Dunnett's t-test within ANCOVA model with terms for baseline PEC, treatment, and pseudocenter

There were no apparent differences in response to treatment between subgroups based on age, gender, race, baseline PEC score, or between bipolar I patients with manic or mixed episodes.

ADASUVE was not associated with qualitatively excessive or adverse sedation (see Section 8.7).

7.2 Key Secondary Endpoint: CGI-I Score

Two efficacy endpoints used the CGI-I (improvement) scale, CGI-I score at 2 hours after ADASUVE administration (key secondary endpoint) and incidence of CGI-I responders. CGI-I scores were assessed 2 hours after ADASUVE administration to assess improvement in agitation.

Both doses of ADASUVE were statistically significantly superior to placebo for the key secondary efficacy endpoint in the 2 Phase 3 studies. At 2 hours after Dose 1, the CGI-I mean scores in both ADASUVE groups were significantly lower than those of the placebo group, indicating less agitation in the ADASUVE groups than the placebo group (Figure 14 and Table 9).

Figure 14. Key Secondary Efficacy Endpoint: CGI-I Score at 2 Hours − Studies 004-301 (Schizophrenia) and 004-302 (Bipolar I Disorder)

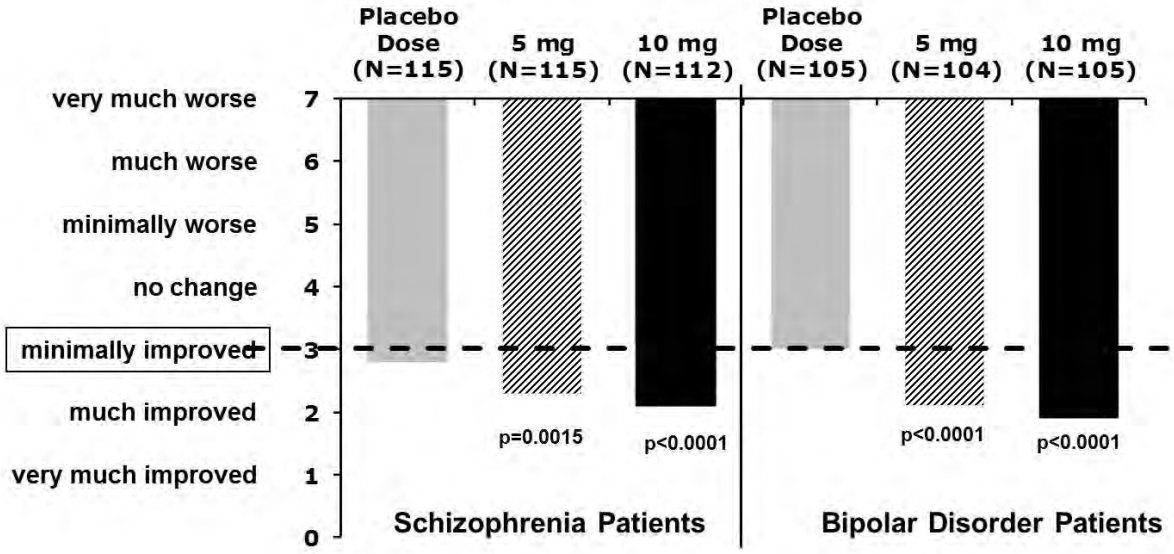


Table 9. Key Secondary Efficacy Endpoint: CGI-I Score at 2 Hours − Studies 004-301 (Schizophrenia) and 004-302 (Bipolar I Disorder)

Study 004-301 (Schizophrenia)	**Placebo (N=115)**	**ADASUVE 5 mg (N=116)[a]**	**ADASUVE 10 mg (N=112)**
CGI-S Score at Baseline[b]			
Mean (SD)	3.9 (0.53)	4.0 (0.55)	4.1 (0.60)
Median	4	4	4
Min, max	2, 5	3, 6	2, 6
CGI-I Score at 2 hours after dosing[c]			
Mean (SD)	2.8 (1.11)	2.3 (1.24)	2.1 (1.00)
Median	3	2	2
Min, max	1, 5	1, 7	1. 4
p-value for overall treatment effect[d]	p<0.0001	—	—
p-values for active/placebo comparisons[e]	—	p=0.0015	p<0.0001
Study 004-302 (Bipolar I Disorder)	**Placebo (N=105)**	**ADASUVE 5 mg (N=104)**	**ADASUVE 10 mg (N=105)**
CGI-S Score at Baseline[b]			
Mean (SD)	4.1 (0.57)	4.0 (0.53)	4.0 (0.49)
Median	4	4	4
Min, max	2, 6	3, 6	3, 5
CGI-I Score at 2 hours after dosing[c]			
Mean (SD)	3.0 (0.99)	2.1 (1.10)	1.9 (1.14)
Median	3	2	2
Min, max	1, 5	1, 4	1. 6
p-value for overall treatment effect[d]	p<0.0001	—	—
p-values for active/placebo comparisons[e]	—	p<0.0001	p<0.0001

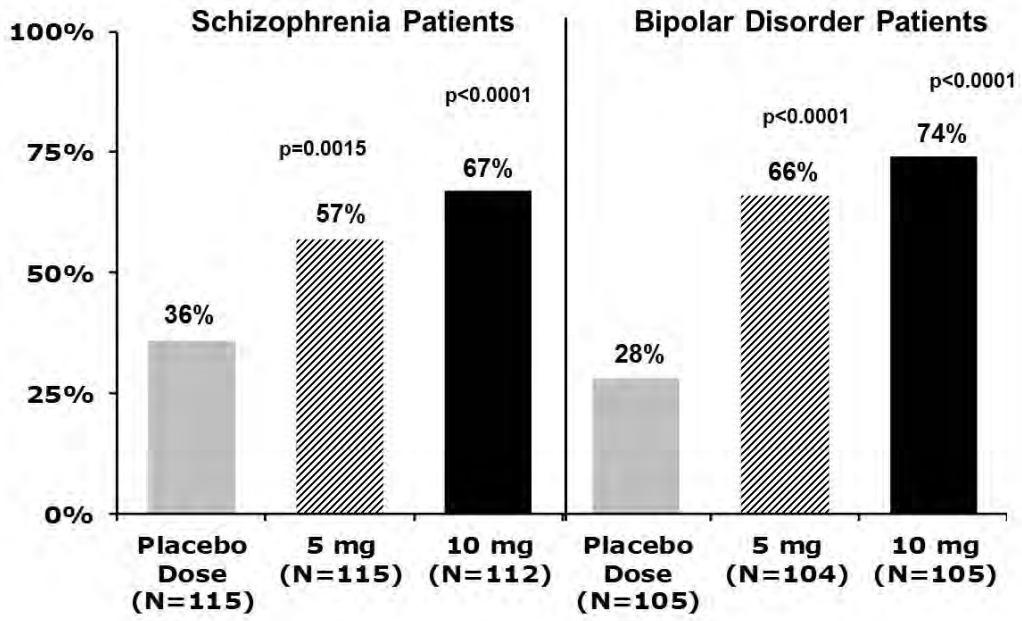
CGI-I=Clinical Global Impression - Improvement Scale; CGI-S=Clinical Global Impression - Severity Scale; SD=standard deviation

a. n=115 (1 patient discontinued before the Hour 2 measurement and there were no data to carry forward)
b. CGI-S scale was used for baseline assessment (0=not assessed, 1=normal, not at all agitated, 2=borderline agitated, 3=mildly agitated, 4=moderately agitated, 5=markedly agitated, 6=severely agitated, 7=among the most extremely agitated patients)
c. CGI-I scale was used for assessment after treatment (0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse)
d. ANOVA with terms for pseudocenter and treatment
e. p-values (adjusted) using Dunnett's t-test within ANOVA model with terms for pseudocenter and treatment

A CGI-I responder was defined as a patient with a score of 1 (very much improved) or 2 (much improved) on the CGI-I scale. CGI-I nonresponders were defined as patients with scores from 3 (minimally improved) through 7 (very much worse).

The percentage of CGI-I responders ("very much improved" or "much improved" at 2 hours after dosing) was statistically significantly higher in both ADASUVE treatment groups than in the placebo group (Figure 15 and Table 10).

Figure 15. Incidence of CGI-I Responders 2 Hours after Dose 1 in Studies 004-301 (Schizophrenia) and 004-302 (Bipolar I Disorder)



Note: A responder was defined as a patient with a CGI-I score of 1 (very much improved) or 2 (much improved) at 2 hours after initial dose of study medication

Table 10. Incidence of CGI-I Responders and Nonresponders 2 Hours after Dose 1 in Studies 004-301 (Schizophrenia) and 004-302 (Bipolar I Disorder)

	Number (%) of Patients		
Study 004-301 (Schizophrenia)	**Placebo (N=115)**	**ADASUVE 5 mg (N=116)[a]**	**ADASUVE 10 mg (N=112)**
CGI-I Responders: n (%)	41 (35.7%)	66 (57.4%)	75 (67.0%)
CGI-I Nonresponders: n (%)	74 (64.3%)	49 (42.6%)	37 (33.0%)
p-values for active/placebo comparisons[b]		p=0.0015	p<0.0001
Study 004-302 (Bipolar I Disorder)	**Placebo (N=105)**	**ADASUVE 5 mg (N=104)**	**ADASUVE 10 mg (N=105)**
CGI-I Responders: n (%)	29 (27.6%)	69 (66.3%)	78 (74.3%)
CGI-I Nonresponders: n (%)	76 (72.4%)	35 (33.7%)	22 (25.7%)
p-values for active/placebo comparisons[b]		p<0.0001	p<0.0001

Note: A responder was defined as a patient with a CGI-I score of 1 (very much improved) or 2 (much improved) at 2 hours after initial dose of study medication

a. n=115 (1 patient discontinued before the Hour 2 measurement and there were no data to carry forward)
b. p-values determined using Fisher's Exact Test (pairwise)

7.3 Time to Dose 2 (prn) of Study Medication

In the 2 Phase 3 studies, Dose 2 of study medication was allowed starting at 2 hours after Dose 1. Approximately one-half (51.4%) of the 5-mg patients and one-third (38.1%) of the 10-mg patients received Dose 2.

Kaplan-Meier plots of the time to Dose 2 of study medication (a prn dose) are presented in Figure 16 for Study 004-301 (schizophrenia) and in Figure 17 for Study 004-302 (bipolar I disorder). Placebo-treated patients were found to have taken Dose 2 significantly sooner than ADASUVE-treated patients overall in each study (004-301: p=0.0239 and 0.0110 for the Log Rank test and the Wilcoxon test, respectively; 004-302: p<0.0001 for the Log Rank test and the Wilcoxon test).

In Study 004-301 (schizophrenia), the pairwise comparisons showed that placebo-treated patients took Dose 2 significantly sooner than those taking ADASUVE 10 mg (p=0.0076 [Log Rank test]; p=0.0035 [Wilcoxon test]), and there was a trend favoring earlier use of Dose 2 in the placebo group relative to the 5-mg group (p=0.1155 [Log Rank test]; p=0.0772 [Wilcoxon test]).

In Study 004-302 (bipolar I disorder), the difference between each ADASUVE group and the placebo group was statistically significant, with placebo-treated patients taking Dose 2 significantly sooner (5-mg placebo, p=0.0058 [Log Rank test], p=0.0048 [Wilcoxon test]; 10-mg/placebo, p<0.0001 [Log Rank test], p<0.0001 [Wilcoxon test]).

In both studies, the time to Dose 2 of study medication provides support for a dose-response pattern for ADASUVE.

Figure 16. Survival Analysis for the Time to Administration of Dose 2 of Study Medication in Study 004-301 (Schizophrenia)

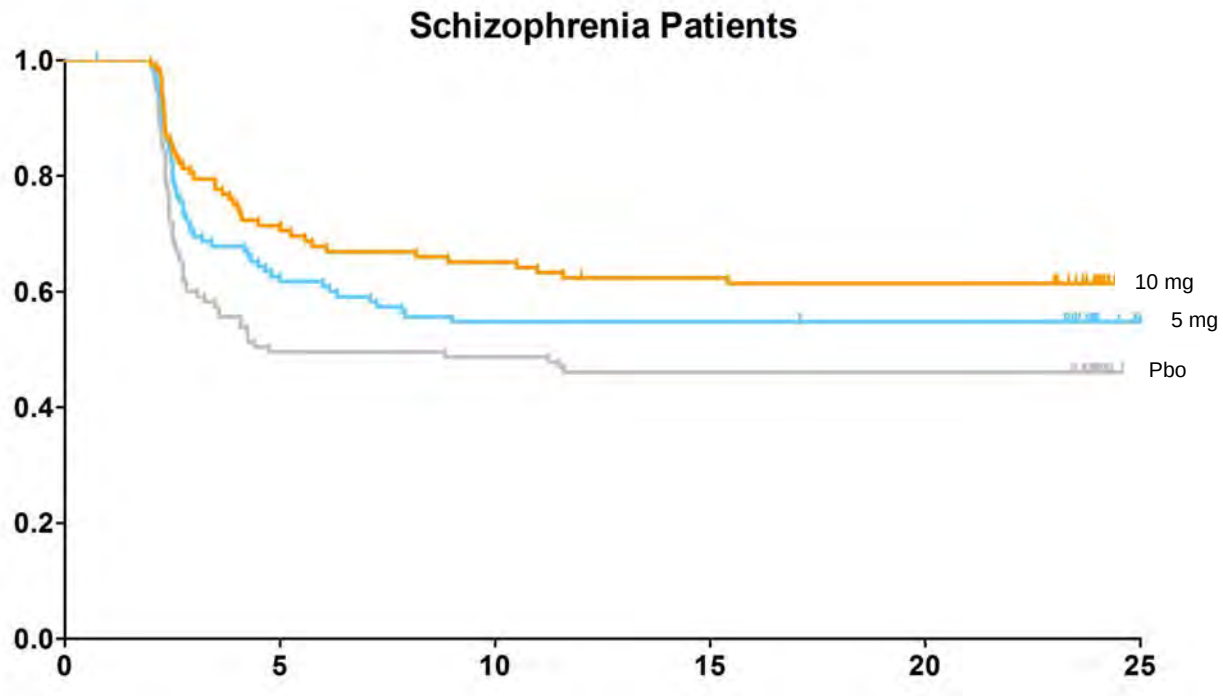
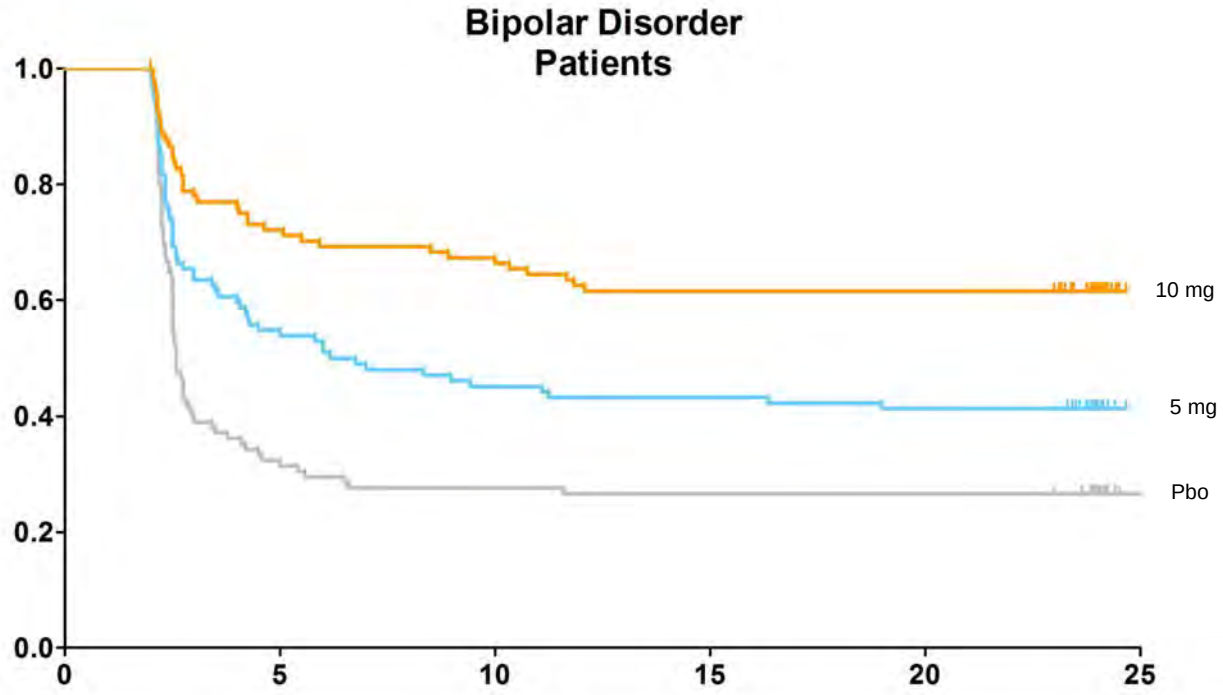


Figure 17. Survival Analysis for the Time to Administration of Dose 2 of Study Medication in Study 004-302 (Bipolar I Disorder)



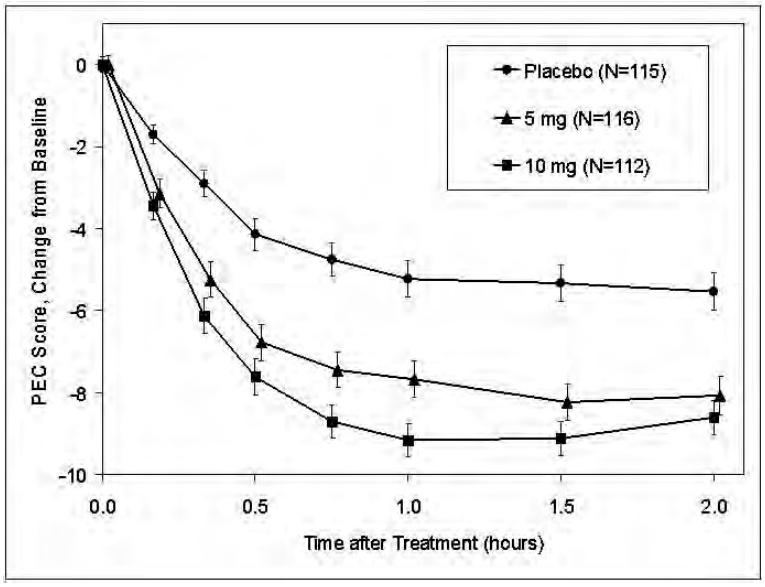
7.4 Onset of Action

Decreased agitation, as reflected in changes from baseline in the PEC score, was evident at the first assessment time, 10 minutes after Dose 1. For the 10 mg/placebo comparison, the difference was statistically significant at each assessment time from 10 minutes through 24 hours. A post hoc analysis of the 5-mg dose group showed statistically significant differences compared to placebo comparison at all time points starting at 10 minutes for both patient groups.

These data demonstrate the rapid onset of ADASUVE effect in the control of agitation in patients with schizophrenia and in patients with bipolar disorder.

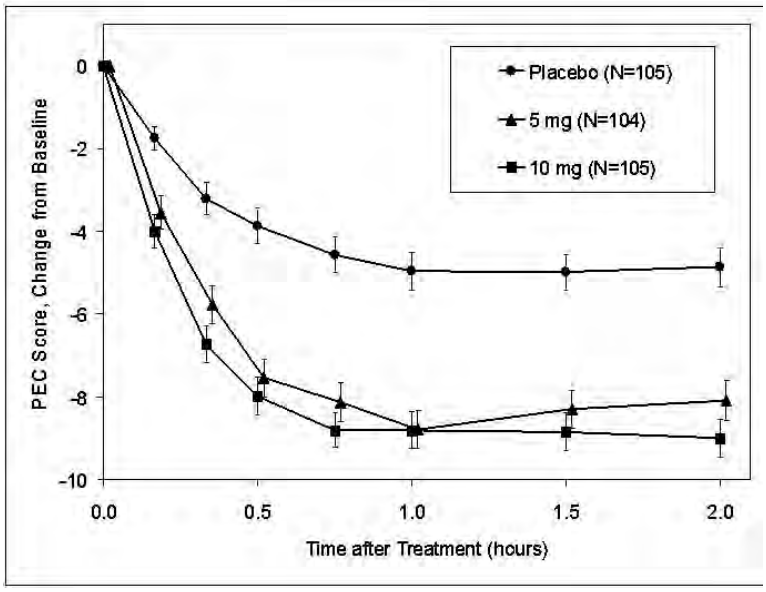
The changes in PEC score by time points from baseline to 2 hours after Dose 1 are presented by treatment in Figure 18 (schizophrenia) and Figure 19 (bipolar I disorder).

Figure 18. Mean (SEM) Change in PEC Score from Baseline Over Time − Study 004-301 (Schizophrenia)



Time after Dose 1	10 minutes	20 minutes	30 minutes	45 minutes	1 hour	1.5 hours	2 hours	4 hours	24 hours
p-values vs. placebo:									
10 mg:	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Figure 19. Mean (SEM) Change in PEC Score from Baseline Over Time − Study 004-302 (Bipolar I Disorder)



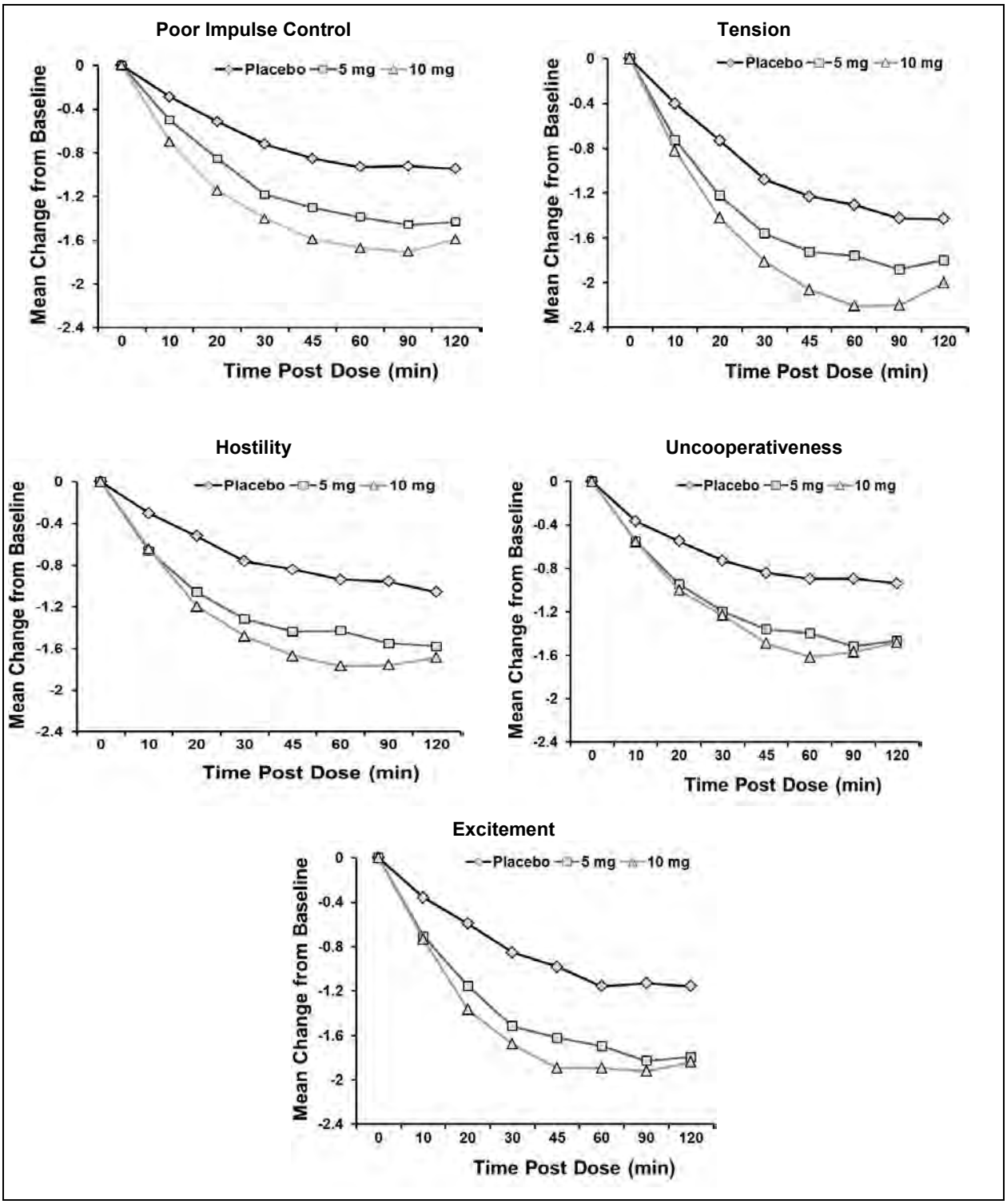
Time after Dose 1	10 minutes	20 minutes	30 minutes	45 minutes	1 hour	1.5 hours	2 hours	4 hours	24 hours
p-values vs. placebo:									
10 mg:	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0011

7.5 Individual PEC Item Analysis

In order to assess if the changes in the PEC scale were driven primarily by 1 or 2 items, post hoc analyses were conducted to assess the changes in each of the individual PEC items at each assessment time from 10 minutes to 2 hours after Dose 1.

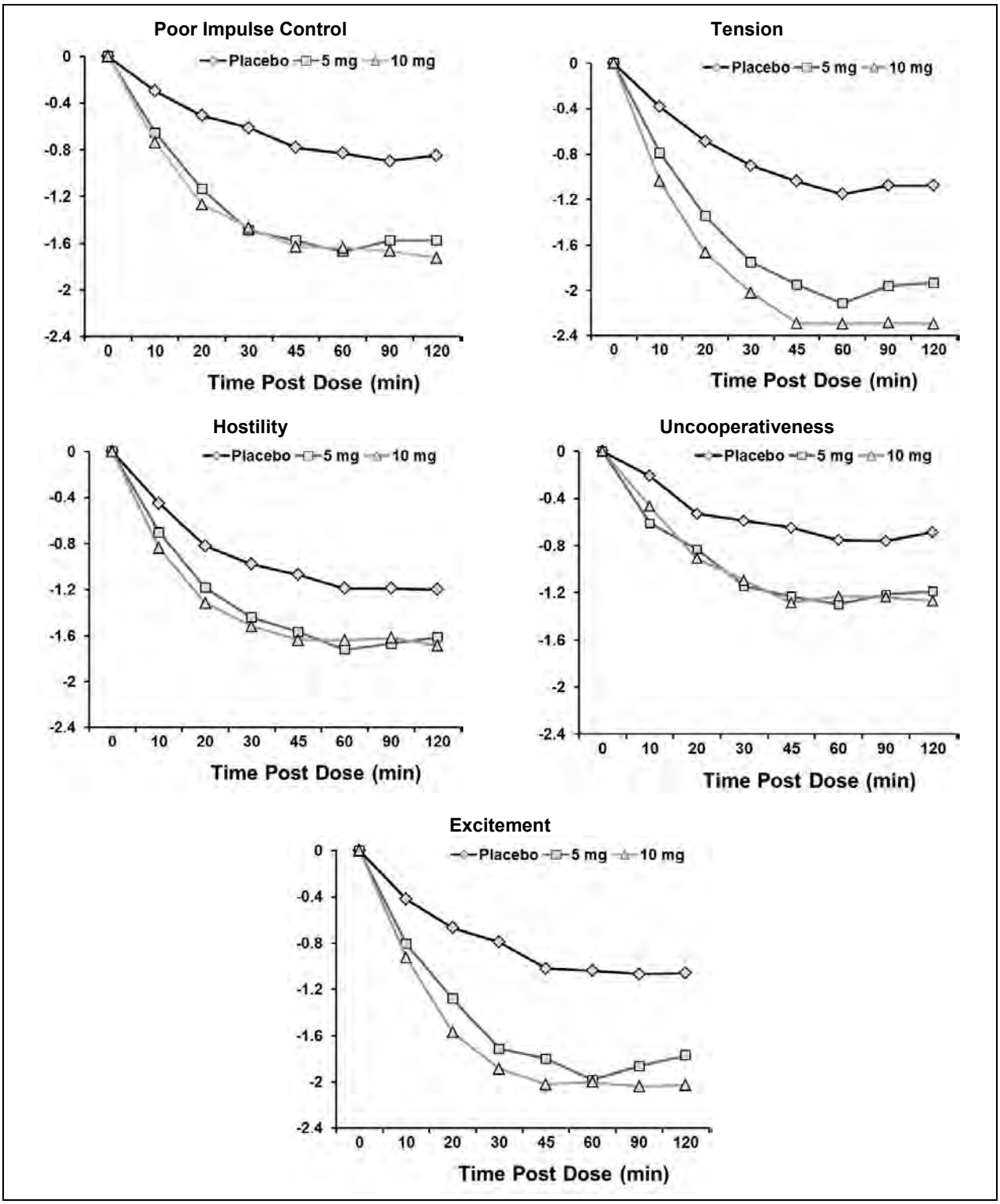
As seen in Figure 20 (schizophrenia) and Figure 21 (bipolar I disorder), each PEC scale item showed improvement after treatment with ADASUVE, and the improvement was evident at the first assessment time, 10 minutes after Dose 1. For the 10-mg groups in both studies, both active/placebo comparisons were statistically significant for each PEC scale item at each assessment time from 10 minutes through 2 hours after Dose 1 ($p<0.05$). For the 5-mg groups, both active/placebo comparisons were statistically significant for each PEC item at each assessment ($p<0.05$), with 1 exception (poor impulse control at 10 minutes for 5-mg dose in Study 004-301 (schizophrenia, $p=0.0853$). These data suggest that the change in total PEC score is comprised of rapid and significant improvement in each of the 5 symptom domains assessed by the PEC scale (hostility, excitement, poor impulse control, uncooperativeness, and tension).

Figure 20. Changes in Individual PEC Scale Items in the First 2 Hours after Dose 1 in Study 004-301 (Schizophrenia)



Note: Active/placebo comparisons for both doses were statistically significant for each PEC scale item at each assessment time from 10 minutes through 2 hours after Dose 1 ($p<0.05$, 2-way nonparametric ANCOVA by ranks [within strata]), with 1 exception (5-mg dose, poor impulse control at 10 minutes, $p=0.0853$).

Figure 21. Changes in Individual PEC Scale Items in the First 2 Hours after Dose 1 in Study 004-302 (Bipolar I Disorder)



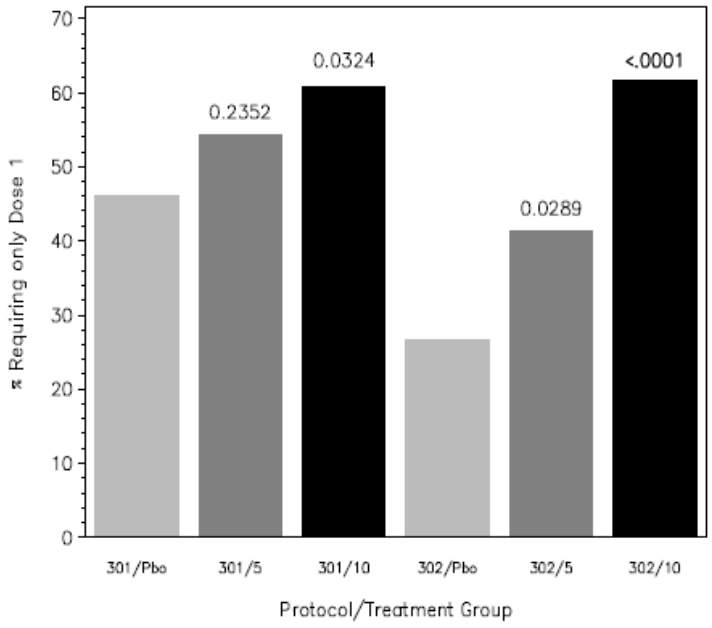
Note: Active/placebo comparisons for both doses were statistically significant for each PEC scale item at each assessment time from 10 minutes through 2 hours after Dose 1 ($p<0.05$, 2-way nonparametric ANCOVA by ranks [within strata]).

7.6 Additional Study Medication

In each of the Phase 3 studies, the maximum number of doses of study medication was 3. Consistent with clinical practice, the decision to administer a second or third dose of study medication was based on investigator judgment. Patients received 1 to 3 doses of study medication during a 24-hour study period, with Doses 2 and 3 administered only if needed. (Dose 2 could be given >2 hours after Dose 1, and Dose 3 could be given ≥4 hours after Dose 2.)

By 24 hours after the initial dose of study medication, 46.1%, 54.4%, and 60.9% of patients in Study 004-301 (schizophrenia) required only 1 dose of study medication or rescue medication with placebo, 5 mg, and 10 mg, respectively; and 26.7%, 41.3%, and 61.5% of patients in Study 004-302 (bipolar I disorder) required only 1 dose of study medication, respectively. Comparisons of active treatment groups versus placebo showed statistically significantly greater percentages of patients did not require additional medication in the ADASUVE 10-mg groups in both studies and in the 5-mg group in Study 004-302 (bipolar I disorder) (Figure 22).

Figure 22. Percentage of Patients Requiring Only Dose 1 by 24 Hours − Studies 004-301 (Schizophrenia) and 004-302 (Bipolar I Disorder)



The proportions of patients in Studies 004-301 (schizophrenia) and 004-302 (bipolar I disorder) who required 1, 2, or 3 doses of study medication within 24 hours are illustrated in Figure 23 and Figure 24, respectively, for patients who did not require rescue medication. In these patients, a clear dose response can be seen for the 2 active treatment groups (fewer additional doses of study medication were required in the 10-mg group compared with the 5-mg group).

Figure 23. Percentage of Patients Receiving 1, 2, or 3 Doses of Study Drug Among Those Not Requiring Rescue Medication − Study 004-301 (Schizophrenia)

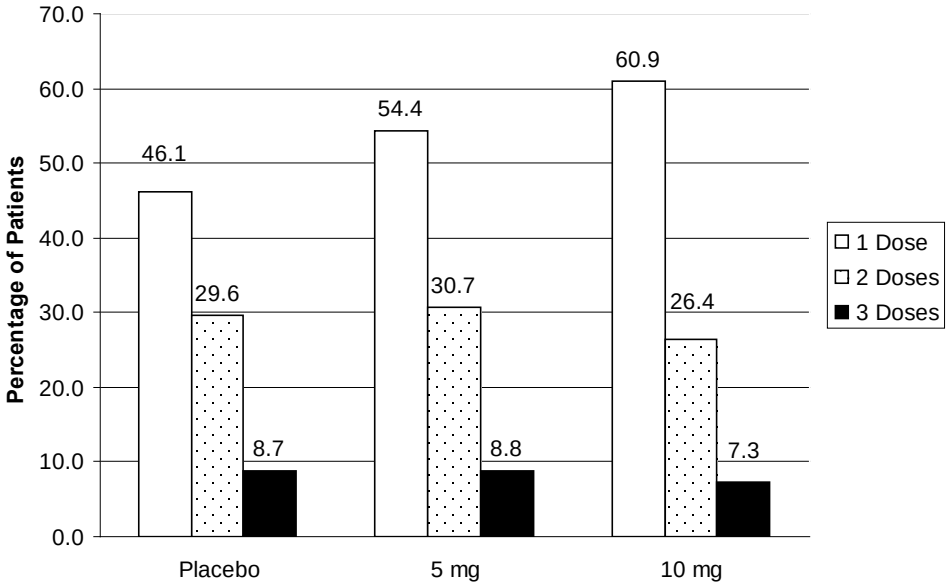
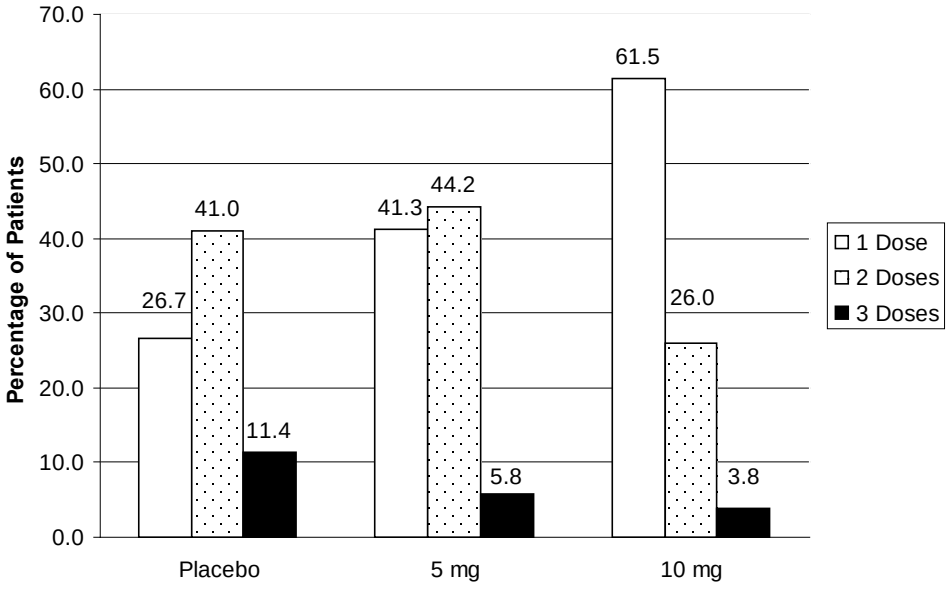


Figure 24. Percentage of Patients Receiving 1, 2, or 3 Doses of Study Drug Among Those Not Requiring Rescue Medication − Study 004-302 (Bipolar I Disorder)



7.7 PEC Responder Analysis

To assess the efficacy of ADASUVE in producing a clinically significant reduction in agitation, post hoc responder analyses evaluated the total PEC scores from all the time points within the first 2 hours after Dose 1. In these analyses, a "responder" was defined as a patient with a ≥40% decrease from baseline in the total PEC score—the same criterion that was used in responder analyses of PEC scale data from the pivotal trials of IM Abilify and IM Zyprexa.

In Studies 004-301 (schizophrenia) and 004-302 (bipolar I disorder), at each assessment time from 10 minutes through 2 hours after Dose 1, the percentage of responders was significantly larger in the groups treated with ADASUVE compared with placebo, and the difference was highly significant (Study 004-301 [schizophrenia], $p<0.01$ at all time points, Figure 25; Study 004-302 [bipolar disorder], $p<0.01$ at all time points, Figure 26). Furthermore, at each assessment time from 10 minutes through 2 hours, the responder rate was numerically larger in the 10-mg group compared with the 5-mg group.

In patients with schizophrenia (Study 004-301), the responder rate in the 10-mg group was 18.8% at 10 minutes post-dose ($p=0.0012$, active/placebo), 42.9% at 20 minutes ($p<0.0001$), and 69.6% at 2 hours ($p<0.0001$). In the 5-mg group, it was 17.2% at 10 minutes ($p=0.0056$), 29.3% at 20 minutes ($p=0.0088$), and 62.9% at 2 hours ($p=0.0002$).

In patients with bipolar disorder (Study 004-302), the responder rate in the 10-mg group was 21.9% at 10 minutes post-dose ($p=0.0017$, active/placebo), 49.5% at 20 minutes ($p<0.0001$), and 73.3% at 2 hours ($p<0.0001$). In the 5-mg group, it was 18.3% at 10 minutes ($p=0.0059$), 36.5% at 20 minutes ($p<0.0001$), and 62.5% at 2 hours ($p<0.0001$).

The responder rates at each assessment from 10 minutes to 2 hours after Dose 1 are presented in Figure 25 and Figure 26.

Figure 25. PEC Scale Responders (≥40% Decrease from Baseline) in the First 2 Hours after Dose 1 in Study 004-301 (Schizophrenia)

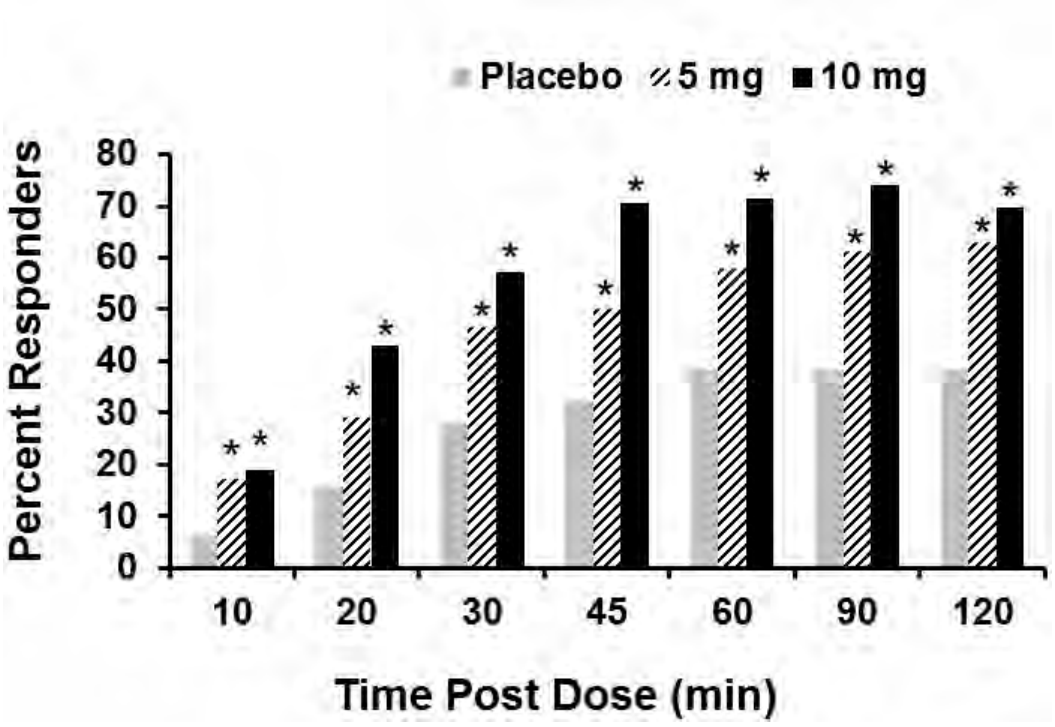
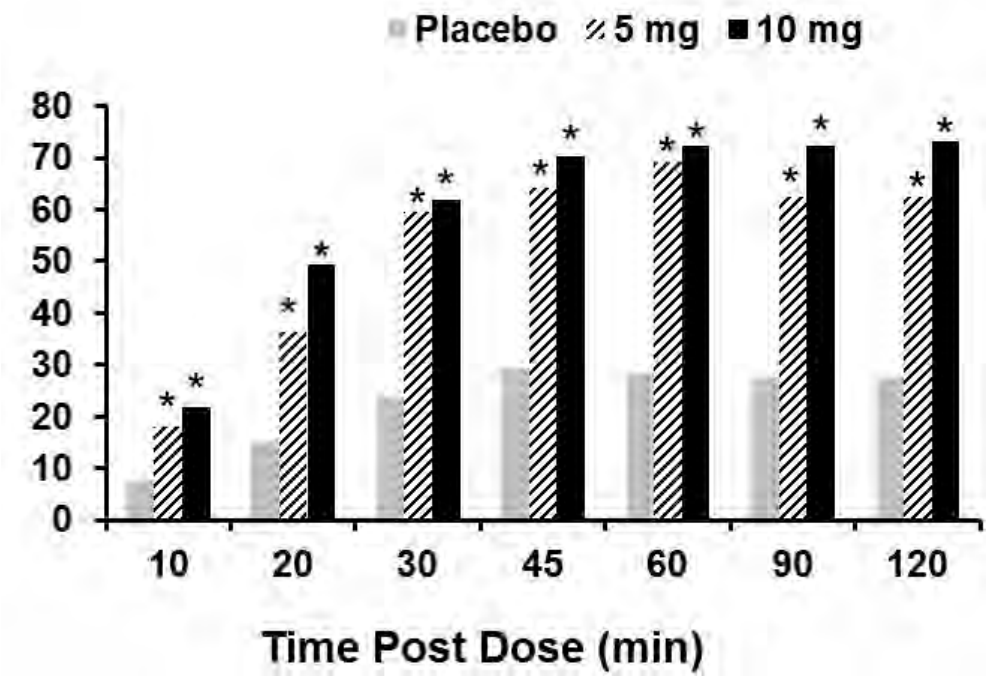


Figure 26. PEC Scale Responders (≥40% Decrease from Baseline) in the First 2 Hours after Dose 1 in Study 004-302 (Bipolar I Disorder)



7.8 Clinical Relevance

The mean difference between the 10 mg and placebo groups for the primary efficacy endpoint (change from baseline to 2 hours after Dose 1) was clinically and statistically robust with effect sizes of 0.60 and 0.94 in the schizophrenia and bipolar I disorder studies, respectively. As early as 10 minutes after Dose 1, the first time point, the effect sizes for mean change in PEC from baseline were 0.59 and 0.64 in the schizophrenia and bipolar I disorder studies, respectively. A comparison of effect sizes for mean change in PEC score from baseline to 2 hours for ADASUVE, IM Abilify, and IM Zyprexa is provided in Appendix 1.

The numbers needed to treat were consistent between the CGI-I and PEC responder results. Based on CGI-I responders, the number needed to treat for the 10-mg group was 3.2 for schizophrenia and 2.1 for bipolar I disorder. Based on PEC responder data, the number needed to treat for the 10-mg group was 3.2 for schizophrenia and 2.2 for bipolar I disorder.

Table 11. CGI-I Responder and PEC Responder: Effect Sizes and Numbers Needed to Treat for ADASUVE 10 mg

Endpoint	Schizophrenia	Bipolar I Disorder
	Effect Size[a]	
Decrease in PEC score from baseline to 2 hours after Dose 1	0.60 (8.7-5.8)/4.84	0.94 (9.2-4.7)/4.78
Decrease in PEC score from baseline to 10 minutes after Dose 1	0.59 (3.5-1.7)/3.07	0.64 (4.0-1.7)/3.58
	Number Needed to Treat[b]	
Percentage of CGI-I responders at 2 hours[c]	3.2 (100/67.0-35.7)	2.1 (100/74.3-27.6)
Percentage of PEC responders at 2 hours[d]	3.2 (100/69.6-38.3)	2.2 (100/73.3-27.6)

a. Effect size was calculated as: (LSmean decrease to 2 hours or 10 minutes after Dose 1 for ADASUVE 10 mg minus LSmean decrease to 2 hours or 10 minutes after Dose 1 for placebo)/pooled standard deviation.
b. Number needed to treat was calculated as: 100/(percentage of responders in the ADASUVE 10 mg group-percentage of responders in the placebo group).
c. A CGI-I responder was defined as a patient with a CGI-I score of 1 (very much improved) or 2 (much improved) at 2 hours after initial dose of study medication.
d. A PEC responder was defined as a patient with a ≥40% decrease from baseline in the total PEC score at 2 hours after initial dose of study medication.

7.9 Efficacy Conclusions

Two double-blind, placebo-controlled Phase 3 studies were conducted in agitated patients from 2 distinct patient populations to support the efficacy of ADASUVE in the rapid control of agitation in different patient populations. One study was conducted to demonstrate the efficacy of ADASUVE in agitated patients with schizophrenia and the other was conducted in agitated patients with bipolar I disorder (manic or mixed episodes).

The findings of the Phase 3 studies demonstrate the efficacy of both the 5- and 10-mg doses of ADASUVE in the treatment of agitation in patients with schizophrenia or bipolar disorder. Across multiple endpoints, the effects of the 5- and 10-mg doses were statistically different from placebo, and typically there was a numerically larger treatment effect in the 10-mg group than the 5-mg group. These data support the administration of 1 to 3 doses of ADASUVE (up to a total of 30 mg/day) during a 24-hour period. This efficacy was demonstrated in clinically agitated patients with significant and long-standing disease who presented or were referred for study treatment through normal channels by which psychiatric patients obtain treatment for agitation.

Specifically, the Phase 3 studies support the following conclusions:

- Both the 5- and 10-mg doses of ADASUVE were statistically significantly superior to placebo for the primary efficacy endpoint, the change in the PEC score from baseline to 2 hours (5 and 10 mg versus placebo).

- For both doses, the treatment effect was evident 10 minutes after Dose 1 and was sustained at all assessment times through 24 hours.

- The findings for post hoc analyses of PEC (ie, the percentage of patients with ≥40% decrease from baseline in the total PEC score and mean changes in each of the individual PEC items at each assessment time from 10 minutes to 2 hours after Dose 1) also support the efficacy and clinical relevance of ADASUVE. These latter data suggest that the change in total PEC score is comprised of rapid and significant improvement in each of the 5 symptom domains assessed by the PEC scale (hostility, excitement, poor impulse control, uncooperativeness, and tension).

- Both doses of ADASUVE were statistically significantly superior to placebo for the key secondary efficacy endpoint, the CGI-I score at 2 hours (5 and 10 mg versus placebo).

- The findings for additional endpoints also support the efficacy of ADASUVE. These include the percentage of patients judged by the investigator to be very much improved or much improved 2 hours after Dose 1 (CGI-I responder analysis), the use of additional doses of study medication, and time to Dose 2 of study medication.

- There were no apparent differences in response to treatment between subgroups based on age, gender, race, baseline PEC score, or between bipolar I disorder patients with manic or mixed episodes.

- Across multiple endpoints, the magnitude of the treatment effect was larger in the 10-mg group than the 5-mg group, supporting a dose-response pattern for ADASUVE 5 and 10 mg.

- All of the agitated patients in the clinical studies were able to use the product successfully.

8 GENERAL SAFETY RESULTS

Safety data are presented for the Phase 2/3 agitated patient population (ie, patients from Phase 3 Studies 004-301 and 004-302 and Phase 2 Study 004-201)—agitated patients with schizophrenia (this includes 21% in the Phase 2 study who had schizoaffective disorder) or bipolar I disorder. This population includes 524 patients who received at least 1 dose of ADASUVE and 263 patients who received at least 1 dose of placebo.

Assessment of QT interval prolongation was assessed in a Phase 1 thorough QT/QTc study. Results from this study are discussed in Section 8.6.

Safety data from the 2 migraine studies are not presented in this section. However, ADASUVE was well tolerated in those 2 studies. None of the AEs was serious or led to premature discontinuation.

8.1 Safety Methodology

The general safety of ADASUVE for the treatment of agitation has been evaluated by assessment of treatment-emergent AEs, clinical laboratory values, vital signs, and ECG evaluations (Phase 1 thorough QT/QTc study).

The potential association of ADASUVE with excessive sedation was assessed using the Agitation-Calmness Evaluation Scale (ACES) and by conventional AE collection.

Extrapyramidal symptoms were assessed by conventional AE collection.

Treatment-Emergent Adverse Events

All AEs summarized are treatment emergent AEs, which occurred at any time starting immediately following the first dose of study medication (Day 1) and until the end of the study. Adverse events noted by the investigator or study personnel during study assessments or when spontaneously reported by the patient were recorded and the severity and relationship to study medication were determined by the investigator. Adverse events for the 11 studies in the agitation clinical program were coded using Medical Dictionary for Regulatory Activities.

Clinical Laboratory Data

In the 2 Phase 3 studies, laboratory data were collected at screening and again at the end of the 24-hour evaluation period; all tests were performed at local laboratories. Three standard approaches to the analysis of laboratory data were applied: change from baseline, shifts from normal to abnormal, and identification of laboratory abnormalities considered by the investigator to be clinically significant.

Vital Sign Data

Across the clinical program, vital sign data were collected at different time points, and as sitting, supine or standing measurements. In the Phase 2/3 agitated patient population, vital signs were collected at 1, 2, 4, and 24 hours post-dose. Vital sign (systolic and diastolic blood pressures, heart rate, and respiration rate) data were analyzed for changes from baseline and for marked abnormalities.

Electrocardiogram

The timing of ECG observations in the thorough QT/QTc study was consistent with the pharmacokinetics of ADASUVE, with intensive observations in the first hour after inhaled drug administration. The QT intervals were measured using a high-resolution, manual, onscreen caliper method in compliance with the suggested standards set forth in the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E14 guideline (2005).

Agitation-Calmness Evaluation Scale (ACES)

In the Phase 3 studies, the ACES (shown below) was used by the investigator to rate the patient's level of sedation on a continuum of agitated-calm-sleeping. Assessments were made at baseline and 2 hours after study medication dosing. Scores range from 1 (marked agitation) to 9 (unarousable), with a score of 4 indicating "normal."

1 = Marked agitation

2 = Moderate agitation

3 = Mild agitation

4 = Normal

5 = Mild calmness

6 = Moderate calmness

7 = Marked calmness

8 = Deep sleep

9 = Unarousable

Raters were trained by an independent contract research organization in the use of the ACES.

8.2 Deaths, Discontinuations Due to Adverse Events, and Serious Adverse Events

No deaths occurred among ADASUVE-treated agitated patients during or within 30 days of the last dose of study medication.

Three patients in the ADASUVE 10-mg group in the Phase 2/3 agitated patient population experienced AEs that led to discontinuation: 1 patient experienced bronchospasm and 2 patients experienced anxiety. All 3 events were considered by the investigator to be moderate in severity, and resolved. The bronchospasm was considered by the investigator to be probably related to study medication and 1 event of anxiety was considered by the investigator to be possibly related to study medication.

Serious AEs (SAEs) were identified in accordance with Title 21CFR312.32 of the Code of Federal Regulations. Only 3 SAEs in total were reported in ADASUVE patients in the Phase 2/3 agitated patient population (5 mg: 1 patient [hypertension] and 10 mg: 2 patients [exacerbation of schizophrenia and gastroenteritis, respectively]), none of which were considered related to ADASUVE by the investigator. These were the only SAEs in ADASUVE-treated patients across the clinical development program.

8.3 Treatment-Emergent Adverse Events

For the purpose of identifying adverse reactions associated with ADASUVE, AEs that occurred at a rate of ≥2% in either the 5-mg or 10-mg ADASUVE groups and for which the rate exceeds the rate for placebo are summarized in Table 12. Four AEs met these criteria: dysgeusia, sedation (including sedation combined with somnolence), fatigue, and throat irritation.

Only dysgeusia had an incidence greater than 5% and twice that of placebo. The incidence of dysgeusia was significantly higher in both the 5-mg ADASUVE (11.3%; p=0.0102) and 10-mg ADASUVE (14.3%; p=0.0003) dose groups than for the placebo group (4.9%). The incidence of sedation and the combination of sedation and somnolence were numerically higher for both ADASUVE dose groups compared with placebo, but the differences were not statistically significant. Throat irritation was significantly higher in the 10-mg ADASUVE dose group (2.7%; p=0.0364) compared with placebo (0.4%); there was no significant difference in the incidence of throat irritation between the 5-mg ADASUVE dose group and the placebo group.

Table 12. ADASUVE AEs with an Incidence of At Least 2% and Greater than Placebo (Phase 2/3 Agitated Patient Population)

MedDRA Preferred Term, n (%)	Placebo (N=263)	ADASUVE 5 mg (N=265)	ADASUVE 10 mg (N=259)
Dysgeusia	13 (4.9%)	30 (11.3%)	37 (14.3%)
p-value[a]		0.0102	0.0003
Sedation/Somnolence[b]	25 (9.5%)	32 (12.1%)	31 (12.0%)
p-value[a]		0.4005	0.3978
Sedation	20 (7.6%)	28 (10.6%)	27 (10.4%)
p-value[a]		0.2894	0.2866
Fatigue	5 (1.9%)	6 (2.3%)	3 (1.2%)
p-value[a]		1.0000	0.7245
Throat Irritation	1 (0.4%)	2 (0.8%)	7 (2.7%)
p-value[a]		1.0000	0.0364

a. p-values are from Fisher's exact test.
b. Incidence for the preferred terms of sedation and somnolence combined. The incidence of somnolence was 4 (1.5%) in each ADASUVE group and 5 (1.9%) in the placebo group.

8.4 Clinical Laboratory Data

In Studies 004-301 (schizophrenia) and 004-302 (bipolar I disorder), there were no clinically important mean changes in any treatment group in hematology, blood chemistry, or urinalysis parameters. The incidences of marked hematology, blood chemistry, and urinalysis abnormalities were similar for the ADASUVE 5-mg and 10-mg treatment groups and the placebo treatment group. No liver toxicity was observed.

8.5 Vital Sign Data

8.5.1 Mean Changes from Screening

Overall, the mean changes from screening in vital signs in the Phase 2/3 agitated patient population were small. No clinically important effects of ADASUVE on mean change from screening in vital signs were observed.

Heart Rate: There were numerically greater mean reductions in heart rate in the Phase 2/3 agitated patient population in the ADASUVE 5-mg and 10-mg groups and All ADASUVE groups than in the placebo group at 1, 2, and 4 hours but not at 24 hours post-dose. The mean change from screening in heart rate in the All ADASUVE group (-2.1 beats per minute [bpm]) was statistically significant at 2 hours (p=0.0142) post-dose compared with that for placebo (-0.3 bpm). The mean reductions in heart rate were similar between the ADASUVE 5-mg and 10-mg groups at 1, 2, and 4 hours post-dose and were not considered to be clinically important.

Systolic Blood Pressure: There were numerically greater mean reductions in systolic blood pressure in the Phase 2/3 agitated patient population in the ADASUVE 5-mg and 10-mg groups and All ADASUVE groups than placebo at 1, 2, and 4 hours but not at 24 hours post-dose. The mean changes from screening in systolic blood pressure at 2 and 4 hours post-dose in the All ADASUVE group (-3.4 and -2.5 mm Hg, respectively) were statistically significant (p=0.0045 and p=0.0154, respectively) compared with the placebo group (-0.9 and -0.2 mm Hg, respectively). The mean reductions in systolic blood pressure were slightly greater in the ADASUVE 10-mg group than the 5-mg group at 1, 2, and 4 hours post-dose but the differences between the 2 doses were within < 2 mm Hg. None of these changes are considered clinically significant.

Diastolic Blood Pressure: There were numerically greater mean reductions in diastolic blood pressure in the Phase 2/3 agitated patient population in the ADASUVE 5-mg and 10-mg groups and All ADASUVE groups than the placebo group at 1, 2, and 4 hours but not at 24 hours post-dose. The mean change from screening in diastolic blood pressure at 2 hours post-dose in the All ADASUVE group (-2.5 mm Hg) was statistically significant (p=0.0017) compared with the placebo group (-0.5 mm Hg). The mean reductions in diastolic blood pressure were slightly greater in the ADASUVE 10-mg group than the 5-mg group at 1, 2, and 4 hours post-dose but the differences between the 2 doses were within < 2 mm Hg.

Respiratory Rate: There were numerically greater mean reductions in respiratory rate in the Phase 2/3 agitated patient population in the ADASUVE 5-mg and 10-mg groups and All ADASUVE groups than placebo at 1 and 2, but not at 4 and 24 hours post-dose; none of the differences was statistically significant. The mean reductions in respiratory rate appeared numerically greater in the ADASUVE 10-mg group than the 5-mg group at 1, 2, and 4 hours post-dose.

8.5.2 Marked Abnormalities in Vital Signs

The criteria that were applied to identify marked abnormalities in vital signs are shown below.

Variable	Low	High
Systolic blood pressure (any position) – mm Hg	≤90 & decrease from screening ≥20	≥180 & increase from screening ≥20
Diastolic blood pressure (any position) – mm Hg	≤50 & decrease from screening ≥15	≥105 & increase from screening ≥5
Heart rate (beats/min)	≤50 & decrease from screening ≥20	≥120 & increase from screening ≥20
Respiratory rate (breaths/min)	≤6 & decrease from screening ≥5	≥ 30 & increase from screening ≥5

Overall, there were relatively few marked abnormalities in vital signs in the ADASUVE 5-mg and 10-mg and placebo groups in the Phase 2/3 agitated patient population. The most frequently reported marked abnormalities in vital signs were: systolic blood pressure ≤90 mm Hg and decrease ≥20 mm Hg in 7 patients (1.3%) in the All ADASUVE group

(3 of which were in the 5-mg group, 1.1% and 4 of which were in the 10-mg group, 1.5%) vs 2 placebo patients (0.8%); and diastolic blood pressure ≤50 mm Hg and decrease ≥15 mm Hg in 3 patients (0.6%) in the All ADASUVE group (1 of which was in the 5-mg group, 0.4% and 2 of which were in the 10-mg group, 0.8%) vs 1 placebo patient (0.4%).

The marked decreases in diastolic blood pressure in the Phase 2/3 agitated patient population were primarily isolated abnormalities (without other abnormalities in systolic blood pressure or heart rate at the same time); only 1 patient in the ADASUVE 5-mg group had a single time point with both low diastolic and low systolic measurements.

Other marked abnormalities in vital signs involved only 1 patient in a treatment group: heart rate ≤50 bpm and decrease ≥20 (1 patient in ADASUVE 10-mg group) and respiratory rate ≥30 breaths/min and increase ≥5 breaths/min (1 placebo patient).

Vital sign findings that were reported as AEs, but that did not meet criteria for marked abnormalities included hypertension in 3 patients (1.2%) in the ADASUVE 10-mg group, 2 patients (0.8%) in the ADASUVE 5-mg group, and 2 patients (0.8%) in the placebo group. In addition, hypotension was reported for 1 patient (0.4%) in the ADASUVE 10-mg group, 2 patients (0.8%) in the ADASUVE 5-mg group, and 2 patients (0.8%) in the placebo group. There were no reports of orthostatic hypotension, pre-syncope or syncope in the Phase 2/3 agitated patient population.

8.6 Phase 1 Thorough QT/QTc Study

Designed in accordance with the ICH E14 guideline (2005), a thorough QT/QTc study was performed to assess the potential for ADASUVE to delay cardiac repolarization using the corrected QT interval (QTc) duration. This was a double-blind, double-dummy, active- and placebo-controlled, 3-period crossover study investigating single doses of ADASUVE (10 mg, the anticipated maximum therapeutic dose), a positive control known to prolong QT/QTc (oral moxifloxacin, 400 mg), and oral and inhaled placebos.

The study demonstrated that ADASUVE at a dose of 10 mg did not increase QT intervals since the upper bound of the 95% 1-sided confidence interval for the largest time-matched mean effect of loxapine on the individually corrected QT interval (QTcI) excluded 10 milliseconds. No important differences were seen between males and females in the time-matched difference from placebo in pre-dose-subtracted QTcI (ΔΔQTcI) results. As defined in the ICH E14 guideline (2005), the study was negative for an effect on cardiac repolarization. The study outcome was validated by the demonstrated assay sensitivity using the positive control moxifloxacin.

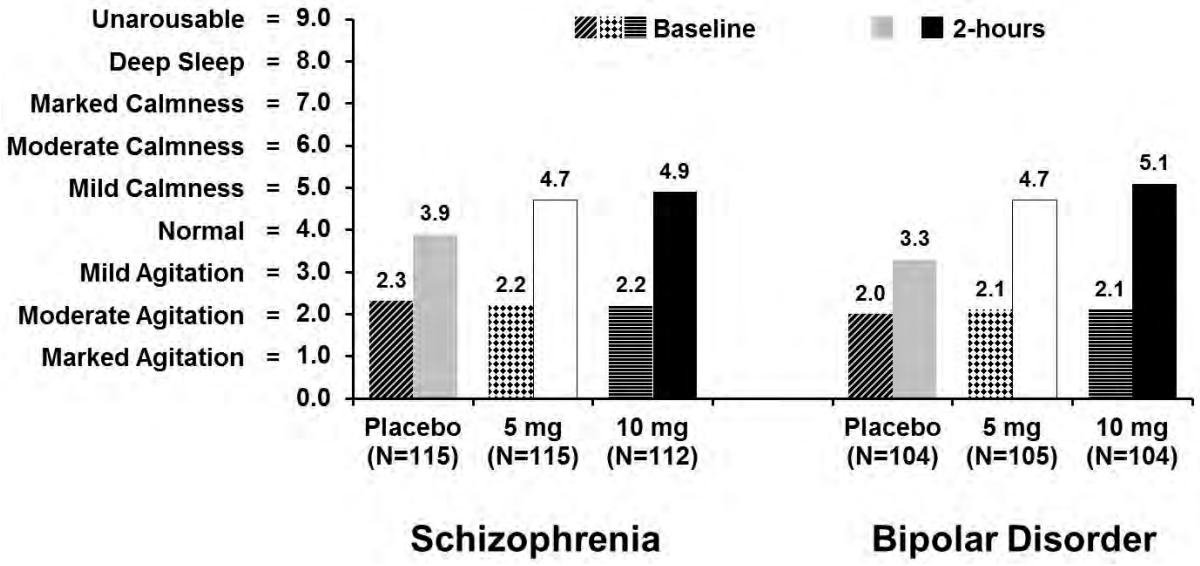
8.7 Sedation

This section discusses the potential association of ADASUVE with excessive sedation. This potential association was evaluated by ACES data from the Phase 3 studies and conventional AE collection in the Phase 2 and 3 studies.

8.7.1 Agitation-Calmness Evaluation Scale (ACES)

Because the ACES rates the patient on the continuum of agitated-calm-sleeping, it is useful in identifying patients with marked sedation. Two hours after Dose 1, no patient in the Phase 3 studies had an ACES score of 9 (ie, unarousable). The mean and median ACES scores in the 10-mg group 2 hours after Dose 1 were approximately 5 (ie, mild calmness) in Study 004-301 (schizophrenia). In Study 004-302 (bipolar I disorder), the mean ACES score the in the 10-mg group 2 hours after Dose 1 was 5.1 (5=mild calmness) with median score of 6 (moderate calmness). Results are shown graphically in Figure 27.

Figure 27. Mean ACES Scores at Baseline and 2 Hours in Studies 004-301 (Schizophrenia) and 004-302 (Bipolar I Disorder)



8.7.2 Incidence of Sedation-Related Adverse Events

Adverse events of sedation, somnolence, and fatigue were identified as potentially related to excessive sedation by sponsor review of all MedDRA preferred terms from the Phase 2/3 agitated patient population.

The sedation-related AE (specific MedDRA preferred term) with the highest incidence in each treatment group was sedation, which was numerically greater in the All ADASUVE group compared with the placebo group (10.5% vs 7.6%) (Table 13). Somnolence (1.5% and 1.9%, respectively) and fatigue (1.7% and 1.9%, respectively) were experienced by similar percentages of patients in the All ADASUVE and placebo groups.

There was no clinically important difference in the incidence of any of these sedation-related AEs between the 5-mg and 10-mg ADASUVE dose groups.

Table 13. Sedation-Related AEs (Phase 2/3 Agitated Patient Population)

MedDRA Preferred Term, n (%)	Placebo (N=263)	ADASUVE Dose		All ADASUVE (N=524)
		5 mg (N=265)	10 mg (N=259)	
Sedation	20 (7.6%)	28 (10.6%)	27 (10.4%)	55 (10.5%)
Somnolence	5 (1.9%)	4 (1.5%)	4 (1.5%)	8 (1.5%)
Fatigue	5 (1.9%)	6 (2.3%)	3 (1.2%)	9 (1.7%)

8.7.3 Sedation Conclusions

Based on the ACES results and the low incidence of treatment-emergent AEs related to sedation, ADASUVE was not associated with excessive or adverse sedation. No ADASUVE-treated patients were given an ACES rating of 9.

8.8 Extrapyramidal Symptoms

Most adverse effects of loxapine represent extensions of its central nervous system (CNS) pharmacological effects, which may include EPS (akathisia, dystonia, rigidity, and tremors). Less common CNS adverse effects of loxapine reported in the prescribing information for the oral formulation include tardive dyskinesia, neuroleptic malignant syndrome, and seizures (Watson Pharmaceuticals, US prescribing information, 2010).

The percentage of patients in the Phase 2/3 agitated patient population who experienced EPS symptoms (as indicated by MedDRA preferred terms) was <0.5% for each specific term. Adverse events considered to represent EPS are summarized for the Phase 2/3 agitated patient population in Table 14.

Table 14. EPS AEs by Treatment Group (Phase 2/3 Agitated Patient Population)

MedDRA Preferred Term, n (%)	Placebo (N=263)	ADASUVE Dose		All ADASUVE (N=524)
		5 mg (N=265)	10 mg (N=259)	
Any EPS AE	1 (0.4%)	5 (1.9%)	4 (1.5%)	9 (1.7%)
Akathisia	0 (0.0%)	1 (0.4%)	1 (0.4%)	2 (0.4%)
Tremor	0 (0.0%)	2 (0.8%)	0 (0.0%)	2 (0.4%)
Muscle twitching	1 (0.4%)	1 (0.4%)	1 (0.4%)	2 (0.4%)
Dyskinesia	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)
Dystonia	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Oculogyration	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Grimacing	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)
Restlessness	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Gait disturbance	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

8.9 General Safety Conclusions

ADASUVE is safe and well tolerated for the treatment of agitation in patients with schizophrenia or bipolar disorder. Only 3 SAEs in total were reported in ADASUVE patients in the Phase 2/3 agitated patient population (5 mg: 1 patient [hypertension] and 10 mg: 2 patients [exacerbation of schizophrenia and gastroenteritis, respectively]), none of which were considered related to ADASUVE by the investigator. Similarly, a very low incidence of AEs that led to premature discontinuation of study medication was reported in the Phase 2/3 agitated patient population: 1 patient experienced bronchospasm and 2 patients experienced anxiety. All 3 events were considered by the investigator to be moderate in severity, and resolved. The bronchospasm was considered by the investigator to be probably related to study medication and 1 event of anxiety was considered by the investigator to be possibly related to study medication.

The main safety findings in the Phase 2/3 agitated patient population were as follows:

- Adverse events were reported for a similar percentage of ADASUVE- and placebo-treated patients (All ADASUVE, 36.5%; placebo, 37.3%). The most frequently reported AEs in patients treated with ADASUVE were dysgeusia (All ADASUVE 12.8%) and sedation (All ADASUVE 10.5%).

- Dysgeusia, sedation (including sedation combined with somnolence), fatigue, and throat irritation were identified as potential adverse reactions associated with ADASUVE (incidence rate of ≥2% and greater than placebo in either the 5-mg or 10-mg ADASUVE groups).

- Of other AEs of interest, dizziness (a known adverse effect of loxapine administered by other routes) was slightly more common in placebo-treated patients than

ADASUVE-treated patients and did not show a dose-response pattern between the 5-mg and 10-mg ADASUVE groups.

- ADASUVE was not associated with qualitatively excessive or adverse sedation.

- No clinically important effects of ADASUVE on mean clinical laboratory values or mean vital signs were observed. Few marked laboratory or vital sign abnormalities were identified. A thorough QT/QTc study was negative according to ICH E14 criteria.

9 PULMONARY SAFETY RESULTS

9.1 Pulmonary Safety Methodology

Comprehensive examinations of pulmonary safety were conducted in 3 spirometry-based studies: a study in healthy volunteers, a study in subjects with asthma, and a study in subjects with COPD. The design of these Phase 1 studies was discussed with the FDA at the EOP2 meeting and subsequently finalized with input from the FDA. The primary safety measure for these studies was FEV_1, the volume of air exhaled in the first second of a forced exhalation (starting from a position of full inspiration). FEV_1 data were examined using means, as well as change categories (≥10%, ≥15%, ≥20%) for changes from same-day baseline. In the study in healthy subjects, evaluation of the spirometry results also included an external blinded review of the spirometry tests from all subjects with any ≥10% decrease in FEV_1 from baseline; this review was conducted by an independent pulmonologist expert.

All spirometry tests in the pulmonary safety studies used the same controlled clinical standards. Tests were conducted according to American Thoracic Society/European Respiratory Society standards (Miller et al, 2005) using NHANES III predicted values (Hankinson et al, 1999). Tests were assessed for adequacy by a different, external, blinded, pulmonologist rater; tests were judged adequate if there were a minimum of 3 acceptable forced vital capacity (FVC) maneuvers (ie, flow-volume loops). Repeatability criteria were used to determine when more than 3 acceptable FVC maneuvers were required but were not used to exclude results. For each test, the largest FVC and the largest FEV_1 were recorded from among the acceptable FVC maneuvers. Spirometers were calibrated daily.

Baseline spirometry measurements were documented in the hour before the first dose of each treatment period (ie, same-period baseline). In the study in healthy subjects, 2 doses of study medication were administered 8 hours apart, and in the asthma and COPD studies, 2 doses were administered 10 hours apart (based on the well known sedative effects of antipsychotics in healthy volunteers). Post-treatment assessments were performed at specified time points through 24 hours after Dose 2 (including just before Dose 2).

(The first Phase 1 safety and pharmacokinetic study also included spirometry testing, but only at baseline, 2 hours, and 6 hours after dosing. No trends were observed, and there were no airway AEs in the study.)

9.2 Overview of Pulmonary Safety in the ADASUVE Clinical Program

The subjects evaluated for pulmonary safety in the clinical development program fall into 2 categories (Table 15): those who, in accordance with study exclusion criteria, did not have active airways disease, and those who had currently treated asthma or COPD and were enrolled in spirometry-based safety studies. Among the 1,095 patients without active airways disease who were treated with ADASUVE, most were the agitated patients in the Phase 2 and Phase 3 studies, and most of these patients were smokers. The other subjects without active airways disease were healthy volunteers and other subjects in the overall safety population.

In ADASUVE-treated subjects without active airways disease, the incidence of airway-related AEs was very low. Furthermore, all airway AEs in these subjects were of mild or moderate severity, none was judged to be a serious AE, and only 1 of the 1095 subjects (0.1%) experienced an airway AE that required intervention—bronchospasm that resolved after 2 puffs of albuterol via MDI. Cough was the most common airway AE in these ADASUVE-treated subjects (19/1095, 1.7%), and these events were all rated as mild (18) or moderate (1) and were self-limiting.

Table 15. All Airway AEs in the ADASUVE Clinical Studies

Analysis Population	Rx	N	Cough	Chest Tightness or Discomfort	Dyspnea	Bronchospasm	Wheezing	Other
Subjects without Active Airways Disease								
Agitated patients	P	263	0	0	0	0	0	0
	A	524	1	0	0	1	2	0
Stable schizophrenia	P	8	0	0	0	0	0	0
	A	24	3	0	0	0	0	0
Healthy volunteers	P	90	2	0	0	0	0	0
	A	177	13	0	0	0	0	0
Migraine	P	164	2	0	0	0	0	0
	A	370	2	1	2	0	0	0
Total	**P**	**525**	**4 (0.8%)**	**0**	**0**	**0**	**0**	**0**
	A	**1095**	**19 (1.7%)**	**1 (0.1%)**	**2 (0.2%)**	**1 (0.1%)**	**2 (0.2%)**	**0**
Subjects with Active Airways Disease (Phase 1 Pulmonary Safety Studies)								
Asthma	P	26	0	2	0	1	0	0
	A	26	1	6	3	7	4	2[1]
COPD	P	27	1	0	1	1	0	0
	A	26	3	0	3	0	2	2[2]
Total	**P**	**53**	**1 (1.9%)**	**2 (3.8%)**	**1 (1.9%)**	**2 (3.8%)**	**0**	**0**
	A	**52**	**4 (7.7%)**	**6 (11.5%)**	**6 (11.5%)**	**7 (13.5%)**	**6 (11.5%)**	**4 (7.7%)**

A=ADASUVE; P=placebo; Rx=study medication
[1]Throat tightness (1), Forced expiratory volume decreased (1)
[2]Pulmonary congestion (1), Forced expiratory volume decreased (1)

Among ADASUVE-treated patients in the Phase 2/3 agitated patient population, there were only 4 airway AEs. All were mild or moderate, none was judged to be a serious AE, and only

one required intervention (the use of albuterol cited above), which led to resolution. In patients in the migraine program, there were 3 airway AEs, all of which were self-limiting: 2 instances of dyspnea (1 mild, 1 moderate) and 1 instance of mild chest tightness.

The pulmonary safety study conducted in healthy volunteers provides further confirmation of safety in subjects without active airways disease. An intensive regimen of serial spirometry testing confirmed that ADASUVE had no effect on airway function, and there were no airway AEs.

In contrast to these findings in subjects without airways disease, ADASUVE treatment resulted in more airway AEs in subjects with asthma or COPD (Table 15), as well as changes in measures of pulmonary function. Airway AEs were common in subjects with mild-to-moderate persistent asthma (53.8% after ADASUVE, 11.5% after placebo), and less common in subjects with mainly moderate-to-severe COPD (19.2% after ADASUVE, 11.1% after placebo). As described Section 9.5.3, the airway AEs were consistent with an irritant effect of the inhaled aerosol (ie, bronchospasm) that occurs shortly after dosing and responds to a standard dose of a bronchodilator (albuterol) without clinical sequelae.

The pulmonary safety studies have thus identified a population of patients who are not suitable for treatment with ADASUVE due to a risk of bronchospasm, ie, those who are taking medications to treat asthma or COPD, and, by extension, those with acute respiratory signs/symptoms such as wheezing. The sponsor proposes that mitigating the risk of bronchospasm in clinical practice (in part by excluding this patient population) can be accomplished via product labeling and a REMS program (see Section 10).

Details of the relevant information that characterizes the incidence and nature of bronchospasm in the Phase 2/3 agitated patient population and in subjects in the Phase 1 pulmonary safety studies are provided in Sections 9.3, 9.4, and 9.5.

9.3 Phase 2/3 Agitated Patient Population

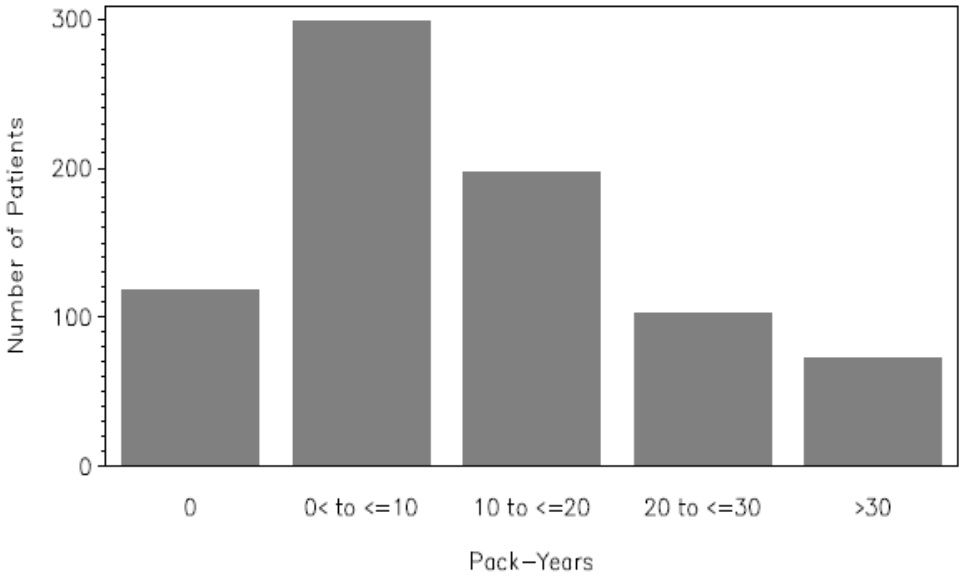
9.3.1 Smoking and Pulmonary Disease History

A high percentage of patients in the Phase 2/3 agitated patient population (86.7%) were current or ex-smokers (Table 16), with 22.1% (174/787) of the Phase 2/3 agitated patient population having ≥20 pack-years of cigarette use (Figure 28). (Pack-years is defined as average number of packs per day multiplied by years of smoking; eg, 1 pack per day for 20 years or 2 packs per day for 10 years). Considering the Phase 3 studies only, the percentage of subjects who were current or ex-smokers was 86.2% (567/658).

Table 16. Smoking History (Phase 2/3 Agitated Patient Population)

Smoking History, n (%)	Agitated Patient Population			
	Study 004-201 Schizophrenia (N=129)	Study 004-301 Schizophrenia (N=344)	Study 004-302 Bipolar I Disorder (N=314)	Overall (N=787)
Never smoked	14 (10.9%)	36 (10.5%)	55 (17.5%)	105 (13.3%)
Current smoker	106 (82.2%)	281 (81.7%)	234 (74.5%)	621 (78.9%)
Ex-smoker	9 (7.0%)	27 (7.8%)	25 (8.0%)	61 (7.8%)

Figure 28. Smoking History in Pack-Years (Phase 2/3 Agitated Patient Population)



Patients were excluded from these studies if they had current clinically significant or clinically apparent pulmonary disease. The medical histories of the patients enrolled in the Phase 2 and 3 clinical studies reveal that 90 of them had a history of respiratory illness or disease (and reported a total of 103 respiratory illnesses or diseases). Of these 90 patients, 52 had a history of asthma and/or COPD (deemed not disqualifying by the investigator), with 17 of them receiving placebo treatment and the remaining 35 receiving at least 1 dose of ADASUVE. Considering the Phase 3 studies only, the percentage of patients with a medical history of asthma or COPD was 6.1% (40/658).

9.3.2 Pulmonary Safety Results

Safety data for agitated patients from the Phase 2 and 3 clinical studies indicate a very low risk of bronchospasm in this population. In a total of 524 patients who received 756 doses of ADASUVE in these studies, 4 events related to bronchospasm were reported (Table 17). None occurred in patients with a medical history of asthma or COPD. Of the 4 events, 3 were considered by the investigator to be possibly or probably related to treatment and 1 was judged unrelated. Therefore, the rate of occurrence of airway AEs judged by the investigator

to be related to ADASUVE in the Phase 2/3 agitated patient population was 3/756 exposures (0.4%).

These 4 airway AEs were as follows. There was 1 AE of bronchospasm (ADASUVE 10 mg), which was judged by the investigator to be moderate and probably treatment related, and resolved with 2 puffs of albuterol via MDI. There were 2 AEs of mild wheezing, both of which were temporally unrelated to treatment (ie, occurred the next day) and resolved without intervention: 1 was judged to be probably treatment related (ADASUVE 5 mg) by the investigator and the other was judged to be unrelated to treatment (ADASUVE 5 mg). There was 1 AE of a mild intermittent cough that was judged possibly treatment related by the investigator and resolved without intervention (ADASUVE 10 mg).

Table 17. Airway AEs Related to Bronchospasm (Phase 2/3 Agitated Patient Population)

Airway Adverse Event* MedDRA Preferred Term, n (%)	Placebo (N=263)	ADASUVE Dose		All ADASUVE (N=524)
		5 mg (N=265)	10 mg (N=259)	
Wheezing	0 (0.0%)	2 (0.8%)	0 (0.0%)	2 (0.4%)
Bronchospasm	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Cough	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)

*Airway AEs include bronchospasm, dyspnea, wheezing, chest discomfort, and cough

There was no evidence for additional risk of an airway-related AE following a second or third dose of ADASUVE.

Among patients with pulmonary risk factors in the Phase 2/3 agitated patient population, the pulmonary safety outcomes were as follows:

- Overall, 86.7% of the agitated patients were current or ex-smokers and 22.1% had ≥20 pack years of cigarette use. Based on this smoking history, it is reasonable to conclude that some patients had a degree of respiratory impairment at baseline. It is notable that none of the patients with a ≥20 pack-year history of cigarette use had an airway AE. Therefore, smoking per se (even heavy smoking) did not appear to confer a significant risk of an airway AE.

- Patients were excluded from these studies if they had clinically significant or clinically apparent pulmonary disease. Review of the medical histories for enrolled patients identified 52 patients (7%) who had a history of asthma or COPD, of whom 35 received at least 1 dose of ADASUVE. None of the 35 patients with a medical history of asthma or COPD who received ADASUVE had an airway AE and none required intervention with a bronchodilator following dosing with ADASUVE.

In summary, the AE profile in this population of agitated patients, a majority of whom were smokers, demonstrates a very low risk of bronchospasm-related AEs. These studies excluded patients considered at screening to have to clinically active airways disease (11 total;

10 patients with asthma and 1 patient with emphysema). Therefore, this population represents, from a pulmonary safety standpoint, the patients most likely to be treated with ADASUVE with the proposed REMS program in place (see Section 10).

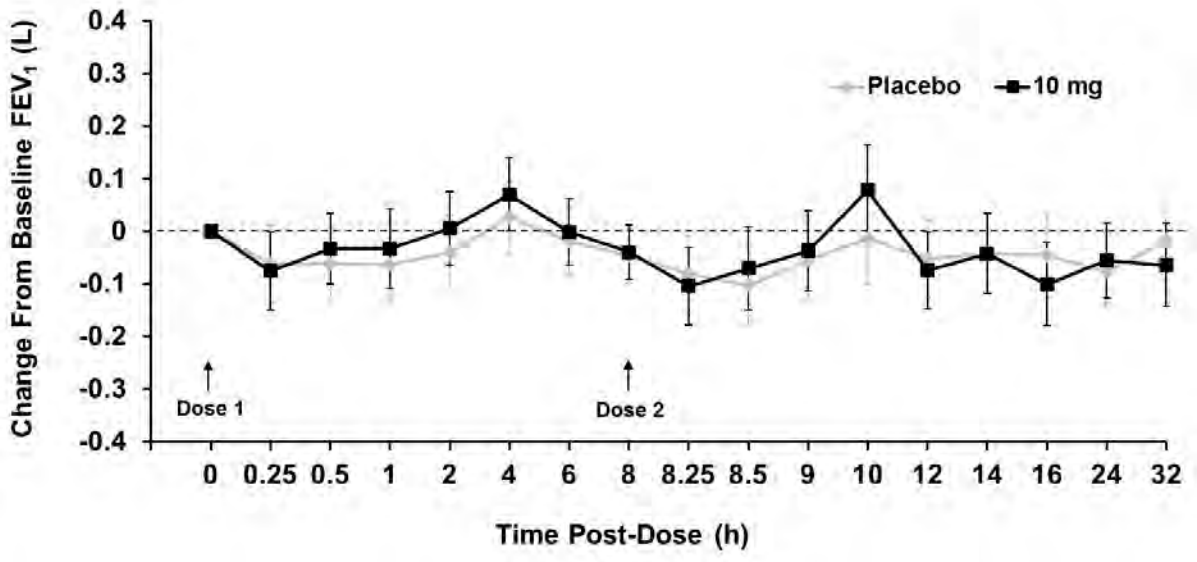
9.4 Phase 1 Study in Healthy Subjects

The pulmonary safety of ADASUVE 10 mg was evaluated in a placebo-controlled, 2-period crossover study of 30 nonsmoking healthy subjects with normal lung function and no history of airways disease. In each period, 2 doses of study medication were administered, with 8 hours separating the doses. Safety was assessed by serial spirometry testing (16 post-treatment assessment times in each 32-hour observation period), AEs, vital signs, sedation (measured by VAS), and oxygen saturation by pulse oximetry. The primary safety measure was FEV_1. Comparison of FEV_1 to the total volume exhaled (forced vital capacity, FVC) served as an additional measure of airway patency (see below).

Baseline FEV_1 was similar before administration of ADASUVE and placebo. The FEV_1 was 4.01 L (3.72, 4.30) before Dose 1 of ADASUVE, and 4.07 L (3.78, 4.36) before Dose 1 of placebo [LSmean (90% LSmean CI)].

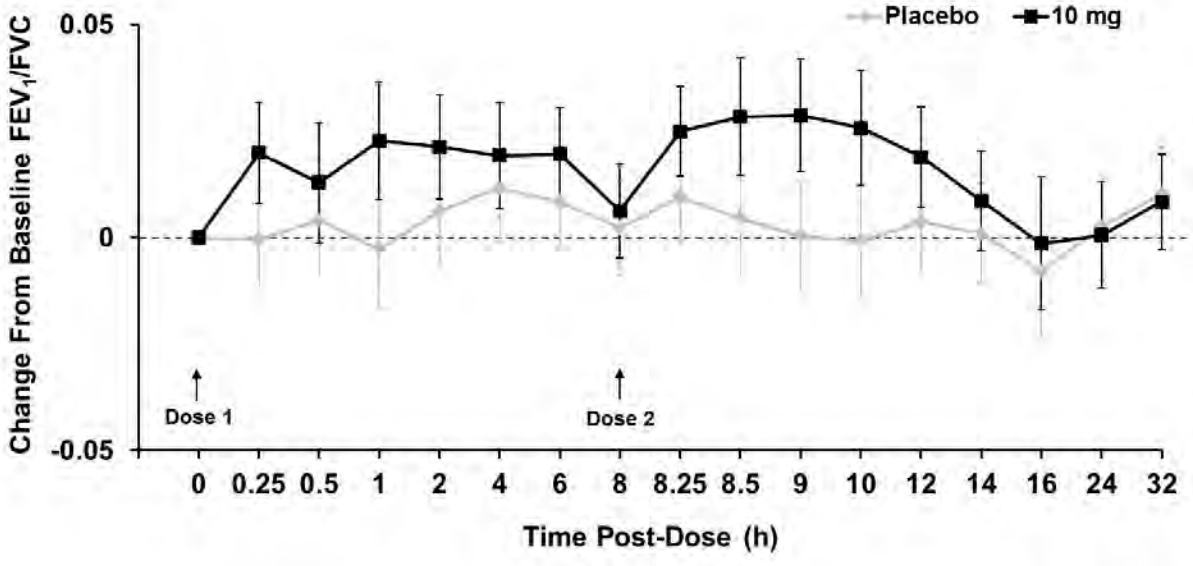
The group mean changes from same-period baseline FEV_1 were similar over the 16 assessment times in the 32-hour observation period after ADASUVE and placebo treatment (Figure 29). No systematic changes from same-period baseline in FEV_1 were observed with either treatment. The largest change in FEV_1 following ADASUVE treatment was -0.104 L (-0.178, -0.031) [LSmean (90% LSmean CI)], which occurred 8.25 hours after the first dose (ie, 0.25 hours after the second dose). The largest change following placebo treatment was -0.103 L (-0.181, -0.024) [LSmean (90% LSmean CI)], which occurred 8.5 hours after the first dose (ie, 0.5 hours after the second dose).

Figure 29. FEV_1 Change from Same-Period Baseline in Healthy Subjects



A possibility of suboptimal testing effort during the series of spirometry tests was indicated by the group data for the FEV_1/FVC ratio. LSmean FEV_1/FVC increased from same-period baseline at 15 of the 16 assessment times after ADASUVE treatment (as well as at 12 of the 16 assessment times after placebo treatment) as seen in Figure 30. This finding is inconsistent with an obstructive defect, which typically causes a *decrease* in flow (FEV_1) out of proportion to the accompanying decrease in exhaled volume (FVC), and therefore, a decrease in the FEV_1/FVC ratio (Pellegrino et al, 2005). There is no biologic process that results in a rise in FEV_1/FVC, but an increase in FEV_1/FVC is seen with decreased effort at the end of exhalation (eg, with sedation or testing fatigue). The increases in FEV_1/FVC were larger after ADASUVE treatment than after placebo treatment, particularly after Dose 2.

Figure 30. FEV_1/FVC Change from Same-Period Baseline in Healthy Subjects



Individual FEV_1 decreases from baseline of ≥10% were observed after both ADASUVE (n=7) and placebo (n=7). Both the sponsor's review and an independent expert review of the spirometry tests found no evidence for new treatment-related obstructive defects on spirometry tracings in these individuals with decreases in $FEV_1 \geq 10\%$. However, both reviews identified a number of subjects with evidence for suboptimal testing effort. Additionally, no respiratory AEs or significant changes in respiratory rate or O_2 saturation were observed.

In summary, analysis of all the safety data following administration of ADASUVE in this study, including a blinded independent assessment of the spirometry tracings for the 14 subjects with FEV_1 decreases ≥10% at any time, did not demonstrate treatment-related bronchospasm. Instead, the results suggested that the categorical decreases in FEV_1 are most likely attributable to variations in testing effort.

9.5 Studies in Subjects with Asthma or COPD

The pulmonary safety of ADASUVE 10 mg was further evaluated in 2 placebo-controlled, parallel-group studies in subjects with airways disease and without agitation: a study in 52 subjects with mild or moderate persistent asthma by National Heart, Lung, and Blood Institute criteria, and a study in 53 subjects with COPD, most of whom had moderate or severe disease by Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (Table 18). Approximately two-thirds of the asthma subjects had a screening FEV_1 in the *well-controlled* category (FEV_1 ≥80% of predicted); one-third of the subjects had a screening FEV_1 in the *not well controlled* category (FEV_1<80% of predicted). Approximately 88% of the COPD subjects were in the moderate to severe category by FEV_1.

Table 18. Phase 1 Asthma and COPD Population: Severity at Screening

Asthma Study	**N=52**
Screening pre-bronchodilator FEV_1 (% of predicted): Median (range)	85.5% (60.0%-117.0%)
Asthma classification at screening, n (%)	
FEV_1 in the well controlled category (FEV_1 ≥80% of predicted)	34 (65.4%)
FEV_1 in the not well controlled category (FEV_1 <80% of predicted)	18 (34.6%)
COPD Study	**N=53**
Screening post-bronchodilator FEV_1 (% of predicted): Median (range)	55.0% (40.0%-96.0%)
COPD severity at screening (GOLD criteria), n (%)	
Mild (FEV_1 ≥80% of predicted and FEV_1/FVC ≤0.7)	6 (11.3%)
Moderate (FEV_1 50% to <80% of predicted)	30 (56.6%)
Severe (FEV_1 30% to <50% of predicted)	17 (32.1%)

GOLD= Global Initiative for Chronic Obstructive Lung Disease

In each study, 2 doses of study medication were administered, with 10 hours separating the doses. Safety was assessed by serial spirometry testing (15 post-treatment assessment times in each 34-hour observation period), AEs, vital signs, sedation (measured by VAS), and pulse oximetry. Controller medications were continued throughout the study, but quick-relief bronchodilators were withheld for a span of 40 hours (6 hours before Dose 1 through 34 hours after Dose 1), except if required as rescue treatment, as determined by investigator clinical judgment.

9.5.1 Asthma

9.5.1.1 Spirometry Findings

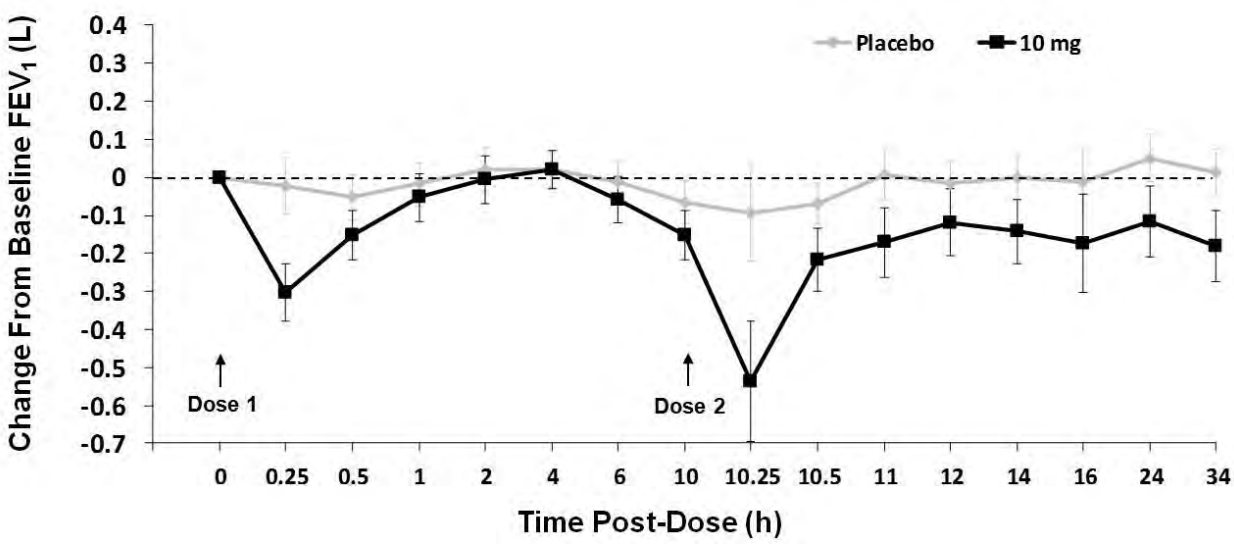
Baseline FEV_1 values were similar before administration of placebo and ADASUVE. FEV_1 was 3.33 ± 0.74 L before Dose 1 of placebo, and 2.92 ± 0.69 L before Dose 1 of ADASUVE (mean ± SD).

After placebo treatment (Figure 31), there were no systematic changes from baseline in LSmean FEV_1, and the largest change from baseline was -0.093 L (-0.221, 0.035) [LSmean

(90% LSmean CI)] at 10.25 hours after Dose 1. (Note: in order to avoid bias in the data toward a return to baseline, subjects who used rescue medication and/or did not receive Dose 2 at Hour 10 were excluded from the spirometry population at all subsequent time points [ie, after rescue for those who received rescue; after Hour 10 for those who did not receive Dose 2]; consequently, the population size represented on the figure decreases over time.)

After ADASUVE treatment, there were notable decreases in LSmean FEV_1, especially at the 0.25- and 10.25-hour time points (ie, 15 minutes after the administration of Dose 1 and Dose 2, respectively). These decreases were short-lived and the LSmean returned quickly toward baseline. The decreases in LSmean FEV_1 were larger after Dose 2 than after Dose 1, and beyond the 10.25-h time point, there was a small (approximately 200 mL) difference between the treatment groups for those subjects remaining in the analysis. However, in 24 of the 26 ADASUVE-treated subjects, FEV_1 was within 10% of baseline at 24 hours, and in the remaining 2 subjects it was within 10% of baseline at 34 hours. The intensive nature of the spirometry testing (15 post-treatment spirometry sessions in subjects with compromised pulmonary function) and the half-life of the (sedative) drug (mean half-life of about 7 hours) are potentially confounding factors in interpretation of the Dose 2 effects.

Figure 31. FEV_1 Change from Baseline in the Phase 1 Asthma Study



Note: As shown in the time chart below, the number of subjects represented in this figure decreases from left to right because subjects who received rescue medication, and/or did not receive Dose 2 at Hour 10, were excluded from the spirometry population at all subsequent time points.

Time (h):	0	0.25	0.5	1	2	4	6	10	10.25	10.5	11	12	14	16	24	34
No. Placebo	26	26	26	26	25	25	25	25	24	24	21	23	23	23	23	23
No. 10 mg:	26	26	22	22	22	21	20	20	17	12	12	12	12	12	11	10

In asthma subjects, decreases from baseline FEV_1 of ≥10%, ≥15%, and ≥20% occurred much more frequently in ADASUVE subjects than placebo subjects (Table 19). The maximum change from baseline FEV_1 occurred within the first 1 hour after dosing (either Dose 1 or Dose 2) in 16 of 22 ADASUVE subjects with a ≥10% decrease in FEV_1.

Table 19. Maximum FEV_1 Decrease from Baseline at Any Assessment − Decreases of ≥10%, ≥15%, or ≥20% in the Phase 1 Asthma Study

Maximum FEV_1 Decrease[a]	Placebo (N=26)	ADASUVE (N=26)
≥10%	3 (11.5%)	22 (84.6%)
≥15%	1 (3.8%)	16 (61.5%)
≥20%	1 (3.8%)	11 (42.3%)

Table presents number (%) of subjects with indicated percentage decrease.

a. FEV_1 categories are cumulative (eg, a subject with a maximum decrease of 21% would be included in the ≥10%, ≥15%, and ≥20% categories)

9.5.1.2 Airway Adverse Events

Bronchospasm (which encompasses several specific events, including wheezing, dyspnea, and cough) occurred in 14 (53.8%) subjects after ADASUVE and in 3 (11.5%) subjects after placebo (Table 20). In 12 of the 14 ADASUVE subjects who experienced bronchospasm, the event occurred within 25 minutes of dosing. Bronchospasm was mild or moderate in severity and was not associated with clinically significant changes in respiratory rate or oxygen saturation. All respiratory symptoms developing after treatment were either self-limiting (1 subject) or treated (13 subjects) with an inhaled bronchodilator (albuterol).

Table 20. Airway AEs in the Phase 1 Asthma Study

Adverse Event, n (%)	Placebo (N=26)	ADASUVE (N=26)
No. (%) of subjects with any airway AE	3 (11.5%)	14 (53.8%)
Bronchospasm	1 (3.8%)	7 (26.9%)
Chest discomfort	2 (7.7%)	6 (23.1%)
Wheezing	0	4 (15.4%)
Dyspnea	0	3 (11.5%)
Cough	0	1 (3.8%)
Throat tightness	0	1 (3.8%)
Forced expiratory volume decreased	0	1 (3.8%)

Note: All AEs presented in this study report were treatment emergent. Subjects with more than 1 occurrence of a specific AE are counted only once.

Albuterol was used by a total of 14 (53.8%) asthma subjects after ADASUVE treatment (13 with bronchospasm, 1 without an airway AE) compared with 3 subjects (11.5%) after placebo. In ADASUVE subjects who received albuterol for bronchospasm, 9 of 13 (69.2%)

had a documented return of their FEV_1 to within 10% of baseline in the subsequent 1 hour time period; the remainder had documented recovery to within 10% of baseline at later, scheduled spirometry evaluation time points.

More information about these subjects who received albuterol is provided in Section 9.5.3.

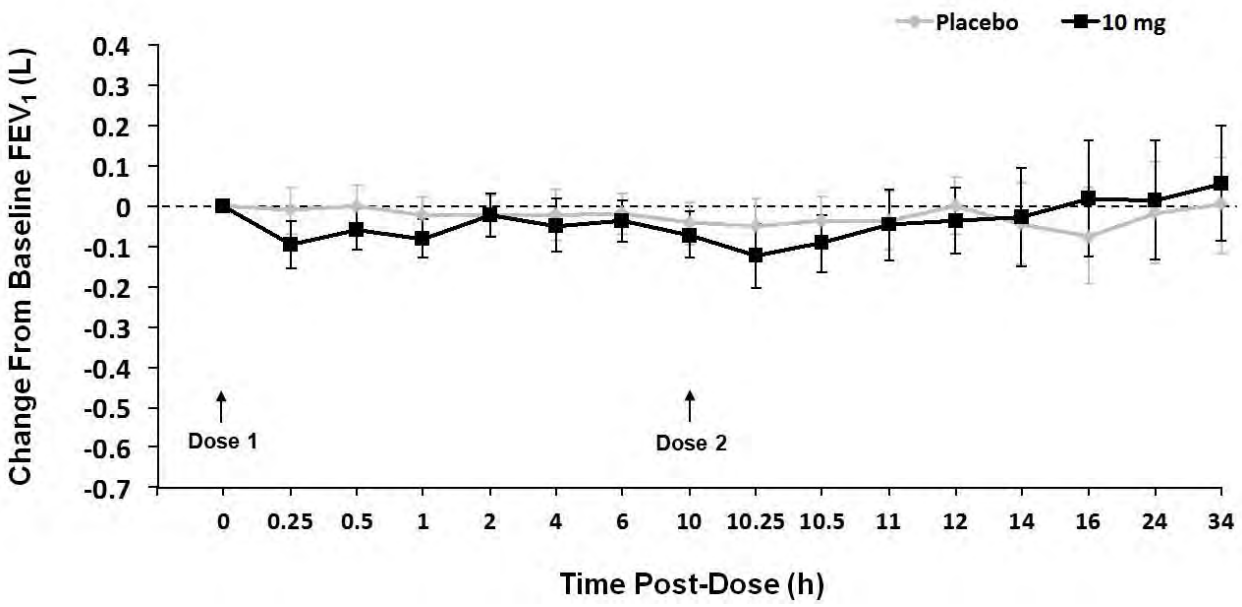
9.5.2 COPD

9.5.2.1 Spirometry Findings

Baseline FEV_1 was similar before administration of placebo and ADASUVE. The FEV_1 was 1.603 ± 0.588 L before placebo treatment, and 1.551 ± 0.411 L before ADASUVE treatment (mean ± SD).

There were very small decreases from baseline in the LSmean FEV_1 at most assessment times after placebo or ADASUVE treatment, with a slightly larger decrease after ADASUVE treatment (Figure 32). The difference, while small, was most noticeable in the hour after each dose. The largest change following placebo treatment was -0.077 L (-0.195, 0.042), which occurred at a late-night assessment, 16 hours after Dose 1 (ie, 6 hours after Dose 2) [LSmean (90% LSmean CI)]. The largest change from baseline FEV_1 following ADASUVE treatment was -0.125 L (-0.204, -0.045), which occurred 10.25 hours after Dose 1 (ie, 0.25 hours after Dose 2) [LSmean (90% LSmean CI)].

Figure 32. FEV_1 Change from Baseline in the Phase 1 COPD Study



Note: As shown in the time chart below, the number of subjects represented in this figure decreases from left to right because subjects who received rescue medication, and/or did not receive Dose 2 at Hour 10, were excluded from the spirometry population at all subsequent time points.

Time (h):	0	0.25	0.5	1	2	4	6	10	10.25	10.5	11	12	14	16	24	34
No. Placebo	27	27	27	27	27	26	25	25	25	25	25	25	25	24	23	23
No. 10 mg:	25	25	24	24	24	24	23	23	19	18	17	18	17	16	16	15

In these COPD subjects, decreases from baseline FEV_1 of ≥10%, ≥15%, and ≥20% were more common in ADASUVE subjects than placebo subjects (Table 21). The maximum change from baseline FEV_1 occurred within the first 1 hour after dosing (either Dose 1 or Dose 2) in 12 of 21 ADASUVE subjects with a ≥10% decrease in FEV_1.

Table 21. Maximum FEV_1 Decrease from Baseline at Any Assessment – Decreases of at Least 10%, 15%, or 20% in the Phase 1 COPD Study

Maximum FEV_1 Decrease[a]	Placebo (N=27)	ADASUVE (N=25)
≥10%	18 (66.7%)	20 (80.0%)
≥15%	9 (33.3%)	14 (56.0%)
≥20%	3 (11.1%)	10 (38.5%)

Table presents number (%) of subjects with indicated percentage decrease.
a. FEV_1 categories are cumulative (eg, a subject with a maximum decrease of 21% would be included in the ≥10%, ≥15%, and ≥20% categories)

9.5.2.2 Airway Adverse Events

Bronchospasm-associated events occurred in 5 (19.2%) subjects after ADASUVE and in 3 (11.1%) subjects after placebo (Table 22). In 4 of the 5 ADASUVE subjects, bronchospasm occurred within 25 minutes of dosing. Bronchospasm was mild or moderate in severity, and was not associated with clinically significant changes in respiratory rate or oxygen saturation. All respiratory symptoms developing after treatment were either self-limiting (3 subjects) or treated (2 subjects) with an inhaled bronchodilator.

Table 22. Airway AEs in the Phase 1 COPD Study

Adverse Event, n (%)	Placebo (N=27)	ADASUVE (N=26)
No. (%) of subjects with any airway AE	3 (11.1%)	5 (19.2%)
Dyspnea	1 (3.7%)	3 (11.5%)
Cough	0	3 (11.5%)
Wheezing	0	2 (7.7%)
Forced expiratory volume decreased[a]	0	1 (3.8%)
Pulmonary congestion	0	1 (3.8%)
Bronchospasm	1 (3.7%)	0
Productive cough	1 (3.7%)	0

Note: All AEs presented in this study report were treatment emergent. Subjects with more than 1 occurrence of a specific AE are counted only once.
a. For Subject 05-033, the investigator reported a "greater than 20% drop in FEV_1 from baseline" as an AE; there were no other airway AEs for this subject.

Albuterol was used by a total of 6 (23.1%) COPD subjects (7 total uses) after ADASUVE treatment compared with 4 subjects (14.8%) after placebo. In 4 of the 7 (57.1%) uses of albuterol by ADASUVE -treated subjects, a return of FEV_1 return to within 10% of baseline was documented in the subsequent 1 hour time period, and in the remainder, recovery to within 10% of baseline was documented at later, scheduled spirometry evaluation time points.

More information about these subjects who received albuterol is provided in Section 9.5.3.

9.5.3 Response to Albuterol Treatment in Patients with Notable Respiratory Signs and Symptoms

In both the asthma and COPD pulmonary safety studies, notable respiratory signs or symptoms were defined as any FEV_1 decrease from baseline of ≥20%, an airway AE, or use of rescue medication. Eighteen (69.2%) of the ADASUVE-treated subjects with asthma and 15 (57.7%) of the ADASUVE-treated subjects with COPD had notable respiratory signs and/or symptoms. Relief of post-treatment respiratory symptoms in both asthma and COPD subjects required only treatment with albuterol.

In the Phase 1 asthma study, 14 of the ADASUVE-treated subjects were treated with albuterol, 13 of them for airway-related AEs. Three of the 18 subjects with a notable respiratory sign and/or symptom had a ≥20% decrease in FEV_1 but were not treated with albuterol. Of the 14 ADASUVE-treated asthma subjects who received rescue medication, 11 received only 1 treatment from an MDI, which is a standard prn treatment for such patients at home. The others received albuterol via nebulizer +/- MDI.

In the Phase 1 COPD study, only 6 ADASUVE-treated subjects were treated with albuterol-3 of them for airway-related AEs and 2 for a decrease in FEV_1. Nine subjects (almost two-thirds of the 15 subjects) with notable respiratory signs and symptoms did not require albuterol treatment. Of the 6 subjects treated with albuterol, 5 (83%) received only 1 treatment from a MDI. The other received albuterol via a nebulizer.

In the ADASUVE-treated subjects who received albuterol in both studies, there was a prompt FEV_1 response to rescue medication.

In the Phase 1 asthma study, 10 of 14 subjects who received albuterol had an FEV_1 within 10% of baseline documented in the subsequent 1 hour. The other 4 had recovery to within 10% of baseline documented at later scheduled spirometry time points (Table 23). Of the latter 4, 2 (subjects M and N) had airway AEs that began 6-12 hours after dosing (and were therefore scored as unrelated to treatment), and 2 (subjects E and K) had steady improvements with each follow-up test, and no evidence of respiratory distress (all respiratory rates were ≤20 and O_2 saturations ≥93%).

Table 23. Phase 1 Asthma Study: Time from Rescue to Return of FEV_1 to within 10% of Baseline

Subject	Reason for Albuterol Use	Albuterol Rescue	Last FEV_1 Before Rescue (change from baseline)	Post-rescue FEV_1[a] (change from baseline)
A	Increase in asthma	MDI	–21.7% at 3 min pre-rescue	–8.0% at 12 min post-rescue
B	Increased asthma symptoms	MDI	–22.9% at 5 min pre-rescue	–7.4% at 30 min post-rescue
C	Increased asthma	MDI	–10.3% at 1 min pre-rescue	–18.5% at 14 min post-rescue –7.5% at 28 min post-rescue
D	Bronchospasm	MDI	–21.7% at 4 min pre-rescue	+1.4% at 9 min post-rescue
E	1 AE of bronchospasm	MDI MDI Nebulizer	–31.0% at 2 min pre-rescue #1	–19.5% at 13 min post-rescue #1 –13.5% at 1 h 43 min post-rescue #1[b] –3.3% at 3 h 39 min post-rescue #1[b]
F	Asthma	MDI	–36.8% at 5 min pre-rescue	–13.0% at 11 min post-rescue +0.5% at 40 min post-rescue
G	Asthma	MDI	–25.0% at 3 min pre-rescue	+3.2% at 11 min post-rescue
H	Chest tightness	MDI	–3.0% at 20 min pre-rescue	+0.4% at 32 min post-rescue
I	Wheezing FEV_1 reduced 23%	Nebulizer	–19.3% at 7 min pre-rescue	+3.0% at 19 min post-rescue
J	Cough	MDI	+9.1% at 14 min pre-rescue	+8.1% at 7 min post-rescue
K	Wheezing shortness of breath	Nebulizer	–50.2% at 1 min pre-rescue	–14.1% at 8 min post-rescue –13.5% at 31 min post-rescue +0.9% at 1 h 20 min post-rescue[b]
L	Wheezing	Nebulizer	–31.8% at 3 min pre-rescue	+2.3% at 23 min post-rescue
	Tight chest shortness of breath	MDI	–8.7% at 9 min pre-rescue	+16.1% at 6 min post-rescue
M	Chest tightness	MDI	–18.0% at 3 min pre-rescue	–6.3% at 7 h 57 min post-rescue
N	Bronchoconstriction	MDI	–12.4% at 7 min pre-rescue	–9.4% at 1 h 53 min post-rescue[b]

AE=adverse event; MDI=metered-dose inhaler

a. Data obtained after FEV_1 returned to within 10% of baseline are not in this table.

b. Unscheduled spirometry test(s) should have preceded this test and were not done (ie, if FEV_1 decreased from baseline by ≥20% or there was AE of wheezing, dyspnea, or bronchospasm, repeat spirometry was to be performed every 30 minutes—for a maximum of 2 hours—until FEV_1 returned to within 10% of baseline)

In the Phase 1 COPD study, in 4 of the 7 instances (in 6 ADASUVE-treated subjects) in which albuterol was administered, subjects had an FEV_1 within 10% of baseline documented in the subsequent 1 hour. In the 3 remaining instances recovery to within 10% of baseline or higher was documented at later scheduled spirometry time points (Table 24). In the latter 3 instances, subjects had airway AEs (subjects Q and R) or received albuterol (subject P) several hours after dosing (3, 24 and 6h, respectively). The AEs were scored as unrelated to treatment by the investigator.

Table 24. Phase 1 COPD Study: Time from Rescue to Return of FEV_1 to within 10% of Baseline

Subject	Reason for Albuterol Use	Albuterol Rescue	Last FEV_1 Before Rescue (change from baseline)	Post-rescue FEV_1[a] (change from baseline)
P	Shortness of breath due to COPD	MDI	–17.7% at 1 h 59 min pre-rescue	–12.4% at 2 min post-rescue –11.8% at 7 h 58 min post-rescue +6.5% at 17 h 58 min post-rescue
Q	Shortness of breath due to COPD	MDI	–7.7% at 1 h 53 min pre-rescue	–16.7% at 8 min post-rescue –4.2% at 2 h 7 min post-rescue
R	Increased wheezing	MDI	pre-rescue test was the baseline test	–10.0% at 2 min post-rescue +0.9% at 18 min post-rescue
	Increased shortness of breath	MDI	–12.7% at 8 min pre-rescue	+22.7 at 9 h 40 min post-rescue[b]
S	FEV_1 drop	MDI	–46.1% at 4 min pre-rescue	–25.0% at 13 min post-rescue –2.6% at 43 min post-rescue
T	Decreased FEV_1	Nebulizer	–28.5% at 5 min pre-rescue	–0.9% at 51 min post-rescue[c]
U	COPD - 20% drop from baseline	MDI	–28.7% at 4 min pre-rescue	+2.1% at 35 min post-rescue

AE=adverse event; MDI=metered-dose inhaler

a. Data obtained after FEV_1 returned to within 10% of baseline are not in this table.

b. Unscheduled spirometry test(s) should have preceded this test and were not done (ie, if FEV_1 decreased from baseline by ≥20% or there was AE of wheezing, dyspnea, or bronchospasm, repeat spirometry and chest auscultation were to be performed every 30 minutes—for a maximum of 2 hours—until FEV_1 returned to within 10% of baseline)

c. This unscheduled spirometry test was 21 minutes late.

In summary, in both the asthma and COPD pulmonary safety studies, all respiratory signs and symptoms that required treatment were readily managed with inhaled albuterol. The susceptibility to airway AEs in subjects with active airways disease was thus well characterized. The AE data and FEV_1 results are consistent with an irritant effect of the inhaled drug that typically occurs shortly after dosing and responds to standard bronchodilator therapy without clinical sequelae.

9.6 Pulmonary Safety Conclusions

- The enrolled subjects in the ADASUVE clinical development program comprise two distinct populations vis a vis pulmonary safety: subjects without airways disease, and subjects with currently treated asthma or COPD who participated in spirometry-based pulmonary safety studies. Among the 1095 study subjects without airways disease, only 1 (0.09%) required treatment for post-treatment airway-related symptoms (ie, bronchospasm).

- In the agitated patient population, there was a very low rate of airway AEs (3 treatment-related events in 756 ADASUVE exposures [0.4% of exposures], among 524 patients), in which 6.7% of ADASUVE-treated patients had a history of asthma or COPD, and others were likely to have some degree of respiratory impairment due to a long history of cigarette smoking. There was no evidence for additional risk of an airway AE following a second or third dose of ADASUVE.

- Respiratory function was not adversely affected in normal healthy subjects given 2 doses of ADASUVE within a day in a Phase 1 study. A thorough examination of spirometry findings determined that there was no effect on airways; observed post-dose decreases in FEV_1 were not accompanied by symptoms or evidence for a new obstructive defect, and were suggestive of reduced testing effort, possibly related to testing fatigue (16 spirometry sessions in 32 hours) and/or sedative effects of ADASUVE.

- In contrast to these findings in subjects without airways disease, ADASUVE treatment resulted in more airway AEs in subjects with asthma or COPD, as well as changes in measures of pulmonary function:

    - Respiratory symptoms and/or changes in flow parameters (ie, FEV_1) were common in subjects with asthma after ADASUVE treatment, and were less common in subjects with COPD in Phase 1 studies. All airway AEs in these subjects were mild or moderate.

    - All respiratory signs or symptoms requiring treatment in the Phase 1 asthma and COPD studies were readily managed with an inhaled bronchodilator.

    - The susceptibility to airway AEs in subjects with active airways disease was well characterized. The AE data and FEV_1 results are consistent with an irritant effect of the inhaled drug that typically occurs shortly after dosing and responds to standard bronchodilator therapy without clinical sequelae.

    - In the asthma study, some subjects had a greater FEV_1 response (and required albuterol) after Dose 2. A small (~200 mL) sustained treatment difference in FEV_1 remained at the end of the evaluation period. The latter finding suggests a minor component of the airway effect that persists out to 24-h after dosing that is detectable with spirometry but doesn't manifest clinically. (Note: there was no such treatment difference in the healthy volunteers or COPD studies). All asthma

subjects' FEV_1 values returned to within 10% of baseline by the end of the evaluation period.

- The clinical development program confirms that the pulmonary safety profiles of subjects with and without active airways disease are notably different, which allowed development of a risk mitigation strategy based on screening for evidence of active airways disease. The clinical data demonstrate that a brief pulmonary assessment (ie, history and screening physical examination) allows successful selection of appropriate patients for ADASUVE treatment.

- The sponsor proposes that the risk of bronchospasm from ADASUVE treatment can be addressed via product labeling and a REMS program, as described in Section 10.

10 RISK MANAGEMENT

The goal of the risk management program is to mitigate the safety risk associated with bronchospasm related to ADASUVE treatment. In the clinical development program that included a comprehensive assessment of pulmonary safety in the Phase 1 asthma and COPD studies, the population of patients at risk for bronchospasm after treatment with ADASUVE was identified. Alexza is proposing a contraindication to exclude these patients from the population of patients to receive ADASUVE.

ADASUVE is contraindicated in patients with acute respiratory signs/symptoms (eg, wheezing) or who are taking medications to treat asthma or COPD.

The REMS program will identify and exclude those patients at risk for bronchospasm from receiving ADASUVE. In addition, knowing that not all patients who are at risk for bronchospasm will be identified for exclusion from treatment with ADASUVE in clinical practice, the proposed REMS program is designed to mitigate the risk of bronchospasm should it occur. The REMS comprises measures to help healthcare professionals monitor for bronchospasm and treat it as quickly as possible in a setting equipped to treat it. Specifically, the REMS includes a Medication Guide, Communication Plan, and an Element to Assure Safe Use (ensuring that ADASUVE is only available in enrolled healthcare facilities where there is ready access to a short-acting beta-agonist bronchodilator).

10.1 Background

In the Phase 3 studies, patients with clinically significant acute or chronic pulmonary disease (eg, clinically apparent asthma, chronic bronchitis, emphysema) were excluded from enrollment. The rate of treatment-related airway AEs was very low (0.4%) in this agitated patient population. The Phase 1 pulmonary safety studies identified the subset of patients who would be susceptible to bronchospasm following treatment with ADASUVE: patients with clinically active airways disease, including those who have acute respiratory signs/symptoms (eg, wheezing) or who are taking medications to treat their respiratory conditions.

Thus, in an effort to mitigate the risks associated with ADASUVE, the sponsor has developed the product labeling and a REMS with the goal of excluding those patients at risk for bronchospasm following ADASUVE treatment. The risk management program is designed to ensure that healthcare professionals identify and exclude such patients, detect bronchospasm promptly and, in the event that bronchospasm does occur, manage it as quickly as possible in a setting equipped to treat it. Specifically, the REMS includes a Medication Guide, Communication Plan, and an Element to Assure Safe Use that will ensure that ADASUVE is only available in enrolled healthcare facilities where there is ready access to a short-acting beta-agonist bronchodilator.

In addition, the REMS includes an observation period. For cases of bronchospasm in the clinical program, symptoms began within 25 minutes of treatment in the significant majority of cases. The sponsor proposes that an appropriately conservative, but not unduly

burdensome, goal is to have healthcare professionals observe patients for respiratory signs and symptoms for 1 hour after treatment.

Finally, to ensure that bronchospasm is managed appropriately if it occurs, the sponsor has designed the REMS with the goals of educating healthcare professionals about the importance of having access to a short-acting beta-agonist bronchodilator and limiting the use of the ADASUVE to facilities that attest to the ready access to a short-acting beta-agonist bronchodilator.

The proposed REMS relies on standard medical practices (for patient screening and observation) and logistically feasible processes (ie, enrollment of facilities). Therefore the proposed REMS should attain a high level of compliance while not creating an undue burden on the healthcare system.

The risk management program (comprised of labeling and REMS) will ensure that the risk of bronchospasm is mitigated in the clearly defined subpopulation and consequently, that the overall benefits of ADASUVE clearly outweigh its risks.

10.2 Goals of the REMS and Design Rationale

10.2.1 The Goals of the ADASUVE REMS Are to:

1. Inform healthcare professionals about how to mitigate the risk of bronchospasm associated with ADASUVE treatment by:
    - Identifying and selecting only appropriate patients for treatment.
    - Observing patients for respiratory signs and symptoms for 1 hour after each treatment.
    - Having a short-acting beta-agonist bronchodilator (eg, albuterol) readily accessible to manage bronchospasm if it occurs.
2. Ensure ADASUVE is available only in enrolled healthcare facilities where there is ready access to a short-acting beta-agonist bronchodilator.

To meet these goals, the sponsor proposes a multifaceted Communication Plan for healthcare professionals as part of the REMS that includes a Dear Healthcare Professional Letter, a Prescriber Brochure, a Safety Use Checklist, and an Education Program. The Communication Plan, in concert with the full Prescribing Information and its accompanying Medication Guide, will ensure that health care professionals are fully informed about how to avoid and mitigate the risk of bronchospasm associated with ADASUVE.

An Element to Assure Safe Use will ensure that ADASUVE is available only in enrolled healthcare facilities where there is ready access to a short-acting beta-agonist bronchodilator.

Each of the goals of the REMS is discussed in Sections 10.2.2.2, 10.2.2.3, and 10.2.2.4.

10.2.2 Design Rationale

10.2.2.1 Population at Risk for Developing Bronchospasm

Since the pulmonary safety studies with ADASUVE suggest that the treatment of active airways disease is an important predictor of bronchospasm in these patients, the sponsor sought to determine the extent of the patient population with schizophrenia or bipolar disorder in which ADASUVE might not be used. Through an assessment of insurance claims, the extent of the patient population with schizophrenia or bipolar disorder that also has active airways disease, and is therefore not appropriate for treatment with ADASUVE, was quantified.

The SDI database was searched to determine the prevalence of respiratory medication use in patients diagnosed with schizophrenia or bipolar disorder. SDI is a US longitudinal patient claims database using multi-payer transactional healthcare claims data, that covers 3 billion transactions per year (60% of the total US pharmacy claims universe) across multiple sources, including but not limited to pharmacies, payers, and hospital systems.

The query was designed to identify the concomitance between a primary ICD-9-coded diagnosis of either schizophrenia (ICD-9 295) or episodic mood disorders (ICD-9 296) and either 1) a respiratory diagnosis and / or 2) a prescription for a respiratory medication. The data are from a one-year period (Nov 2009 – Oct 2010) and were limited to patients 18 years or older. Starting with a set of patients with a primary diagnosis of schizophrenia or bipolar disorder, the concomitance for respiratory conditions was determined using a predefined list of respiratory conditions that could be associated with bronchospasm, including: COPD, bronchitis, asthma, wheezing and other related pulmonary conditions. The search looked for medications typically prescribed to treat asthma or COPD (eg, beta agonists, inhaled steroids, anticholinergics, inhaled steroids, and leukotriene antagonists) in these patients. The integrated data system used for this query included SDI's Dx Patient Claims Data based on 1 billion claims per year, and 860,000 practitioners per month, and SDI's Rx Retail Prescription Data based on over 1.4 billion prescriptions per year. The patient and prescription counts are raw data counts and are not projected to the universe of patients or prescriptions.

The result from this query indicated that 5.4% of patients with a primary diagnosis of either schizophrenia or episodic mood disorder, including bipolar disorder, had a prescription for at least 1 respiratory medication in the 12-month period evaluated (Table 25).

Table 25. Results of SDI Database Search

DIAGNOSED PATIENTS	TOTAL PATIENTS	% OF PATIENTS
Total Schizophrenia and Episodic Mood Disorder patients (ICD-9 295+296)	3,164,278	100%
Patients with concomitant respiratory medication (with or without concomitant respiratory diagnosis)	170,722	5.4%

In summary, the SDI database search indicates that approximately 5% of schizophrenia and bipolar disorder patients are actively being treated for asthma or COPD and therefore would not be appropriate patients for treatment with ADASUVE.

The medical literature (PubMed) over the last 10 years was also surveyed to determine the degree to which psychiatric patients have asthma or COPD. However, due to the variations in study designs and populations, it is not possible to determine a precise estimate of prevalence. Based on the literature review, the comorbidity of respiratory diseases in psychotic patients may be as high as 16% (Carney et al, 2006; Jones et al, 2004; Koran et al, 1989; Beyer et al, 2005; Goodwin et al, 2003; Olshaker et al, 1997).

Based on the insurance claims query and literature review, the sponsor estimates the risk of comorbidity of schizophrenia or bipolar disorder with active airways disease to be between 5% and 16%. The risk management program is designed to significantly reduce the risk of bronchospasm from the 5 – 16% of patients who may represent the at-risk population.

10.2.2.2 Identification and Selection of Appropriate Patients for Treatment: Excluding Patients with Clinically Active Airways Disease

The prescribing clinician's obligation to screen patients for active airways disease can be accomplished via medical history, medication history, and physical examination, all of which fall within current standards of care for the evaluation of patients presenting with an acute psychiatric illness.

The first message of the REMS informs of the risk of bronchospasm and instructs the healthcare provider to identify and select appropriate patients for treatment with ADASUVE. Specifically they will need to determine if the patient has active airways disease and/or is taking medications to treat such a condition. A reasonable and practical way to do so is through medical (including medication) history and physical examination, which is consistent with current medical practice in the proposed institutional treatment settings.

Medical screening assessments are routinely conducted as part of the evaluation of the acutely ill psychiatric patient. When a patient with an acute psychiatric illness presents to the emergency department, the emergency physician is responsible to "medically clear" the patient (Emembolu and Zun, 2010; Lukens et al, 2006). In all cases, and at a minimum, a basic medical history and physical examination are expected to be conducted on all patients including those with primarily psychiatric complaints. In many cases in the emergency room setting, the patient will already have a medical record or established history so that existence of any significant airways disease will be known. Additionally, consultation with emergency

room physicians confirms that patients who present to emergency rooms with agitation are frequently accompanied by family members. In a minority of cases, acutely agitated patients present with no medical history established from prior admissions and no accompanying family members. In this situation medical clearance procedures require that patients are adequately assessed to determine possible medical reasons for the agitation and medications they may be currently using, eg, an inhaler.

Identifying and selecting appropriate patients for treatment with ADASUVE can be appropriately and responsibly accomplished through the medical clearance process. The need to understand pulmonary history or status prior to administering ADASUVE is consistent with the existing standard practices of the physician during the evaluation of the acutely ill psychiatric patient. Moreover, if the patient has already been admitted to the hospital and needs treatment for agitation, the health care provider has access to medical records where the information might be obtained. The feasibility of excluding patients with a respiratory contraindication to ADASUVE treatment was demonstrated in the Phase 2 and 3 clinical trials, which successfully excluded patients with active airways disease, and experienced a very low rate of treatment-related airway AEs (3/756 [0.4%] exposures).

10.2.2.3 Observation of Patients for Respiratory Signs and Symptoms for 1 Hour After Each Treatment

The REMS anticipates the possibility that even with a medical screening program, some patients with active airways disease may receive ADASUVE. It should be noted that this will likely represent a small number of patients because, in addition to the anticipated effectiveness of the standard medical screening process, only about 5 – 16 % of patients with schizophrenia or bipolar disorder receive medication for respiratory conditions (Section 10.2.2.1). Assuming that this population represents the majority of patients at risk of bronchospasm, failing to medically screen will be a small percentage of a small number.

Through the communication and education aspect of the REMS, the healthcare provider is instructed to observe all patients for 1 hour after dosing with ADASUVE. As noted previously, a high percentage of the asthma and COPD subjects who experienced bronchospasm did so within the first 25 minutes after administration. Therefore, recommending a 1-hour observation period following each treatment appears suitable for detection of an airway AE, if it were to occur. Physicians who regularly treat agitation note that policies are in place that require monitoring and assessment of treated agitated patients for a period of time for both medical and psychiatric reasons. Therefore, this component of the REMS is also readily accomplished because it is consistent with established medical practices.

10.2.2.4 Ready Access to a Short-Acting Beta-Agonist Bronchodilator

Albuterol was effective when it was administered to patients with bronchospasm in the clinical program and no patients required additional therapy. Through the communication component of the REMS, healthcare providers will be advised of the ability of a short-acting beta agonist bronchodilator like albuterol to resolve bronchospasm and the need to have it accessible if bronchospasm occurs following treatment with ADASUVE.

The proposed ADASUVE REMS also includes an Element to Assure Safe Use under 505-1(f)(3)(C) of the Federal Food, Drug, and Cosmetic Act; ADASUVE will only be dispensed to patients in healthcare facilities where there is ready access to a short-acting beta-agonist bronchodilator.

In the healthcare settings where agitation treatment occurs, it is highly probable that a short-acting beta-agonist bronchodilator (eg albuterol) is routinely accessible. In order to understand the current availability of albuterol in the treatment settings for agitation, the sponsor conducted market research with nurses and physicians who work in a medical emergency department, psychiatric emergency department, and psychiatric inpatient unit. A national market research firm conducted 476 web interviews with healthcare providers involved with treating agitated patients and asked specific questions about the availability of albuterol in their work setting. Only 1 unit out of 476 units surveyed did not currently have access to albuterol. Specifically, the Medical ED and Psychiatric inpatient units each reported 100% availability and the Psychiatric ED units reported 99% availability. Additionally, more than 80% of the units reported that the elapsed time from ordering albuterol to administration is less than 10 minutes (93% of Medical ED units, 86% of Psychiatric ED units, 80% of Psychiatric inpatient units reported 10 minutes or less). Therefore, based on this market research, it appears reasonable that ready access to a short-acting beta-agonist bronchodilator as a component of the REMS is achievable and would not unduly limit use of ADASUVE.

The ready access to a short-acting beta-agonist bronchodilator is considered a key component of the risk mitigation strategy for ADASUVE. While it is likely that treatment settings already have drugs like albuterol available, the sponsor believes that assurance of ready access is required before ADASUVE can be distributed to the healthcare facility. Therefore, through the Element To Assure Safe Use provision, the sponsor is requiring that an authorized healthcare facility representative attest that a short-acting beta-agonist bronchodilator is readily accessible in the treatment settings within their healthcare facility.

10.3 Prescribing Information

The Prescribing Information will communicate the risk of bronchospasm, which patients should not be treated with ADASUVE, and the need to observe patients and to have a short-acting bronchodilator beta-agonist bronchodilator readily accessible (in the Boxed Warning, Contraindications, and Warnings and Precautions sections).

Specifically, a Boxed Warning is included in the draft prescribing information as follows: ***Patients with active airways disease, such as asthma or chronic obstructive pulmonary disease (COPD), are at risk of bronchospasm after dosing with*** ADASUVE***. Patients with acute respiratory signs/symptoms (eg, wheezing) or who are taking medications to treat asthma or COPD should not be treated with*** ADASUVE***.*** ADASUVE ***should be used with caution in patients with a history of asthma or COPD.*** ADASUVE ***should be administered only in enrolled healthcare facilities where an inhaled short-acting beta-agonist bronchodilator (eg, albuterol) is readily accessible and where the patient can be observed for one hour after treatment.***

Additionally, the Contraindications section will include the following statement: ***Do not use in patients with acute respiratory signs/symptoms (eg, wheezing) or who are taking medications to treat asthma or COPD***. This instruction will also be made clearly visible on the primary packaging (product pouch). A Medication Guide that informs patients and their caregivers about the risks and proper use of ADASUVE will also be dispensed with each single unit of the product.

In the Warning and Precautions section, the following will be included: ***In placebo-controlled clinical trials in subjects with asthma or chronic obstructive pulmonary disease (COPD), adverse events of bronchospasm (which includes reports of wheezing, shortness of breath and cough) were reported in patients following administration of*** ADASUVE***. Bronchospasm was reported in 14 of 26 subjects (53.8%) with mild-to-moderate persistent asthma, and in 5 of 26 subjects (19.2%) with mainly moderate-to-severe COPD. These events occurred within 25 minutes of dosing in 12 of the 14 asthma subjects and in 4 of the 5 COPD subjects. The events were mild to moderate in severity, and were either self limiting or treated with an inhaled bronchodilator. [see BOXED WARNING AND ADVERSE REACTIONS (6.1)].***

Patients with acute respiratory signs/symptoms (eg, wheezing) or who are taking medications to treat asthma or COPD should not be treated with ADASUVE ***[See CONTRAINDICATIONS].*** ADASUVE ***should be used with caution in patients with a history of asthma or COPD.***

ADASUVE ***should be administered only in enrolled healthcare facilities where an inhaled short-acting beta-agonist bronchodilator (eg, albuterol) is readily accessible. Patients should be observed during the first hour after each dose for signs and symptoms of bronchospasm. A short-acting beta-agonist bronchodilator should be administered if bronchospasm occurs, and additional doses of*** ADASUVE ***should not be given.***

Patients should be advised of the risk of bronchospasm if they have active airways disease (eg, asthma or COPD) and to inform their healthcare professional if they develop any breathing problems such as wheezing, shortness of breath, or other signs or symptoms of bronchospasm following treatment with ADASUVE ***[see Patient Counseling Information (17.1)].***

10.4 Phase 4 Observational Study

In addition to labeling and REMS, the sponsor proposes to conduct a large post-marketing observational study to evaluate the safety and effectiveness of ADASUVE in agitated patients in real-world medical or psychiatric emergency settings in the US and EU (50 sites, approximately 1400 patients). This study will provide important information in particular with respect to risk of bronchospasm and use patterns in the post-marketing setting.

The synopsis for this study is provided in Appendix 2.

10.5 Summary of REMS

The ADASUVE REMS is designed to mitigate the risk of bronchospasm at every step of treating a patient with agitation. Via a Communication Plan, healthcare providers are informed of the risk of bronchospasm, the need to identify the appropriate patient to receive ADASUVE, the need to observe the patient for respiratory signs and symptoms following treatment, and the need to have a short acting beta-agonist bronchodilator accessible. As a further enhancement to the risk mitigation strategy, the Element To Assure Safe Use requiring a short-acting beta-agonist bronchodilator to be readily accessible in the treatment setting provides assurance that the appropriate medication is available in the unlikely event that bronchospasm occurs. Current clinical practice and the availability of albuterol in treatment settings for agitation indicate that the individual components of the REMS are highly achievable and would not create an undue burden on the healthcare system.

11 BENEFITS AND RISKS CONCLUSIONS

Alexza Pharmaceuticals, Inc (Alexza) developed ADASUVE to improve treatment of agitation for adults with schizophrenia and bipolar disorder. Patients with agitation are dealing with a severe and disruptive condition, starting with an inner distress that then progresses to a dysfunctional state. Patients can feel frightened and out of control, have difficulty controlling impulses, and show an increased potential for violence that is unsafe for themselves and those around them. While the time course for agitation to require treatment may take minutes, hours or days, once the patient escalates to this point, urgent treatment is required.

Treatment goals in emergency psychiatric patients are to quickly calm the patient so that they can be more accurately assessed by the physician. Ideally, these patients should be treated in a non-coercive manner. The Consensus Guidelines for Treatment of Behavioral Emergencies identified requirements for an anti-agitation treatment, including speed of onset, control of aggressive behavior, patient preference, preservation of the physician-patient relationship, and reliability of delivery (Allen et al, 2001). Currently available agitation treatments do not meet all of the needs identified by this expert panel; they are lacking because they either work slowly or they are invasive and are likely to require coercive measures to deliver the medication.

ADASUVE is an important new therapeutic option for the management of agitation since it provides a rapid onset of anti-agitation effects in a non-invasive treatment option. Currently, there is no agitation product that meets these criteria, which are preferred by patients, and serve to maintain the therapeutic alliance between patient and healthcare professional. ADASUVE begins to control patients' agitation within 10 minutes and provides this relief in a noninvasive manner.

The efficacy and safety findings, the potential benefits for both patients and healthcare providers, and the risk management program all support a positive risk-benefit assessment for ADASUVE in the proposed indication, as follows:

Benefits

ADASUVE is the first anti-agitation product to provide all of the desired attributes for an agitation treatment, as outlined by treatment guidelines, because:

- ***It is effective in controlling agitation.*** The efficacy of ADASUVE was demonstrated in agitated patients across multiple measures and across multiple time points. Starting at 10 minutes, ADASUVE showed a clinical benefit on all domains of the PEC scale (hostility, excitement, poor impulse control, uncooperativeness, and tension), total PEC scores and PEC 40 responder analysis.
    - In the 2 Phase 3 studies, both the 5- and 10-mg doses of ADASUVE were statistically significantly superior to placebo for the primary and the key secondary efficacy endpoints. Two hours after Dose 1, there were statistically

significant differences favoring each ADASUVE group over the placebo group in the change from baseline in the PEC scores.

- Efficacy was confirmed by study investigators using the CGI-Improvement assessments at 2 hours post-dose with ADASUVE.

- Based on CGI-I responders, the number needed to treat for the 10-mg group was 3.2 for schizophrenia and 2.1 for bipolar disorder. Based on PEC responder data, the number needed to treat for the 10-mg group was 3.2 for schizophrenia and 2.2 for bipolar disorder.

- ***It provides a rapid onset of therapeutic effect.*** The treatment effect on agitation signs and symptoms, as reflected in the change from baseline in the PEC score, was evident 10 minutes after the first dose and was sustained at all assessment times through the post-treatment evaluation period for both doses of ADASUVE. The ability to quickly intercept the escalation of agitation relieves patients from distress, and protects them and others from a potentially dangerous situation.

- ***It is very well tolerated in the intended treatment population.*** In agitated patients with schizophrenia or bipolar disorder (excluding patients with active airways disease, as in the proposed prescribing information), the most frequently reported AEs in patients treated with ADASUVE were dysgeusia and sedation. The pulmonary safety profile was favorable in both the agitated patient population and healthy subjects. There were few AEs that suggested an airway effect in the agitated patient population, which, notably, contained predominantly smokers, and included some patients with a history of asthma and/or COPD. Based on the spontaneous reports of bronchospasm in the Phase 2/3 population, the number needed to harm for the 10-mg group was 250.

- ***It provides an acceptable, easy to use, and noninvasive method of treatment.*** This orally inhaled formulation is likely to provide a preferred treatment option for many patients that allows clinicians to preserve the therapeutic alliance with their patients. Even with a high degree of agitation, no patient in the pivotal studies refused or was unable to use the product. Clinicians do not need to trade off speed of onset for ease of delivery, potentially compromising the management of agitated patients with schizophrenia or bipolar disorder.

Risks

In the Phase 2/3 agitated patient population, the most common AEs were either known effects of loxapine administered by other routes, or common to orally inhaled medications (eg, dysgeusia). There were few CNS or airway AEs, and few AEs of hypotension—events that were of interest, based on the pharmacology of the drug and its route of administration.

Pulmonary safety results identified a population of patients in whom ADASUVE should not be used due to risk of bronchospasm.

- Airway AEs (bronchospasm) and categorical decreases in FEV_1 were documented after treatment with ADASUVE in the Phase 1 pulmonary safety studies conducted in asthma and COPD subjects (without psychiatric illness) who had clinically active airways disease and whose quick-relief bronchodilator agents were withheld.

- By challenging these subjects under test conditions that would make them particularly susceptible to irritant effects of an aerosol, the clinical program for ADASUVE has identified the subset of patients who are susceptible to bronchospasm following treatment with ADASUVE. These subjects correspond to patients in clinical practice who present with respiratory signs or symptoms (eg, wheezing) or who are taking medications to treat airways disease. All subjects in the asthma and COPD studies who had notable respiratory signs or symptoms (defined as an airway AE, need for rescue albuterol, or $\geq$20% post-dose decrease in FEV_1) fell into one or both of these categories.

In summary, ADASUVE has been shown to be safe and effective in the intended population for its proposed use in adult patients with agitation associated with schizophrenia or bipolar I disorder. This risk of bronchospasm in agitated patients with active airways disease can be addressed via product labeling and a REMS program to ensure appropriate patient selection and management of bronchospasm if it occurs.

ADASUVE provides an option to healthcare providers in treating agitation that they have not yet had access to and which is expected to meet the most important treatment requirements cited in expert consensus guidelines. For agitated patients who come in to the medical setting requiring urgent care, ADASUVE can address their needs for a rapidly acting and non-invasive treatment for their distress.

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APPENDICES

Appendix 1 Baseline Agitation and Efficacy Results Comparison of the Pivotal Studies for ADASUVE and the Intramuscular Formulations of Abilify (Aripiprazole) and Zyprexa (Olanzapine)

Baseline Agitation

Agitation level at baseline was assessed with a variety of scales across the trials. In all the programs and across both patient groups, baseline PEC scores served as a key entry criteria for randomization. In addition, baseline agitation was also assessed with other scales, including Clinical Global Impression – Severity (CGI-S) and the Agitation-Calmness Evaluation Scale (ACES). The assessed baseline agitation levels in each trial are reported in Table 26 and Table 27. Within the groups diagnosed with schizophrenia or bipolar disorder, there were no substantial differences in baseline level of agitation among patients treated with ADASUVE, IM Zyprexa, or IM Abilify.

Table 26. Baseline Agitation Scores for Patients with Schizophrenia

Study	Treatment	N	Mean PEC	Mean CGI-S	Mean ACES
ADASUVE 004-301	Placebo	115	17.4	3.9	2.3
	5 mg	116	17.8	4.0	2.2
	10 mg	113	17.6	4.1	2.2
IM Zyprexa F1D-MC-HGHB	Placebo	54	18.4	NR	2.4
	10 mg	131	18.4	NR	2.6
	Haloperidol	126	18.2	NR	2.5
IM Zyprexa F1D-MC-HGHV	Placebo	45	18.8	NR	2.4
	2.5 mg	48	18.3	NR	2.4
	5 mg	45	19.7	NR	2.2
	7.5 mg	46	18.9	NR	2.3
	10 mg	46	19.3	NR	2.3
	Haloperidol	40	19.3	NR	2.2
IM Abilify CN 138050	Placebo	62	19.5	4.9	2.1
	1 mg	57	18.9	4.9	2.1
	5.25 mg	63	19.1	4.8	2.1
	9.75 mg	57	19.0	5.1	2.1
	15 mg	58	19.2	4.9	2.1
	Haloperidol	60	18.7	5.0	2.1
IM Abilify CN 138012	Placebo	88	18.7	4.4	2.2
	9.75 mg	175	18.8	4.4	2.2
	Haloperidol	185	18.8	4.4	2.2

NR: Not Reported
CGI-S scores: 1=normal, not at all agitated, 2=borderline agitated, 3=mildly agitated, 4=moderately agitated, 5=markedly agitated, 6=severely agitated, 7=among the most extremely agitated patients
ACES scores: 1 = Marked Agitation, 2 = Moderate Agitation, 3 = Mild Agitation, 4 = Normal, 5 = Mild Calmness, 6 = Moderate Calmness, 7 = Marked Calmness, 8 = Deep Sleep, 9 = Unarousable
Note: Schizophrenia includes patients with schizoaffective and/or schizophreniform disorder.
Sources include:
Zyprexa: Wright et al, 2001, Brier et al, 2002; NDA 21-253, Medical Review and Statistical Review
Abilify: Tran-Johnson et al 2007; NDA 21-866, Medical Review and Statistical Review

Table 27. Baseline Agitation Scores for Patients with Bipolar Disorder

Study	Treatment	N	Mean PEC	Mean CGI-S	Mean ACES
ADASUVE 004-302	Placebo	105	17.7	4.1	2.0
	5 mg	104	17.4	4.0	2.1
	10 mg	105	17.3	4.0	2.1
IM Zyprexa F1D-MC-HGHW	Placebo	50	12.7*	NR	2.3
	10 mg	98	13.0*	NR	2.2
	Lorazepam	51	12.4*	NR	2.3
IM Abilify CN 138013	Placebo	73	18.0	4.1	2.4
	9.75 mg	75	18.8	4.2	2.3
	15 mg	75	18.3	4.1	2.4
	Lorazepam	68	18.5	4.2	2.4

* PEC scale scoring in this study ranged from 0-6 instead of 1-7; adding 5 to the number approximates the 1-7 scoring system
NR: Not Reported
CGI-S scores: 1=normal, not at all agitated, 2=borderline agitated, 3=mildly agitated, 4=moderately agitated, 5=markedly agitated, 6=severely agitated, 7=among the most extremely agitated patients
ACES scores: 1 = Marked Agitation, 2 = Moderate Agitation, 3 = Mild Agitation, 4 = Normal, 5 = Mild Calmness, 6 = Moderate Calmness, 7 = Marked Calmness, 8 = Deep Sleep, 9 = Unarousable
Sources include:
Zyprexa: Meehan et al, 2001; NDA 21-253, Medical Review and Statistical Review
Abilify: Zimbroff et al 2007; NDA 21-866, Medical Review and Statistical Review

Change from Baseline in PEC

In the pivotal studies conducted for ADASUVE, as well as those for IM Abilify and IM Zyprexa, the primary efficacy endpoint was the change from baseline in PEC at 2 hours after the first administration of study medication. Table 28 presents the primary efficacy endpoint data from the pivotal studies. The mean changes from baseline to 2 hours in PEC scores were similar for ADASUVE compared with the other 2 drugs. This confirms the relative effectiveness of ADASUVE at both dose levels, based on comparison to the historical data for IM Abilify and IM Zyprexa from studies with designs and endpoints similar to those in the pivotal trials of ADASUVE.

Table 28. Mean Change in PEC Score from Baseline to 2 Hours in ADASUVE Phase 3 Studies and Comparator Studies

ADASUVE Studies

Study	Population	Placebo	Loxapine Dose (Inhaled)	
			5 mg	10 mg
004-301	Schizophrenia	-5.5	-8.1	-8.6
004-302	Bipolar Disorder	-4.7	-8.2	-9.2

IM Abilify Studies

Study	Population	Placebo	Active Comparator	Abilify Dose (IM)			
				1 mg	5 mg	10 mg	15 mg
CN138012	Schizophrenia, Schizoaffective	-5.68	-8.25 (Haloperidol)	NT	NT	-7.99	NT
CN138050	Schizophrenia, Schizoaffective, Schizophreniform	-4.78	-7.32 (Haloperidol)	-4.87	-6.94	-7.82	-6.94
CN138013	Bipolar Disorder	-5.76	-9.57 (Lorazepam)	NT	NT	-8.74	-8.67

IM Zyprexa Studies

Study	Population	Placebo	Active Comparator	Zyprexa Dose (IM)			
				2.5 mg	5 mg	7.5 mg	10 mg
MC-HGHB	Schizophrenia	-3.55	-7.63 (Haloperidol)	NT	NT	NT	-7.74
MC-HGHV	Schizophrenia	-2.59	-7.29 (Haloperidol)	-5.20	-7.80	-8.42	-8.95
MC-HGHW	Bipolar Disorder	-4.20	-6.08 (Lorazepam)	NT	NT	NT	-8.98

NT: not tested in study
Sources include:
Abilify: NDA 21-866, Statistical Review
Zyprexa: NDA 21-253, Statistical Review

Effect sizes for mean change in PEC score from baseline to 2 hours are shown in Table 29 for ADASUVE, IM Abilify, and IM Zyprexa.

Table 29. Effect Sizes for Mean Decrease in PEC Score from Baseline to 2 Hours in ADASUVE Phase 3 Studies and Comparator Studies

ADASUVE Studies

Study	Population	Loxapine Dose (Inhaled)	
		5 mg	10 mg
004-301	Schizophrenia	0.45 (8.0-5.8)/4.84	0.60 (8.7-5.8)/4.84
004-302	Bipolar I Disorder	0.73 (8.2-4.7)/4.78	0.94 (9.2-4.7)/4.78

IM Zyprexa Studies

Publication	Population	Zyprexa Dose (IM)			
		2.5 mg	5 mg	7.5 mg	10 mg
Brier et al, 2002	Schizophrenia, Schizoaffective, Schizophreniform	0.51 (5.5-2.9)/5.06	1.03 (8.1-2.9)/5.06	1.15 (8.7-2.9)/5.06	1.28 (9.4-2.9)/5.06
Wright et al, 2001	Schizophrenia, Schizoaffective, Schizophreniform	NT	NT	NT	0.74 (7.7-3.6)/5.52
Meehan et al, 2001	Bipolar Disorder	NT	NT	NT	0.98 (9.60-4.84)/4.84

IM Abilify Studies[a]

Study	Population	Abilify Dose (IM)			
		1 mg	5 mg	10 mg	15 mg
CN138012	Schizophrenia, Schizoaffective	NT	NT	0.50 (7.27-4.78)/5.00	NT
CN138050	Schizophrenia, Schizoaffective, Schizophreniform	0.24 (4.47-3.28)/5.00	0.47 (5.65-3.28)/5.00	0.68 (6.69-3.28)/5.00	0.49 (5.72-3.28)/5.00
CN138013	Bipolar Disorder	NT	NT	0.60 (8.74-5.76)/5.00	0.58 (8.67-5.76)/5.00

NT: not tested in study

a. Means were obtained from FDA summary. Standard deviations were not reported in the Abilify publications or FDA summary. Therefore, a standard deviation of 5 was used to calculate effect sizes. A value of 5 is consistent with standard deviations reported for Zypreza.

Sources include:

Abilify: NDA 21-866, Statistical Review

Onset of Effect (PEC)

The approved IM drugs were shown in their pivotal trials to have variable onset of anti-agitation effect. Table 30 presents the time points of the first statistically significant changes from baseline in PEC scores relative to placebo in the ADASUVE, IM Abilify, and IM Zyprexa Phase 3 studies. For IM Abilify and IM Zyprexa, there was variability in the onset of effect based on both the treatment population and the dose of the drug. By contrast, ADASUVE showed a rapid and consistent onset of anti-agitation effect at 10 minutes in both populations and at both doses (5-mg onset data analysis was post hoc). This difference in time to producing a significant reduction in agitation may be more evident in patients with bipolar disorder in whom ADASUVE had effects in 10 minutes, compared with 30 minutes and 60 minutes for the prescribed doses of IM Zyprexa and IM Abilify, respectively. The rapid and consistent onset of anti-agitation effects suggests that ADASUVE is a viable therapy as an acute treatment for agitation.

Table 30. Time to First Statistically Significant Change from Baseline PEC Score in ADASUVE Phase 3 Studies and Comparator Studies

ADASUVE Studies			
Study	**Population**	**Loxapine Dose (Inhaled)**	
		5 mg	**10 mg**
004-301	Schizophrenia	10 min	10 min
004-302	Bipolar Disorder	10 min	10 min

IM Abilify Studies					
Study	**Population**	**Abilify Dose (IM)**			
		1 mg	**5 mg**	**10 mg**	**15 mg**
CN138012	Schizophrenia, Schizoaffective	NT	NT	120 min	NT
CN138050	Schizophrenia, Schizoaffective, Schizophreniform	ns	120 min	45 min	120 min
CN138013	Bipolar Disorder	NT	NT	90 min	60 min

IM Zyprexa Studies					
Study	**Population**	**Zyprexa Dose (IM)**			
		2.5 mg	**5 mg**	**7.5 mg**	**10 mg**
MC-HGHB	Schizophrenia	NT	NT	NT	15 min
MC-HGHV	Schizophrenia	60 min	30 min	30 min	30 min
MC-HGHW	Bipolar Disorder	NT	NT	NT	30 min

NT: not tested in study
ns: not statistically significant (compared with placebo)
Sources include:
Abilify: NDA 21-866, Statistical Review
Zyprexa: NDA 21-253, Statistical Review

PEC Responder Analysis

In the pivotal studies for IM Abilify and IM Zyprexa, responder analyses assessed the percentage of patients with a ≥40% decrease from baseline in the total PEC score at selected time points. The same responder analyses were performed for the pivotal ADASUVE studies at all assessment times from 10 minutes through 2 hours after administration of Dose 1 (post-hoc analyses). The results of these ADASUVE responder analyses, along with available data for IM Abilify and IM Zyprexa, are summarized in Table 31 (schizophrenia) and Table 32 (bipolar I disorder).

With ADASUVE treatment, the number of responders was significantly larger than placebo at each assessment time; the onset of effect was rapid, with statistically significant differences from placebo starting 10 minutes after Dose 1; and consistent efficacy was evident in both schizophrenia and bipolar disorder. In the IM Abilify responder analysis in patients with schizophrenia, a statistically significant difference from placebo was documented at 60 and 120 minutes, the only assessment times reported in available data. In patients with bipolar disorder, the IM Abilify/placebo comparison failed to achieve statistical significance at 30, 45, or 60 minutes, but was significant at later assessments, at 1.5 hours (10-mg dose only) and 2 hours (10- and 15-mg doses). In the IM Zyprexa responder analysis in patients with schizophrenia, a statistically significant difference from placebo was documented at 2 hours, the only assessment time reported in available data. In patients with bipolar disorder, the IM Zyprexa responder rate was 50.0% at 30 minutes (no results of pairwise comparison were provided), and the difference was statistically significant at 2 hours.

Table 31. PEC Scale Responder Analysis in ADASUVE Phase 3 Study and Comparator Studies: Schizophrenia Studies

ADASUVE Study

(Percentage 40% Responders)

Study	Minutes after Dose 1	Placebo	Loxapine Dose (Inhaled)	
			5 mg	10 mg
004-301	10	6.1%	17.2% (p=0.0056)	18.8% (p=0.0012)
	20	15.7%	29.3% (p=0.0088)	42.9% (p<0.0001)
	30	27.8%	46.6% (p=0.0016)	57.1% (p<0.0001)
	45	32.2%	50.0% (p=0.0045)	70.5% (p<0.0001)
	60	38.3%	57.8% (p=0.0026)	71.4% (p<0.0001)
	90	38.3%	61.2% (p=0.0004)	74.1% (p<0.0001)
	120	38.3%	62.9% (p=0.0002)	69.6% (p<0.0001)

IM Abilify Studies

(Percentage 40% Responders)

Study	Minutes after Dose 1	Placebo	Abilify Dose (IM)			
			1 mg	5 mg	10 mg	15 mg
CN138012	120	42%	NT	NT	57% (p=0.045)	NT
CN138050[a]	60	25%	20% (ns)	30% (ns)	45% (p<0.05)	45% (p<0.05)
	120	36%	38% (ns)	50% (ns)	54% (p<0.05)	55% (ns)

IM Zyprexa Studies

(Percentage 40% Responders)

Study	Minutes after Dose 1	Placebo	Zyprexa Dose (IM)			
			2.5 mg	5 mg	7.5 mg	10 mg
MC-HGHB[b]	120	33.3%	NT	NT	NT	73% (p<0.01)
MC-HGHV[c]	120	20.0%	50.0% (p=0.003)	62.6% (p<0.001)	73.9% (p<0.001)	80.4% (p<0.001)

NT: not tested in study
ns: not statistically significant (compared with placebo)
Note: All p-values are for active/placebo comparison.
Sources include:
Abilify : NDA 21-866, Statistical Review; [a] Tran-Johnson et al, 2007
Zyprexa: [b] Wright et al, 2001; [c] Breier et al, 2002

Table 32. PEC Scale Responder Analysis in ADASUVE Phase 3 Study and Comparator Studies: Bipolar Disorder Studies

ADASUVE Study
(Percentage 40% Responders)

Study	Minutes after Dose 1	Placebo	Loxapine Dose (Inhaled)	
			5 mg	10 mg
004-302	10	7.6%	18.3% (p=0.0059)	21.9% (p=0.0017)
	20	15.2%	36.5% (p<0.0001)	49.5% (p<0.0001)
	30	23.8%	59.6% (p<0.0001)	61.9% (p<0.0001)
	45	29.5%	64.4% (p<0.0001)	70.5% (p<0.0001)
	60	28.6%	69.2% (p<0.0001)	72.4% (p<0.0001)
	90	27.6%	62.5% (p<0.0001)	72.4% (p<0.0001)
	120	27.6%	62.5% (p<0.0001)	73.3% (p<0.0001)

IM Abilify Study
(Percentage 40% Responders)

Study	Minutes after Dose 1	Placebo	Abilify Dose (IM)			
			1 mg	5 mg	10 mg	15 mg
CN138013	30	18%	NT	NT	12% (ns)	13% (ns)
	45	26%	NT	NT	37% (ns)	35% (ns)
	60	37%	NT	NT	43% (ns)	48% (ns)
	90	41%	NT	NT	57% (p=0.046)	52% (ns)
	120	37%	NT	NT	69% (p<0.001)	63% (p=0.002)

IM Zyprexa Study
(Percentage 40% Responders)

Study	Minutes after Dose 1	Placebo	Zyprexa Dose (IM)			
			2.5 mg	5 mg	7.5 mg	10 mg
HGHW	30	28.0%	NT	NT	NT	50.0%
	120	44.0%	NT	NT	NT	80.6% (p<0.001)

NT: not tested in study
ns: not statistically significant (compared with placebo)
Note: All p-values are for active/placebo comparison.
Sources include:
Abilify: NDA 21-866, Statistical Review
Zyprexa: Meehan et al, 2001

Appendix 2 Protocol Synopsis for Phase 4 Post-Marketing Study

A Post-Marketing Observational Study to Evaluate the Safety and Effectiveness of ADASUVE in Agitated Patients with Schizophrenia or Bipolar Disorder Treated in Real World Emergency Settings

Protocol Synopsis

STUDY SYNOPSIS

Study Title:

A Post-Marketing Observational Study to Evaluate the Safety and Effectiveness of ADASUVE in Agitated Patients with Schizophrenia or Bipolar Disorder Treated in Real World Emergency Settings

Treatments:

ADASUVE drug device combination (single dose, 5 mg or 10 mg), administered according to standard practice as determined by the Investigator; or intramuscular (IM) anti-psychotic and/or IM benzodiazepine medications, used in the treatment of acutely agitated patients in the emergency setting.

Number of Patients: 1400	**Enrollment Period: 18-24 months**
Number of Study Centers: ~50	**Duration of Patient Participation**: up to 24 h

Background and Rationale:

Agitation is frequently reported during acute states of schizophrenia or bipolar mania. Symptoms include excitement, physical and verbal hyperactivity, hostility, tension, and aggression. Such agitation can cause extreme distress and warrants immediate treatment. Clinical studies of ADASUVE, whose active ingredient is loxapine, a dibenzoxazepine antipsychotic, demonstrated a rapid onset of anti-agitation effects within 10 minutes of administration. Therefore, ADASUVE may provide a fast acting, noninvasive therapeutic option for agitated patients with schizophrenia or bipolar disorder. ADASUVE is delivered by the Staccato® drug delivery system, which generates a consistent distribution of aerosolized drug particles of 1-3.5 microns MMAD (optimized for absorption in deep lung tissue) for rapid achievement of peak plasma concentrations.

Alexza Pharmaceuticals, Inc. (Alexza) submitted NDA 022549 on December 11, 2009 to support the approval of ADASUVE as a prescription drug product for the rapid treatment of agitation associated with schizophrenia or bipolar disorder in adults. The Division of Psychiatry Products issued a Complete Response Letter on October 8, 2010. As part of the resubmission of the NDA, the Division requested that a prospective, observational study be conducted to better understand the safety, effectiveness and treatment patterns associated with the real world use ADASUVE.

Objectives:

Primary Safety Objectives

- To assess the occurrence and nature (e.g., severity) of serious adverse events (SAEs) and adverse events (AEs), with a primary focus on respiratory AEs, experienced following the administration of ADASUVE in an emergency setting
- To compare the frequency of AEs and SAEs for ADASUVE vs. IM anti-psychotic and/or benzodiazepine medications used in the acute treatment of agitated patients

Additional Objectives

- To describe the practice patterns for the use of ADASUVE in an emergency setting
- To evaluate the effects of different treatments for agitation using the Positive and Negative Symptom Scale-Excitement Component (PANSS-EC)

Study Population

The study population will consist of a nonrandomized cohort of adult male and female patients with a diagnosis of schizophrenia or bipolar disorder who require treatment for agitation (voluntarily or involuntarily) as determined by the investigator.

Inclusion Criteria

1. ≥ 18 years of age at entry
2. Agitated patient with schizophrenia or bipolar disorder as determined by the investigator and requiring anti-psychotic (IM or aerosol) and/or IM benzodiazepine treatment for agitation in the medical or psychiatric emergency setting
3. Patient (or legal representative) willing and able to provide written informed consent (either at the time before dosing or following treatment after agitation has subsided

Exclusion Criteria

1. Patient diagnosed with dementia
2. Patient ineligible to receive ADASUVE according to the approved Prescribing Information and the approved product REMS (eg, those who have acute respiratory signs/symptoms or who are currently being treated for asthma or COPD will not receive ADASUVE)

Study Design:

This is a multi-center, prospective observational study conducted in medical or psychiatric emergency settings in the U.S., at approximately 50 sites. Sites will be selected and qualified primarily based on their estimated number of eligible patients.

Patients will receive the medication they would have received either voluntarily or involuntarily as usual care for agitation. If the patient is too agitated to give informed consent for enrolling in the study before receiving the medication, consent will be obtained subsequently, after the resolution of the acute episode of agitation. Eligible patients will be enrolled consecutively and timing of informed consent or refusal of consent (prior to treatment or after treatment) will be recorded.

In addition to baseline data, effectiveness data will be collected at 1 h post-treatment and safety data will be collected up to 24 h post-treatment or until discharge/transfer from the emergency department (whichever is earlier). If informed consent is obtained after the resolution of agitation, then information will be obtained retrospectively from the medical charts and the health providers only after consent is provided. Research staff will be in place to collect safety and effectiveness data at the specified time points.

Data Elements:

Outcomes of Interest

Safety Data

- Respiratory AEs (eg, respiratory signs and symptoms such as coughing, wheezing, or shortness of breath).
- Use of short-acting bronchodilator or other medication to treat emergent symptoms (eg bronchospasm, extrapyramidal symptoms)
- Other AEs (including AEs of interest such as sedation/somnolence, extrapyramidal symptoms)
- SAEs

Treatment Pattern/Effectiveness Data

- Baseline PANSS-EC scores for patients treated with ADASUVE compared with patients treated with other anti-agitation medications
- Mean change in PANSS-EC score from baseline to 1 h post-treatment (or at discharge if earlier than 1 h)
- Usability of ADASUVE including the number (and percent) and characteristics of patients who refused or were unable to use ADASUVE when it was offered
- Physician treatment choices for treating agitation in an emergency setting
- Doses of all anti-agitation medications administered (medication, dose, route of administration, timing) up to 24 h from first dose (or at discharge from emergency service if earlier)
- Physical restraints used, if any
- Security personnel or dedicated staff ("sitters") assigned to patient post dosing, if any
- Availability of patient medical/medication history and physical examination results prior to ADASUVE treatment

Other Data of Interest:

- The demographics of patients treated with ADASUVE compared with patients treated with other anti-agitation medications
- Agitation triggers
- Medical information regarding the current emergency visit (diagnoses/comorbidities)
- Information on respiratory history, including presence or absence of COPD, asthma, former and current smoking, past and current treatment for respiratory problems
- Other concomitant medications (type of medication, indication, dose, duration, frequency)

Safety assessments: Patients who receive at least one dose of IM or inhaled medication for the treatment of agitation will be included in the evaluation for safety. All AEs and SAEs will be recorded from the time the patient signs the informed consent (or from the time of dosing if informed consent is obtained post-dosing) until end of the study period. Any SAE related to ADASUVE during the study period should be reported to the Sponsor within 24 hours of learning of its occurrence. The Sponsor is responsible for reporting SAEs to the Food and Drug Administration (FDA).

Statistical Considerations:

Sample Size

The sample size estimation is based on the precision (half the width of the confidence interval [CI]) for the estimated AE rates in persons receiving ADASUVE. In the Phase 3 program, with respiratory exclusion criteria similar to those described in the Prescribing Information, the observed rate of respiratory AEs in persons receiving ADASUVE was 0.8%. Assuming that under the clinical trial conditions the screening of patients is more ideal than in an Emergency Department setting, the rate of respiratory AEs would likely be higher in this study than that previously observed. Thus, for the purpose of these sample size calculations, we estimate a 3-fold higher rate of respiratory AEs than in the Phase 3 program (i.e., yielding a respiratory AE rate of 2.4%), compared to ~<1% in persons receiving comparator IM products. Given a sample size of 600 patients receiving ADASUVE, the estimated precision for the observed respiratory AE rate in persons receiving ADASUVE will be ±1.2%. For comparison purposes, we will also aim to enroll approximately 800 patients receiving other IM anti-psychotics and/or benzodiazepines; thus, the total estimated study population will be 1400 patients.

Analyses

Descriptive and inferential analyses will be performed. Summaries of continuous variables will include mean, standard deviation, median, quartiles and range. Summaries of categorical or ordinal variables will include counts, proportions or percentages with 95% CIs. The primary safety analysis will examine data during the monitoring period immediately following ADASUVE administration for all SAEs and Adverse Events of Special Interest (AESIs) such as respiratory AEs. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by incidence, severity grade, and relationship to study drug. The frequency and percentage will be calculated for patients reporting AEs (e.g. respiratory AEs) and SAEs. Analyses comparing changes in scores of PANSS-EC between patient subgroups will be performed by means of ANCOVA and 95% CIs will also be calculated. ANCOVA models will be fitted using type III sums of squares and adjusted least square means will be computed.

Ethical Considerations: The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, applicable privacy laws, and local regulations for each participating site. This study will follow the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology. An independent ethics committee (IEC) will review and approve the protocol before any patient is enrolled.