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MEDICAL REVIEW(S)

CLINICAL REVIEW
Cycle 3 Addendum

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Reviewer Name Francis E. Becker, M.D.
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Established Name Loxapine
Trade Name Staccato Loxapine for
Inhalation (ADASUVE)
Therapeutic Class Antipsychotic
Applicant Alexza Pharmaceuticals
Related IND 73248

Priority Designation Standard

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1. Introduction

ADASUVE (loxapine) inhalation powder (*Staccato* Loxapine) is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery by inhalation of a thermally generated aerosol of loxapine. *Staccato* Loxapine represents a new dosage form for loxapine, an antipsychotic with dopamine D₂ blocking activity that has been available in the United States (US) since 1975. *Staccato* Loxapine (5-mg and 10-mg dose levels) has been developed by the sponsor for the treatment of agitation in patients with Schizophrenia or Bipolar Disorder. Since agitation in these psychiatric populations is an acute and intermittent condition, it is expected that patients will be treated with *Staccato* Loxapine on an infrequent basis.

Staccato Loxapine is based on the proprietary *Staccato* delivery system developed by the sponsor. Oral inhalation through the *Staccato* Loxapine for Inhalation 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 resulting rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration.

This review is a Cycle 3 Clinical Review based on review of the sponsor's Class 2 Complete Response resubmission dated June 21, 2012. Therefore, this review will focus on issues addressed in the Cycle 2 CR letter, the sponsor's response to those issues in Cycle 3, and any updated or revised information provided by the sponsor in this submission which has not been adequately addressed in the previous cycles. For a complete clinical review, the reader is referred to this reviewer's **Cycle 1 Clinical Review** (September 17, 2010), **Cycle 2 Pre-AC Meeting Clinical Review** (November 8, 2011), and **Post-AC Meeting Clinical Review, Cycle 2 Addendum** (April 9, 2012).

2. Regulatory History

The key aspects of the regulatory history of the application are outlined below:

- August 31, 2005: Alexza submitted an IND application (73-248) for *Staccato* Loxapine in the treatment of acute agitation associated with schizophrenia or bipolar I disorder.
- December 11, 2009: The sponsor submitted the original NDA (22549) for the treatment of acute agitation associated with schizophrenia or bipolar I disorder.
- October 8, 2010: The Division took a Complete Response action, identifying pulmonary toxicity (bronchospasm) as the primary issue.
- December 17, 2010: The Division and Alexza held an End of Review Meeting to discuss the complete response action and potential means of resolving issues. The Division stated that it would be reasonable to propose a REMS program to mitigate the risk of pulmonary toxicity.

- April 29, 2011: Type C Meeting was held with the sponsor to discuss the possible components of a REMS, including Elements to Assure Safe Use (ETASU).
- August 4, 2011: Alexza submitted a Class 2 Complete Response resubmission. The submission included a REMS with the following components: Elements to Assure Safe Use, revised product labeling, a Medication Guide, a Communication Plan, a Healthcare Facility Certification, an Implementation System, and a timetable for submission of Assessments.
- October 14, 2011: REMS Oversight Committee (ROC) meeting: DRISK and DPP presented the review team's minimum requirements for the ADASUVE REMS program. The committee agreed that ETASU would be required. They also recommended obtaining input from outside stakeholders (from the Drug Safety Board, for example) during the development of the REMS.
- November 16, 2011: Drug Safety Oversight Board (DSB) Meeting – DRISK presented the proposed minimum requirements for the ADASUVE REMS. The board commented on the impact the REMS program might have on their healthcare facilities. The discussion did not result in revisions to the Agency's proposed REMS.
- December 12, 2011: Psychopharmacologic Drugs Advisory Committee (PDAC) Meeting. The committee was supplemented with members of the Pulmonary – Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. The committee discussed the potential risks and benefits of treatment of ADASUVE, and they considered the REMS programs proposed by FDA and the sponsor. The Advisory Committee members voted 9 to 8 (with one abstention) to approve ADASUVE with the FDA-recommended REMS and with limiting administration to one dose within a 24-hour period.
- January 10, 2012: Alexza submitted REMS Amendment #2 to take into consideration and align with the Agency's REMS presented at the PDAC meeting.
- January 19, 2012: The Division decided to extend the review by 3 months, in order to review the REMS (a major amendment to the submission).
- Throughout the review cycle, FDA provided comments to the sponsor about the requirements for the REMS with ETASU. During a teleconference with Alexza on March 1, 2012, the Division clarified that "Immediate, on-site access to advanced airway management capabilities" meant that these capabilities must be available within the healthcare facility in which the product would be administered, as opposed to being available by calling emergency response services.
- April 5, 2012: REMS Oversight Committee (ROC) meeting – DPP and DRISK updated the committee on the DSB and PDAC meetings. The ROC members agreed that ADASUVE could be approved with the finalized REMS. In addition, the ROC recommended that the labeling emphasize the pulmonary risk and discourage inappropriate claims not supported by adequate data [REDACTED] (b) (4) [REDACTED].
- April 5, 2012: Alexza submitted a complete proposed protocol for the observational post-marketing study.

- May 2, 2012: The Division took a Complete Response action, citing manufacturing deficiencies noted during a facilities inspection as the primary issue. The Division's currently preferred version of labeling was included in the CR action letter, based on negotiations with the sponsor during this review cycle.
- June 7, 2012: CDRH General Advice Letter issued to the sponsor, specifying the manufacturing deficiencies noted during the facilities inspection.
- June 14, 2012: Alexza notified the Division, CDRH Office of Compliance, and the District Office of [REDACTED] (b) (4)
- June 21, 2012: Alexza submitted a Class 2 Complete Response resubmission. The submission includes complete responses to manufacturing deficiencies, revised draft labeling for ADASUVE, revised proposed REMS document, and required safety update. [REDACTED] (b) (4)
- July 12, 2012: Alexza submitted other revised REMS materials (Order Set Protocol, Safe Use Checklist, Education Program, etc)

3. Manufacturing Deficiencies

During the first review cycle, a preapproval inspection was performed by the FDA at the drug product manufacturing site, Alexza Pharmaceuticals, Mountain View, California, which resulted in a "Withhold" recommendation from CDER Office of Compliance. During the second cycle, the sponsor resolved the main issues uncovered during the inspection concerning the inappropriate stability storage conditions, [REDACTED] (b) (4) and lack of link of stability studies to the final commercial version by initiating new stability studies [REDACTED] (b) (4) with the final commercial version of the device. Other outstanding issues were resolved during the second cycle by including or modifying in-process tests for weight of drug on tray-side, addition of controls [REDACTED] (b) (4), changes [REDACTED] (b) (4) controlled by the thermogram test, and initiation of appropriate heat package stability studies.

However, other issues were not adequately addressed during the second cycle and thus required resolution during the third cycle. In the CDRH General Advice Letter of June 7, 2012, the following manufacturing deficiencies were conveyed to the sponsor:

1. Failure to adequately ensure that when the results of a process cannot be fully verified by subsequent inspection and test that the process shall be validated with a high degree of assurance and approved according to established procedure, as required by 21 CFR 820.75(a). A number of production/manufacturing processes had not been validated under proposed commercial batch conditions (Product Performance Qualification [PPQ]) in order to provide assurance that the process will consistently produce product that meets acceptance criteria throughout the

duration of the manufacturing cycle. In addition, the sponsor had provided the protocol and reports for the completed and approved 10-mg dose PPQ report.

(b) (4)

2. Failure to establish and maintain adequate procedures for implementing corrective and preventive action (CAPA) to include identifying the actions needed to correct and prevent recurrence of nonconforming product and other quality problems, as required by 21 CFR 820.100(a)(3).
3. Failure to establish and maintain adequate procedures for implementing corrective and preventive action (CAPA) to include verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device as required by 21 CFR 820.100(a)(4).
4. Failure to establish and maintain adequate procedures to ensure that complaints are evaluated to determine whether the complaint represents an event which is required to be reported to FDA under part 803, Medical Device Reporting, as required by 21 CFR 820.198(a)(3). Procedures for receiving, reviewing, and evaluating complaints by formally designated unit had not been adequately established. The sponsor provided a revised Commercial Product Complaint Handling Process in January 2012 to add instruction for employees who could potentially receive a complaint to gather or obtain information associated with medical events. However, CDRH did not consider this response adequate because the sponsor had not provided evidence that it implemented systemic corrective actions to include analyzing past complaints to verify that all adverse events have been reported according to the new procedure.
5. Failure to establish adequate procedures for identifying training needs and to ensure that all personnel are trained to adequately perform their assigned responsibilities, and have training documented, as required by 21 CFR 820.25(b).
6. Failure to develop, maintain and implement Medical Device Reporting (MDR) procedures, as required by 21 CFR 803.17. The sponsor provided a revised procedure for Postmarketing Safety Reporting in January 2012. However, CDRH did not consider the response adequate because the sponsor had not provided evidence that it had implemented systemic corrective actions to include analyzing past complaints to verify that all adverse events have been reported according to the new procedure.

(b) (4)

4.1 CMC Review (DPP): David Claffey, Ph.D.

5. Safety Update

In the Class 2 Complete Response Resubmission of June 20, 2012 (received date: June 21, 2012), the sponsor included a safety update as required in accordance with 21 CFR 314.50(d)(5)(iv)(b). The sponsor reports that no clinical studies have been ongoing or initiated in the period since the last patient was administered ADASUVE in the clinical program described in the original submission of NDA 22549. Therefore, there are no new clinical safety data to report in this resubmission.

The safety update also includes an updated literature search relevant to the safety of loxapine. No new clinical or nonclinical safety information was found from the updated search.

6. Updated labeling

6.1 FDA Revised Labeling:

The Division's Complete Response Letter of May 2, 2012 included FDA revisions to the sponsor's proposed labeling. In addition to formatting changes for clarity and to avoid redundancy, FDA included the following important revisions:

1. Broadening of contraindications to include *current diagnosis* (in addition to history) of asthma, COPD, or other lung disease associated with bronchospasm.
2. Under Section 6.1, **Clinical Trials Experience**, deletion of the phrase, [REDACTED] (b) (4) [REDACTED] from the Healthy Volunteers section. FDA considers that this statement is not relevant, because a finding of decreased FEV1/FVC ratio occurs only with severely decreased FEV1 (>20% decreases in most of the subjects) as demonstrated in the asthma study.
3. Under Section 6.1, **Clinical Trials Experience**, deletion of [REDACTED] (b) (4) [REDACTED]
4. Under Section 6.1, **Clinical Trials Experience**, changing the last paragraph of the section describing the COPD trial (COPD Patients section) to read that rescue medication was administered "to **11%** of patients in the placebo group." The sponsor's report of 15% was believed by FDA to be incorrect, resulting from double counting of the patient who received rescue after both the first and second dose.
5. Changing the y-axis of Figure 7, "LS Mean Change from Baseline in FEV1 in Patients with Asthma" from mL to L.
6. Deletion of [REDACTED] (b) (4) [REDACTED] because FDA considers this figure unnecessary.
7. Under Section 8.3, **Nursing Mothers**, revision of wording to conform to required regulatory language.

Thus, FDA revisions to the sponsor's proposed labeling, including some formatting and editing changes, are as follows (base document: sponsor's labeling version of 4/17/12; FDA additions/deletions in track changes):

(b) (4)

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Reviewer's Comments: The sponsor's proposed REMS has been extensively reviewed by DRISK and DPP during this Cycle. As the final labeling has been agreed upon with the sponsor, the focus has been to ensure that the final REMS adequately aligns with the final labeling. The proposed REMS as negotiated with the sponsor and including the elements summarized above is acceptable.

8. Proposed Post-Marketing Study

As part of the resubmission of the NDA in Cycle 2, 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 of *Staccato* Loxapine. Therefore, the sponsor's Cycle 2 submission included a synopsis of a proposed postmarketing study entitled, "A Postmarketing Observational Study to Evaluate the Safety and Effectiveness of *Staccato* Loxapine in Agitated Patients with Schizophrenia or Bipolar Disorder Treated in Real World Emergency Settings." At the Psychopharmacologic Drugs Advisory Committee Meeting on December 12, 2011, the overall goals and design of the study were discussed, and the FDA clarified that the primary interest was in getting additional safety data as opposed to getting comparative data. Alexza stated that they would be agreeable to changing the study design to assess the safety of ADASUVE alone.

On April 5, 2012, the sponsor submitted a complete protocol titled, "A Post-marketing Observational Study to Evaluate the Safety of ADASUVE (*Staccato* Loxapine for Inhalation) in Agitated Patients with Schizophrenia or Bipolar Disorder." Since the protocol was submitted late in Cycle 2, and since a complete response action was taken, a complete review of the proposed protocol was deferred to Cycle 3.

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9. Reviews from other Disciplines

9.1 Division of Epidemiology

During this Cycle, Cary Parker, M.P.H, of the Division of Epidemiology (DEPI) completed a review of the proposed postmarketing observational study. In her review (November 27, 2012), DEPI recommended that the sponsor address concerns regarding the sampling plan, study population (inclusion/exclusion criteria and loss to follow-up), exposure measures, outcome measures, covariates, sample size, and recruitment. Regarding study population, DEPI recommended that “

(b) (4)



DEPI also recommended

(b) (4)



9.2 Division of Medication Error Prevention and Analysis (DMEPA)

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the device label, pouch labeling, carton labeling, and instructions for use submitted by the sponsor on June 21, 2012. The reviewer, Loretta Holmes, BSN, PharmD, noted that the sponsor's labels and labeling submitted on June 21, 2012 were compared against the previous recommendations contained in OSE reviews dated March 12, 2012 and April 9, 2012 as well as follow-up label and labeling negotiations with the sponsor. DMEPA concluded that the sponsor "has implemented all of our previous recommendations and agreed upon changes to the labels and labeling." No additional recommendations were made.

DMEPA also conducted a proprietary name review. In her consult dated October 5, 2012, Dr. Holmes noted that the proposed name, ADASUVE, was previously reviewed in OSE Reviews in the previous cycles and found to be acceptable. In addition, the Office of Prescription Drug Promotion (OPDP) determined the proposed name to be acceptable from a promotional perspective. DMEPA and the Division of Psychiatry Products (DPP) concurred with the findings of OPDP's promotional assessment of the proposed name. DMEPA conducted name simulation studies, solicited comments from other review disciplines, and conducted failure mode and effects analysis of similar names. DMEPA concluded that the proposed proprietary name is acceptable from both a promotional and safety perspective.

9.3 Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

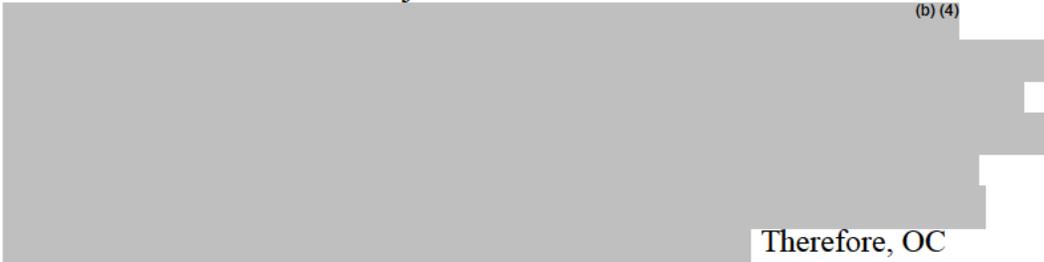
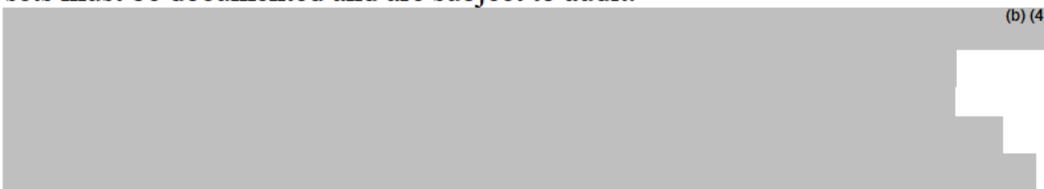
The Division of Pulmonary, Allergy, and Rheumatology Products completed a briefing package review (Cycle 3) on November 26, 2012. During the previous review cycles, DPARP had been extensively involved in assessing the pulmonary risk associated with ADASUVE administration. In addition, DPARP provided significant input in the development of accurate labeling to reflect pulmonary data and in development of effective REMS.

In the Cycle 3 review, Theresa Michele, M.D. of DPARP agreed that, if approved, a post-marketing study to evaluate the safety of ADASUVE in a real-world setting, using the REMS, will be required. Dr. Michele noted that there is significant risk of post-inhalation bronchospasm following administration of ADASUVE, particularly in patients with underlying airway hyperresponsiveness caused by conditions such as asthma and COPD. Dr. Michele pointed out that characteristics of the patient population, including a high prevalence of smoking and inability to give a reliable history, increase the risk of bronchospasm following ADASUVE inhalation. However, Dr. Michele further noted that during this review cycle, DPARP recommendations regarding communication of risk and mitigation strategies are incorporated into the proposed product labeling, REMS, and PMC study. DPARP concluded that these strategies are expected to mitigate, but not eliminate, the risk of severe bronchospasm with inhalation of ADASUVE.

9.4 Office of Compliance

In a review entitled “REMS Memorandum” dated November 1, 2012, Kendra Biddick, Consumer Safety Officer for the REMS Compliance Team, Office of Compliance (OC) noted that OC had participated in meetings (during Cycle 2) between DPP, the Office of Surveillance and Epidemiology (OSE), and the sponsor. In the meetings, it was made clear to the sponsor that in order to prevent deaths, healthcare facilities must have immediate access on-site to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation.

On February 16, 2012, FDA sent an e-mail to the sponsor which included a REMS document that DRISK had drafted. At that time, the following important comments to improve enforceability of the REMS were provided by OC to the sponsor:

1.  (b) (4)
The documentation needs to be required. As a result, OC requested changing the wording from  (b) (4) to “must” as follows: “This training  (b) (4) **must** be documented and is subject to audit.”
2.  (b) (4)
Therefore, OC requested addition of the following: “These procedures, protocols, and/or order sets must be documented and are subject to audit.”
3.  (b) (4)
Therefore, OC requires modification of this section to read as follows: “The health care facility will meet requirements in b. through j. above prior to certification.”
4.  (b) (4)
OC requested addition of the following: “This training must be documented and is subject to audit.”

In the REMS Memorandum of November 1, 2012, OC noted that agreement has been reached between Compliance and OSE on REMS assessment and audit plans and concluded that “all Office of Compliance concerns have been adequately addressed.”

10. Discussion

In this review cycle (Cycle 3), there are no new issues from a clinical standpoint. The sponsor reports that no clinical studies have been ongoing or initiated in the period since the last patient was administered ADASUVE in the clinical program described in the original submission of NDA 22549. Therefore, there are no new clinical safety data to report in this resubmission.

As I noted in my Cycle 2 Review (April 9, 2012), the sponsor’s claim for efficacy in the treatment of acute agitation associated with schizophrenia or bipolar disorder is supported by the results of the two pivotal trials: Trial **004-301** in the acute treatment of agitation associated with schizophrenia, and Trial **004-302** in the acute treatment of agitation associated with bipolar disorder. However, significant pulmonary adverse events, particularly in subjects with asthma or COPD, were reported during the clinical program and are a major safety concern. In both the asthma (Trial **004-105**) and COPD (Trial **004-108**) trials, in which two doses of ADASUVE were given 10 hours apart, airflow obstruction was worse after the second dose.

In Cycle 3, the sponsor and the FDA have reached agreement on labeling and a REMS which should substantially decrease the risk of serious respiratory adverse events and facilitate safer and more effective management of serious respiratory adverse events should they occur. Important agreements between FDA and the sponsor in this regard include:

1. limiting dosing of ADASUVE to a single dose in 24 hours;
2. broadening of contraindications to include *current diagnosis* (in addition to history) of asthma, COPD, or other lung disease associated with bronchospasm;
3. requiring that ADASUVE be administered only in an enrolled healthcare facility that has immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation);
4. requiring that healthcare providers: 1) screen all patients for a history of asthma, COPD, or other pulmonary disease prior to administering ADASUVE; 2) examine patients (including chest auscultation) for respiratory signs (e.g. wheezing) prior to administering ADASUVE; and 3) monitor patients for symptoms and signs (i.e., vital signs and chest auscultation) of bronchospasm at least every 15 minutes for a minimum of one hour following treatment with ADASUVE; and
5. ensuring that relevant staff from healthcare facilities and wholesalers/distributors is adequately trained on the ADASUVE REMS program and procedures; and ensuring that this training is adequately documented and subject to audit.

As noted by DPARP, these strategies are expected to mitigate, but not eliminate, the risk of severe bronchospasm with inhalation of ADASUVE. Therefore, the proposed postmarketing observational study is very important because it will provide important information about utilization and safety of ADASUVE in a real-world setting.

11. Recommendations for Postmarketing Study

I am in agreement with the recommendations made by the Division of Epidemiology as detailed in their final review (November 27, 2012) of the proposed postmarketing study. Based on my review, I have the following additional comments:

1.  (b) (4)

2.  (b) (4)

12. Conclusions and Final Recommendations

In conclusion, from a clinical standpoint, I recommend approval of ADASUVE for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. The negotiated labeling and REMS are acceptable.

As I discussed in detail in my Cycle 2 Review (April 9, 2012), ADASUVE provides a non-invasive, rapid treatment of acute agitation associated with schizophrenia or bipolar disorder. Therefore, it will provide an alternative to current medications approved for this indication which are either invasive (eg, intramuscular) or may be of slower onset (eg, oral medications). Acute agitation is a severe, disruptive complication of schizophrenia and mania. It may progress from inner distress (nervousness, restlessness, panic) to an outwardly apparent dysfunctional state with cursing, hostility, difficulty controlling impulses, uncooperative behavior, and increased potential for violence. The rapid onset and proven efficacy of ADASUVE will quickly prevent escalation of agitation symptoms, decreasing the likelihood of injuries to the patient or medical personnel associated with having to physically restrain the patient.

There is significant risk of bronchospasm associated with ADASUVE use, especially in patients with asthma or COPD. However, the REMS will serve to decrease the risk of respiratory adverse events, increase the likelihood of early detection of respiratory

adverse events should they occur and, ensure that appropriate respiratory support and treatment is available on-site. Although the REMS will not completely eliminate the risk of severe bronchospasm associated with administration of ADASUVE, it will substantially mitigate this risk and ensure that appropriate management of bronchospasm is readily available on-site if needed.

A post-marketing observational study as outlined above and including the Division of Epidemiology recommendations should be required and will be important in identifying safety issues associated with use of ADASUVE in a clinical setting. At the time of this writing, final recommendations from DRISK and CDRH are pending. Therefore, my recommendation is contingent on approval recommendations from these divisions.

Francis E. Becker, M.D., F.A.C.P.
November 27, 2012
Medical Officer,
FDA CDER ODE1 DPP HFD 130

cc: NDA 22549
HFD 130
T Laughren
M Mathis
R Levin
K Updegraff
K Lehrfeld

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

/s/

FRANCIS E BECKER
11/27/2012

ROBERT L LEVIN
11/27/2012
See Cross-Discipline Team Leader review memo to follow.

**DIVISION OF PULMONARY, ALLERGY, and RHEUMATOLOGY PRODUCTS
BRIEFING PACKAGE REVIEW**

Date: November 13, 2012
To: Thomas Laughren, MD
Director, Division of Psychiatry Products
From: Theresa M. Michele, MD
Clinical Team Leader, Division of Pulmonary, Allergy, and
Rheumatology Products
Through: Sally Seymour, MD
Deputy Director for Safety, Division of Pulmonary, Allergy, and
Rheumatology Products
Through: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary, Allergy, and Rheumatology Products
Subject: Pulmonary safety evaluation of Adasuve (loxapine) inhalation powder for
New Drug Application (NDA) 22-549 at a dose of 5 mg or 10 mg every 2
hours as needed to a maximum dose of 30 mg per day for the treatment of
agitation associated with schizophrenia or bipolar disorder in adults

General Information

NDA#: 22-549
Sponsor: Alexza Pharmaceuticals
Drug Product: Adasuve (loxapine) inhalation powder
Materials Reviewed: NDA 22-549 SD#1, original submission dated December 11, 2009;
NDA 22-549 SD#28, complete response dated August 4, 2011;
NDA 22-549 SD#45, second complete response dated June 21, 2012;
various labeling and REMS submissions

1. Executive Summary

This is a consult review from the Division of Pulmonary, Allergy, and Rheumatology Products (DPAAP) regarding the second complete response for NDA 22-549. This consult further addresses labeling and REMS related to the pulmonary safety of loxapine inhalational powder, proposed for treatment of adult patients with agitation associated with schizophrenia and bipolar disorder. Loxapine is a typical first generation antipsychotic drug, similar to haloperidol. It was approved as an oral formulation in 1975 and an intramuscular formulation in 1979, although only the oral dosage form is currently marketed.

On June 21, 2012, Alexza submitted a complete response to the Division's May 2, 2012 action letter for NDA 022549 which provides for the use of Adasuve (loxapine) inhalation powder for the treatment of agitation associated with schizophrenia or bipolar disorder in adults. The original NDA was submitted on December 11, 2009. The Division issued the initial CR letter on October 8, 2010 citing pulmonary safety, CMC, and device

issues. The sponsor responded with a complete response to the October 8, 2010 deficiencies on August 4, 2011. A second CR letter was issued on May 2, 2012 citing CDRH facility inspection issues. During the first and second cycles for this application, DPARP worked closely with the Division of Psychiatry Products (DPP) to evaluate the pulmonary safety issues related to this formulation and provided input during the development of the REMS and labeling.

Pulmonary safety trials conducted with loxapine inhalational powder in healthy volunteers, patients with asthma, and patients with COPD demonstrate that inhaled loxapine can cause bronchospasm. This risk is increased in patients with underlying airway hyperresponsiveness, including asthma and chronic obstructive pulmonary disease (COPD), and is dose related, with greater decreases in lung function, as measured by forced expiratory volume in 1 second (FEV1), after a second dose. See consults dated August 20, 2010 by Dr. Anya Harry and March 16, 2011 by this reviewer for details. In the March 16, 2011 consult, DPARP made the following recommendations to potentially mitigate some of the risk of severe bronchospasm in patients receiving inhaled loxapine:

- Limit the administration of inhaled loxapine to a single dose in a 24 hour period. Studies in patients with asthma and COPD clearly demonstrate a larger decrease in FEV1 following a second dose of inhaled loxapine. In patients with asthma, the FEV1 did not return to baseline for at least 24 hours following a second dose of inhaled loxapine.
- Include the risk of bronchospasm in labeling (Boxed Warning) and contraindicate inhaled loxapine in patients: 1) with a history of asthma, COPD, or other lung disease associated with bronchospasm, 2) with acute respiratory signs or symptoms, 3) using medications to treat asthma or COPD, or 4) with a history of bronchospasm following inhaled loxapine treatment. Detailed labeling comments are discussed in Section 2.
- Require a REMS with Elements to Assure Safe Use (ETASU) to screen patients and avoid use of inhaled loxapine in patients at highest risk of bronchospasm, monitor patients following use of inhaled loxapine, and ensure appropriate personnel and equipment are available to treat bronchospasm. Inhaled loxapine should only be administered in health care facilities with immediate on-site access to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation. The REMS should include a training program for healthcare professionals administering inhaled loxapine, a monitoring plan following dosing, and institutional-level (i.e. pharmacy) controls permitting administration of only a single dose in 24 hours. The REMS will limit, but may not completely eliminate, potentially severe adverse airway events that may occur with inhaled loxapine. Details of the recommended REMS are discussed in Section 3.
- Obtain additional safety information through a post-marketing requirement (PMR) for an observational study to evaluate safety in a real-world setting using the approved REMS and labeling.

In addition, the sponsor has agreed to FDA proposed labeling, REMS, and post-marketing safety study. No new clinical data are provided in the complete response. As such, this review summarizes DPARP input during this review cycle on the PI and REMS.

2. Labeling

2.1. Package insert

Labeling discussions were held with the sponsor in the second review cycle and the majority of language was previously agreed upon. During this review cycle, (b) (4) the labeling language was refined for accuracy and consistency. DPARP agreed to the following language related to pulmonary safety and bronchospasm with DPP, the Division of Risk Management (DRISK), and the sponsor.

Boxed Warning

Bronchospasm

ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. Administer ADASUVE only in an enrolled healthcare facility that has immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation) [see Warnings and Precautions (5.1, 5.2)]. Prior to administering ADASUVE, screen patients regarding a current diagnosis, history, or symptoms of asthma, COPD and other lung diseases, and examine (including chest auscultation) patients for respiratory signs. Monitor for signs and symptoms of bronchospasm following treatment with ADASUVE [see Dosage and Administration (2.2, 2.4) and Contraindications (4)].

Because of the risk of bronchospasm, ADASUVE is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ADASUVE REMS [see Warnings and Precautions (5.2)].

Warnings and Precautions

Bronchospasm

ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. Administer ADASUVE only in an enrolled healthcare facility that has immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation) [see Warnings and Precautions (5.2)].

Prior to administering ADASUVE, screen patients regarding a current diagnosis or history of asthma, COPD, and other lung disease associated with bronchospasm, acute respiratory symptoms or signs, current use of medications to treat airways disease, such as asthma or COPD; and examine patients (including chest auscultation) for respiratory abnormalities (e.g., wheezing) [See *Dosage and Administration* (2.2) and *Contraindications* (4)]. Monitor patients for symptoms and signs of bronchospasm (i.e., vital signs and chest auscultation) at least every 15 minutes for a minimum of one hour following treatment with ADASUVE [see *Dosage and Administration* (2.4)]. ADASUVE can cause sedation, which can mask the symptoms of bronchospasm.

Because clinical trials in patients with asthma or COPD demonstrated that the degree of bronchospasm, as indicated by changes in forced expiratory volume in 1 second (FEV₁), was greater following a second dose of ADASUVE, limit ADASUVE use to a single dose within a 24 hour period.

Advise all patients of the risk of bronchospasm. Advise them to inform the healthcare professional if they develop any breathing problems such as wheezing, shortness of breath, chest tightness, or cough following treatment with ADASUVE.

ADASUVE REMS to Mitigate Bronchospasm

Because of the risk of bronchospasm, ADASUVE is available only through a restricted program under a REMS called the ADASUVE REMS. [see *Warnings and Precautions* (5.1)] Required components of the ADASUVE REMS are:

- Healthcare facilities that dispense and administer ADASUVE must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site access to equipment and personnel trained to provide advance airway management, including intubation and mechanical ventilation.
- Wholesalers and distributors that distribute ADASUVE must enroll in the program and distribute only to enrolled healthcare facilities.

Further information is available at www.adasuverems.com or 888-970-7367.

Adverse Reactions

Bronchospasm and Airway Adverse Reactions in Pulmonary Safety Trials

Clinical pulmonary safety trials demonstrated that ADASUVE can cause bronchospasm as measured by FEV₁, and as indicated by respiratory signs and symptoms in the trials. In addition, the trials demonstrated that patients with asthma or other pulmonary diseases, such as COPD are at increased risk of bronchospasm. The effect of ADASUVE on pulmonary function was evaluated in 3 randomized, double-blind, placebo-controlled clinical pulmonary safety trials in healthy volunteers, patients with asthma, and patients with COPD. Pulmonary function was assessed by serial FEV₁ tests, and respiratory signs and symptoms were assessed. In the asthma and COPD trials, patients with respiratory symptoms or FEV₁ decrease of $\geq 20\%$ were administered rescue treatment with albuterol (metered dose inhaler or nebulizer) as required. These patients were not eligible for a second dose; however, they had continued FEV₁ monitoring in the trial.

Healthy Volunteers: In the healthy volunteer crossover trial, 30 subjects received 2 doses of either ADASUVE or placebo 8 hours apart, and 2 doses of the alternate treatment at least 4 days later. The results for maximum decrease in FEV1 are presented in Table 2. No subjects in this trial developed airway related adverse reactions (cough, wheezing, chest tightness, or dyspnea).

Asthma Patients: In the asthma trial, 52 patients with mild-moderate persistent asthma (with FEV1 \geq 60% of predicted) were randomized to treatment with 2 doses of ADASUVE 10 mg or placebo. The second dose was to be administered 10 hours after the first dose. Approximately 67% of these patients had a baseline FEV1 \geq 80% of predicted. The remaining patients had an FEV1 60-80% of predicted. Nine patients (17%) were former smokers. As shown in Table 2 and Figure 7, there was a marked decrease in FEV1 immediately following the first dose (maximum mean decreases in FEV1 and % predicted FEV1 were 303 mL and 9.1%, respectively). Furthermore, the effect on FEV1 was greater following the second dose (maximum mean decreases in FEV1 and % predicted FEV1 were 537 mL and 14.7 %, respectively). Respiratory-related adverse reactions (bronchospasm, chest discomfort, cough, dyspnea, throat tightness, and wheezing) occurred in 54% of ADASUVE-treated patients and 12% of placebo-treated patients. There were no serious adverse events. Nine of 26 (35%) patients in the ADASUVE group, compared to one of 26 (4%) in the placebo group, did not receive a second dose of study medication, because they had a \geq 20% decrease in FEV1 or they developed respiratory symptoms after the first dose. Rescue medication (albuterol via metered dose inhaler or nebulizer) was administered to 54% of patients in the ADASUVE group [7 patients (27%) after the first dose and 7 of the remaining 17 patients (41%) after the second dose] and 12% in the placebo group (1 patient after the first dose and 2 patients after the second dose).

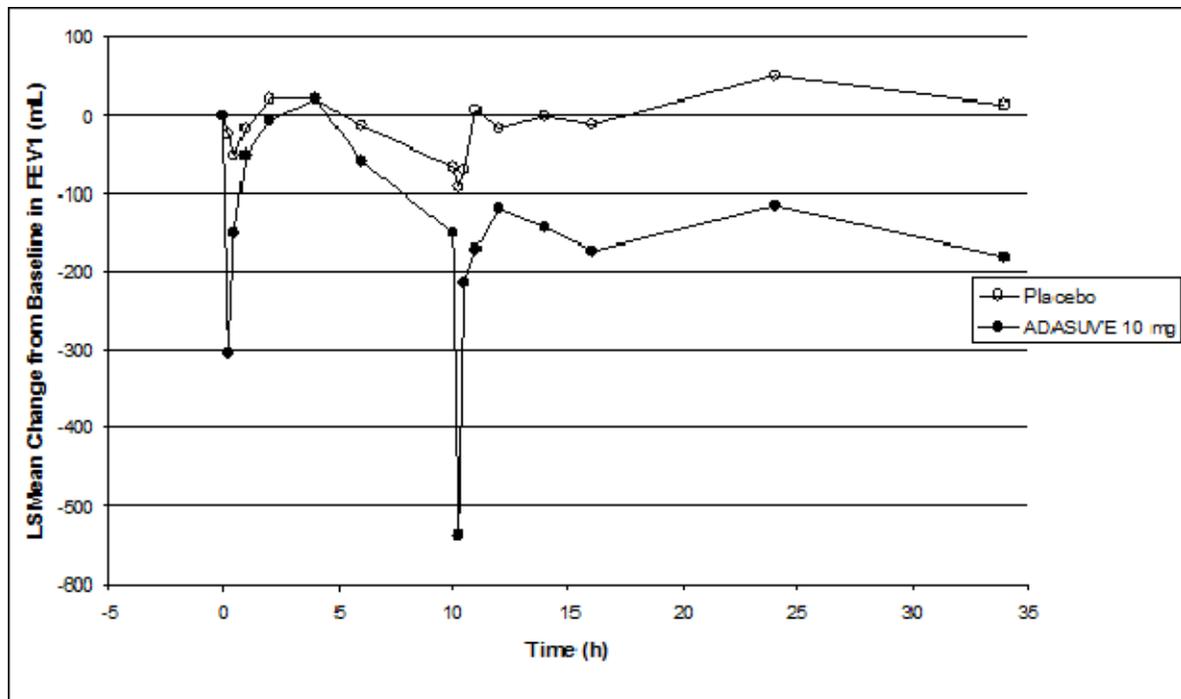
COPD Patients: In the COPD trial, 53 patients with mild to severe COPD (with FEV1 \geq 40% of predicted) were randomized to treatment with 2 doses of ADASUVE 10 mg or placebo. The second dose was to be administered 10 hours after the first dose. Approximately 57% of these patients had moderate COPD [Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage II]; 32% had severe disease (GOLD Stage III); and 11% had mild disease (GOLD Stage I). As illustrated in Table 2 there was a decrease in FEV1 soon after the first dose (maximum mean decreases in FEV1 and % predicted FEV1 were 96 mL and 3.5%, respectively), and the effect on FEV1 was greater following the second dose (maximum mean decreases in FEV1 and % predicted FEV1 were 125 mL and 4.5%, respectively). Respiratory adverse reactions occurred more frequently in the ADASUVE group (19%) than in the placebo group (11%). There were no serious adverse events. Seven of 25 (28%) patients in the ADASUVE group and 1 of 27 (4%) in the placebo group did not receive a second dose of study medication because of a \geq 20% decrease in FEV1 or the development of respiratory symptoms after the first dose. Rescue medication (albuterol via MDI or nebulizer) was administered to 23% of patients in the ADASUVE group: 8% of patients after the first dose and 21% of patients after the second dose, and to 15% of patients in the placebo group.

Table 2: Maximum Decrease in FEV1 from Baseline in the Healthy Volunteer, Asthma, and COPD Trials

	Maximum % FEV ↓	Healthy Volunteer		Asthma		COPD	
		Placebo n (%)	ADASUVE 10 mg n (%)	Placebo n (%)	ADASUVE 10 mg n (%)	Placebo n (%)	ADASUVE 10 mg n (%)
After any Dose		N=26	N=26	N=26	N=26	N=27	N=25
	≥10	7 (27)	7 (27)	3 (12)	22 (85)	18 (67)	20 (80)
	≥15	1 (4)	5 (19)	1 (4)	16 (62)	9 (33)	14 (56)
	≥20	0	1 (4)	1 (4)	11 (42)	3 (11)	10 (40)
After Dose 1		N=26	N=26	N=26	N=26	N=27	N=25
	≥10	4 (15)	5 (19)	2 (8)	16 (62)	8 (30)	16 (64)
	≥15	1 (4)	2 (8)	1 (4)	8 (31)	4 (15)	10 (40)
	≥20	0	0	1 (4)	6 (23)	2 (7)	9 (36)
After Dose 2		N=26	N=25	N=25	N=17	N=26	N=19
	≥10	5 (19)	6 (24)	3 (12)	12 (71)	15 (58)	12 (63)
	≥15	0	5 (20)	1 (4)	9 (53)	6 (23)	10 (53)
	≥20	0	1 (4)	1 (4)	5 (30)	1 (4)	5 (26)

FEV1 categories are cumulative; i.e. a subject with a maximum decrease of 21% is included in all 3 categories. Patients with a $\geq 20\%$ decrease in FEV1 did not receive a second dose of study drug.

Figure 7: LS Mean Change from Baseline in FEV1 in Patients with Asthma



Patients with a $\geq 20\%$ decrease in FEV1 did not receive a second dose of study drug and are not included in the curves beyond hour 10.

2.2 Medication Guide

Alexza submitted a medication guide for this product. Because the product will be given emergently to acutely agitated patients primarily in an emergency room setting, it is unclear if the majority of patients will be able to read or comprehend a medication guide prior to administration. This medication guide is unlikely to assist patients in making an informed decision about whether or not to take inhaled loxapine, so the medication guide was removed from the REMS. However, because a medication guide may be beneficial to a patient's family member or to the patient after the event, it is reasonable to have a medication guide available. DPARP collaborated with DRISK and DPP on the medication guide to assure that the risk of acute bronchospasm is appropriately conveyed. Key language is as follows:

What is the most important information I should know about ADASUVE?

ADASUVE is available only through the ADASUVE Risk Evaluation and Mitigation Strategy (REMS) Program. The healthcare facility must be enrolled in the ADASUVE REMS Program before you can be given ADASUVE.

ADASUVE may cause serious side effects, including:

- **Narrowing of the airways (bronchospasm) that can cause you to have problems breathing or to stop breathing.** People who have asthma or other airway or lung problems, such as chronic obstructive pulmonary disease (COPD), have a higher risk of bronchospasm when taking ADASUVE. Symptoms of bronchospasm may include:
 - wheezing
 - coughing
 - chest tightness
 - shortness of breath

Tell your healthcare provider right away if you have any of these symptoms of bronchospasm after taking ADASUVE.

Your healthcare provider should check you for breathing problems before and after you take ADASUVE.

3. Risk Evaluation and Mitigation Strategy (REMS)

The REMS is intended to both limit administration in patients at highest risk of bronchospasm and monitor patients following use of inhaled loxapine so that developing bronchospasm can be treated early. The ADASUVE REMS program includes Elements to Assure Safe Use (ETASU) that permits dispensation of inhaled loxapine only in health care settings that are specially certified. To become certified, a designated health care facility representative must attest to meeting the following REMS requirements:

- Each health care facility must have immediate access on-site to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation.

- Each health care facility must:
 - Screen patients, prior to treatment with Adasuve, for a history of pulmonary disease and for acute respiratory signs and symptoms by physical exam, including taking vital signs and chest auscultation, and inquiring if patient is taking medication to treat asthma or COPD.
 - Monitor patients at least every 15 minutes for a minimum of one hour following treatment with Adasuve for signs and symptoms of bronchospasm, including taking vital signs and chest auscultation.
 - Limit administration of Adasuve to one dose per patient within 24 hours.
- Each health care facility must establish procedures, protocols and/or order sets to help ensure compliance with the safe use conditions required in the ADASUVE REMS. Healthcare facility procedures, protocols, and/or order sets are subject to audit.
- Each health care facility must train relevant staff (e.g., staff involved in prescribing, dispensing or administering Adasuve and monitoring patients after Adasuve administration) on the safe use of Adasuve, as described in the ADASUVE REMS Education Program. This training must be documented and is subject to audit.

REMS materials included under the ETASU-B Healthcare Facility Certification include: 1) Dear Healthcare Professional Letter (DHCP), 2) ADASUVE REMS Education Program, 3) Steps for the Safe Use of ADASUVE, 3) Healthcare Provider Brochure, 4) Health Care Facility Information and Enrollment Form, 5) Order Set/Protocol Template, and 6) ADASUVE REMS website (www.adasuverems.com). DPARP has worked with DRISK and DPP to ensure that the REMS documents appropriately convey pulmonary risk. In addition the REMS Oversight Committee (ROC) has reviewed the ADASUVE REMS on two separate occasions and agrees to the currently proposed plan.

The sponsor has agreed to submit REMS assessments to the FDA at 6 and 12 months from the date of the REMS approval, and annually thereafter. As noted previously, these restrictions likely will limit, but may not completely eliminate, potentially severe adverse airway events that may occur with inhaled loxapine.

4. Post-marketing Requirement

If approved, a post-marketing study to evaluate the safety of Adasuve in a real-world setting, using the REMS, will be required. The protocol for this study is currently under review by the Division of Epidemiology (DEPI). As of the date of this consult review, the timelines for the PMR have not yet been finalized. DPARP recommends the following or similar language regarding this trial for the post-marketing commitment (PMC).

You are required to conduct a large, non-randomized, open-label, postmarketing observational study to assess the risks of bronchospasm and related respiratory adverse events associated with use of ADASUVE in clinical practice under the requirements of the ADASUVE REMS and per labeling. The study must have a

large sample size (at least 10,000 ADASUVE patients who are enrolled in the study), in order to adequately characterize the frequency, nature, and severity of the risk of bronchospasm (presumably a rare event). The study must collect information regarding all respiratory events following ADASUVE administration, including: 1) shortness of breath, coughing, wheezing, chest tightness, and other respiratory symptoms, 2) short-acting bronchodilator and other respiratory medication use, 3) serious adverse events including hospitalization for respiratory adverse reactions, intubation, and mechanical ventilation, and 4) deaths.

We must agree prospectively on all aspects of the protocol: the study design, site selection methodology, sample size calculation, patient selection criteria, inclusion/exclusion criteria, medical history (e.g. diagnoses for COPD, asthma, former and current cigarette smoking, and past and current treatments for respiratory disease, other comorbidities, concomitant medications), primary and secondary endpoints, exposure definition and measurement, outcome definition and measurement, methods for follow-up and ascertainment of cases, required duration of follow-up post-dosing, statistical analysis plan, ways to minimize potential sources of bias, and types of relevant data to be collected. Additionally, response rates and aggregate data (e.g. demographics, occurrence of serious AEs, if available) on patients who do not agree/consent to participate in the study must be provided. Prior to initiation of study, all aspects of the protocol must be approved. You must submit all protocol amendments.

6. Conclusions

There is a significant risk of post-inhalation bronchospasm following administration of inhaled loxapine, particularly in patients with underlying airway hyperresponsiveness caused by conditions such as asthma and COPD. The severity of obstruction is greater following a second dose and does not return to baseline for 24 hours or more following repeat dosing. Characteristics of the patient population, including a high prevalence of smoking and inability to give a reliable history, increase the risk of bronchospasm following inhaled loxapine administration. During this review cycle, DPARP recommendations regarding communication of risk and mitigation strategies are incorporated into the proposed product labeling, REMS, and PMC study. These strategies are expected to mitigate, but not eliminate, the risk of severe bronchospasm with inhaled loxapine.

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

/s/

THERESA M MICHELE
11/26/2012

SALLY M SEYMOUR
11/26/2012

BADRUL A CHOWDHURY
11/26/2012
Concur

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

DATE: May 1, 2012

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for complete response action for Staccato Loxapine for Inhalation for the treatment of agitation associated with schizophrenia and bipolar disorder.

TO: File NDA 22-549
[Note: This overview should be filed with the 1-10-2012 submission of new information to the NDA.]

1.0 BACKGROUND

Loxapine is a typical antipsychotic (primarily D2 antagonism) approved since 1975 for the treatment of schizophrenia. Staccato Loxapine for Inhalation is a single-use, hand-held drug device combination product intended to provide for rapid systemic delivery by inhalation of a thermally generated aerosol of loxapine. Oral inhalation through the Staccato device triggers the controlled rapid heating of a thin film of loxapine to form a drug vapor that is then inhaled. The vapor condenses to aerosol sized particles for delivery to the deep lung, with expectation of rapid systemic delivery. This new dosage form is intended to be used for the treatment of agitation associated with schizophrenia and bipolar disorder. Patients experiencing exacerbations of schizophrenia or bipolar mania often present with agitation that needs to be treated before they can be transitioned to oral medications. Thus, this is an important clinical problem to address. Three immediate release intramuscular forms of atypical antipsychotics are approved for this indication in the US (Zyprexa, Geodon, and Abilify).

The application was originally submitted on 12-11-09. In support of efficacy, the sponsor submitted the results of 2 placebo-controlled, fixed dose studies (5 and 10 mg). These were both in agitated patients, one in schizophrenia and one in bipolar mania. The endpoint for these trials was change from baseline to a 2 hour time point on the PANSS Excited Component (PEC). The results were highly significant, for both the 5 and 10 mg doses, vs pbo. In addition, looking at time course of response, the effect was observable beginning at the first observation time (10 minutes) for both 5 and 10 mg. The effect size, however, was numerically slightly larger for the 10 mg dose, suggesting a slight advantage for the 10 mg dose over 5 mg. The primary safety concern was a finding of bronchospasm in special safety studies conducted in patients with asthma and COPD. The primary measure in these trials was FEV1. Patients could be given two

10 mg doses, with a 10 hour between dose interval. The 2nd dose could be given only if FEV1 did not decrease more than 20% after the 1st dose. There was a placebo control in both trials. Although there were no serious AEs in asthma, COPD, or healthy control studies, there were important findings in the special studies in asthma and COPD patients.

-For the asthma study, there was a mean decrease in FEV1 of about 300 mL after the 1st dose and over 500 mL after the 2nd dose. 54% of drug exposed patients vs 12% of placebo patients had respiratory symptoms, and the percentages were the same for albuterol rescue use. Nine out of 26 drug-exposed patients did not get the 2nd dose.

-For the COPD study, there was a mean decrease in FEV1 of about 125 mL after the 1st dose and over 500 mL after the 2nd dose. 15% of drug exposed patients vs 11% of placebo patients had respiratory symptoms, and the percentages for albuterol rescue use were 23% vs 15%. Twenty-five out of 26 drug-exposed patients did not get the 2nd dose.

-In the clinical trials (with very thorough screening for asthma and COPD), there were very few respiratory symptoms (0/263 pbo; 2/265 5 mg and 2/259 10 mg). There was only 1 instance of bronchospasm, and that patient required albuterol rescue (no history of asthma).

We issued a Complete Response (CR) letter for this application on 10-08-10. Based on the initial review, we concluded that, although the sponsor had demonstrated the efficacy of this product for the intended claim, we had ongoing concerns about the product's safety for the intended use, and this was one reason for the CR action. In addition, there were a number of manufacturing issues, including a facilities inspection that identified a number of deficiencies. All of these deficiencies were conveyed to the sponsor. The safety concern was bronchospasm, particularly in patients with asthma or COPD. The sponsor responded to the CR letter with an 08-04-11 submission that attempted to address some of our concerns. We reviewed that response, and took the application to the PDAC on 12-12-11. The focus of that meeting was on our concerns about the product's potential for pulmonary toxicity. We argued that a risk evaluation and mitigation strategy (REMS) would be needed to ensure the safety use of this product, if it were to be approved.

2.0 PDAC MEETING

There were both questions for discussion by the committee, and several questions for a vote:

Discussion questions:

- Is it possible to make valid comparisons of the onset of effect for Adasuve and other drugs in the class in the absence of head-to-head studies? (DISCUSSION)
- If yes, how does time of onset of this product compare with that of other products approved for this indication? Is this difference a substantial advantage? (DISCUSSION)
- Would comparative studies with currently approved intramuscular products be needed to demonstrate an advantage(s) for this product? (DISCUSSION)

Discussion: The consensus of the committee was that it is not possible to reach conclusions about the relative efficacy of Adasuve compared to other drugs in the class without actual studies, i.e., they did not feel that pharmacokinetic data would be sufficient. There was, however, no consensus that such studies would be needed as a basis for approval.

- Do you think the sponsor’s proposed Risk Evaluation and Mitigation Strategy (**REMS**) would ensure that the benefits of this product outweigh its risks? (DISCUSSION)
- If yes, could the REMS be less burdensome and still accomplish the level of safety necessary to ensure safe use of this product? (DISCUSSION)
- If no, would strengthening the REMS ensure that the benefits of Adasuve outweigh its risks? How should the REMS be strengthened? (DISCUSSION)
- Would additional steps, beyond strengthening REMS, be needed? (DISCUSSION)
Discussion: The committee felt that something like FDA’s proposed REMS would be needed. Even with that, however, several of the pulmonologists on the committee expressed concern about the possibility of 2nd and 3rd doses at 2 hr intervals, given that these intervals had not been evaluated in the special safety studies.

The sponsor had proposed an observational study, to be conducted after approval. The goal of that study would have been to obtain a better estimate for the risk of serious adverse events, particularly bronchospasm, associated with the use of this product in an emergency room setting.

- Does the committee have any recommendations regarding the proposed post-marketing observational study? (DISCUSSION)
- Should an observational study be considered a preapproval requirement, or would it be sufficient to conduct such a study post-approval? (DISCUSSION)

Discussion: There was general agreement on the committee that such a study should be done, and that it should focus on a large cohort to find out how the product is tolerated in a real world setting (ER).

Voting questions:

Does the committee conclude that Adasuve (loxapine) inhalation powder has been shown to be effective as a treatment for agitation in patients with schizophrenia or bipolar mania?

Vote: Yes= 17 No = 1

Does the committee conclude that Adasuve (loxapine) inhalation powder has been shown to be acceptably safe for use as a treatment for agitation in patients with schizophrenia or bipolar mania:

- When used in conjunction with the REMS proposed by the sponsor?

Vote: Yes= 1 No = 17

- When used in conjunction with the REMS proposed by FDA?

Vote: Yes= 5 No = 12

Committee Discussion: At the current sponsor proposed dose (10 mg every 2 hours, up to 3 doses in 24 hours), the majority of the committee agreed that Adasuve (loxapine) inhalation powder had not been shown to be acceptably safe for use as a treatment for agitation in patients with schizophrenia or bipolar mania when used in conjunction with either the sponsor proposed or the FDA proposed REMS. There were concerns that there were not enough data to support the safe use of two doses within 2 hours, especially when the effectiveness of screening patients in an emergency room setting was not well-established. (see the transcript for details of the committee discussion).

Based on the discussions that transpired, the following question was added during the meeting: If the product was limited to a single dose in 24 hours, does the committee conclude that Adasuve (loxapine) inhalation powder would be acceptably safe for use as a treatment for agitation in patients with schizophrenia or bipolar mania when used in conjunction with the REMS proposed by FDA?

Vote: Yes= 11 No = 5 Abstain = 2

Committee Discussion: The majority of the committee agreed that a single dose of Adasuve (loxapine) inhalation powder in 24 hours would be acceptably safe for use as a treatment for agitation in patients with schizophrenia or bipolar mania when used in conjunction with the REMS proposed by FDA. However, some of the pulmonologists on the committee still disagreed, as they felt that there was not enough information on the safety of even one dose in emergency room settings. (see the transcript for details of the committee discussion).

Based on the discussions that transpired, the following question was added during the meeting: Does the committee conclude that Adasuve (loxapine) inhalation powder should be approved for use as a single dose in 24 hours when used with the FDA proposed REMS as a treatment for agitation in patients with schizophrenia or bipolar mania?

Vote: Yes= 9 No = 8 Abstain = 1

Committee Discussion: A slight majority of the committee was in favor of approving Adasuve as a single dose in 24 hours when used with a REMS as proposed by FDA, given the data now available. The primary disagreement was in regard to the safety of even a single dose despite having the FDA proposed REMS in place. Many of the committee members who voted “No” indicated that an observational study involving a cohort of patients treated with this product in an emergency room setting would be needed prior to approval. Other committee members felt that such a study was not needed as a pre-approval requirement. Within disciplines of committee members, there were some differences in voting, but the differences were not dramatic. Of the 18 voting committee members, there were 6 psychiatrists, 5 pulmonologists, 4 DSARM members who were non-MDs, 1 statistician, 1 consumer rep, and 1 patient rep. The voting was as follows:

<u>Discipline</u>	<u>Yes</u>	<u>No</u>	<u>Abstain</u>
Psychiatry	4	2	
Pulmonologist	2	3	
Statistician		1	
Consumer rep		1	
Patient rep	1		
DSARM	2	1	1

3.0 1-10-12 SUBMISSION OF NEW INFORMATION

On 1-10-12, the sponsor submitted additional information, including new labeling and an extensively revised REMS. Based on this new information, we extended the review clock by 3 months, to 5-5-2012. The 1-10-12 response did not address the numerous manufacturing issues.

Revised REMS

There is agreement that, given the available information on the safety of Adasuve, its use must be limited to settings in which there is immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (nebulization, intubation and mechanical ventilation). Patients being considered for Adasuve must be screened for all those circumstances for which its use would be contraindicated. Following administration of Adasuve, patients must be monitored every 15 minutes for 1 hour for respiratory signs and symptoms, including vital signs and chest auscultation. Dosing is limited to one administration in any 24 hour period.

There is also now agreement that Adasuve's availability must include a REMS that assures its safe use. Therefore, the REMS for which we have obtained agreement with the sponsor includes healthcare facility certification and a communication plan. Certification will include attestations by the healthcare facility that they have the necessary capability to fully manage bronchospasm, that patients are screened and monitored appropriately, and that staff are trained on the safe use of Adasuve. The communication plan will include a Dear Healthcare Provider Letter, a safety use checklist, an education program, and a prescriber brochure.

The REMS for Adasuve was presented twice to the REMS Oversight Committee (ROC): 10-14-11 and 4-5-12. Recommendations were made at the October, 2011 meeting, and the finalized REMS was considered acceptable at the April, 2012 meeting.

Revised Labeling

We have negotiated labeling with the sponsor, and we are close to an agreement on labeling for Adasuve. Importantly, it includes a box warning regarding bronchospasm, and prominently mentions the REMS. Labeling limits dosing to one administration in any 24 hour period. Since the manufacturing issues have not been adequately addressed, and we cannot issue an approval letter in this review cycle, we will include our currently preferred version of labeling in the CR action letter.

4.0 FINAL CLINICAL REVIEWS ON SAFETY ISSUES

DPP Staff

DPP staff, including both Drs. Becker and Levin, have concluded that, with our proposed labeling and REMS, this product can be approved.

DPARP Staff

A final review written by Theresa Michele, M.D., from DPARP, was signed into DARRTS on 3-29-12. This review summarizes the pulmonary safety concerns for Adasuve, and the agreed upon labeling and REMS. DPARP concludes that the proposed labeling and REMS mitigates, but of course does not completely eliminate, the risk of severe pulmonary adverse events associated with the use of this product.

5.0 OTHER ISSUES

HF Study

The sponsor conducted a second human factors study with the revised product and packaging, and this study has been deemed satisfactory.

Observational Study

One of the issues regarding the approval of this product was the fact that the development program did not, for the most part, include use in the setting where the product would likely find extensive use once marketed, namely, a typical emergency room. A concern was whether or not patients in the emergency room setting could be as successfully screened for contraindicated conditions as was the case in the phase 2-3 trials for this program. The sponsor had proposed a relatively small, comparative observational study to address this concern. We held a t-con with the sponsor on 3-1-12 to further discuss the type of study that we considered important. We noted that a comparison with other products for treating agitation was less important than determining if screening would be as successful in the more typical emergency room setting as it appeared to be in the trials conducted in the development program. We also emphasized the importance of studying a large cohort so that the risk of severe pulmonary adverse events could be more precisely estimated. We proposed that a sample of roughly 10,000 exposures would be needed. The sponsor has now agreed to conduct a 10,000 patient cohort study post-approval to estimate the risk of use of Adasuve in a real world setting. We have not had sufficient time to review the complete protocol (submitted very late in this review cycle). We will continue to review this protocol and provide comments to the sponsor during the next review cycle.

Manufacturing Issues

The sponsor has not adequately responded to the manufacturing deficiencies for this product. A 483 was issued to the sponsor in December, 2011, and they have not provided a sufficient response to the listed deficiencies. Once they do respond, there is a need for a follow-up inspection. Therefore, the CDRH Office of Compliance has issued a WITHHOLD recommendation, and CDER Office of Compliance agrees with this recommendation.

Pediatric Use

The sponsor has agreed to a post-approval study in pediatric patients ages 10 and older, and we have internal agreement that such a plan would be acceptable.

6.0 PUBLIC CITIZEN LETTER

Public Citizen Letter:

They urged FDA not approve this product, based on what information they gleaned from the December, 2011 PDAC meeting. Of course, they did not have access to the sponsor's most recent submission of revised labeling and REMS. In my view, their concerns have been addressed in this review cycle.

7.0 CONCLUSIONS AND RECOMMENDATIONS

This is a difficult to manage patient population, and they are often unwilling to accept IM injections; even for those who do, the effect is delayed by 20-30 minutes. Thus, I feel there is a role for this product, which is essentially equivalent to an IV injection. No patients, either in the clinical studies for this product or in the special studies in patients with asthma or COPD experienced serious, unmanageable AEs. We are very close to an agreement with the sponsor on labeling and a REMS program. The sponsor is also agreeable to conducting a postmarketing observational study involving 10,000 patients to better estimate the risks of use in a real world, emergency room setting. The review team is agreeable to approving this product with the proposed labeling and REMS, and I am as well. The one remaining issue that is holding up an approval action is the manufacturing of the product. We will convey these deficiencies in the CR letter.

cc:

Orig NDA 22549

ODE-I/EUnger

HFD-130/TLaughren/MMathis/RLevin/FBecker/KUpdegraff

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/s/

THOMAS P LAUGHREN
05/01/2012

Cross-Discipline Team Leader Review Memo

Date of the review:	April 25, 2012
From:	Robert L. Levin, M.D.
Subject:	Cross-Discipline Team Leader Review
NDA:	22549
Sponsor:	Alexza Pharmaceuticals
Type of Submission:	Complete Response
Submission Date:	August 4, 2011
Related IND:	73248
Cross-referenced NDAs	17-525, 17-658, and 18-039 (Lederle Labs) Loxapine oral tablets, loxapine oral solution, and loxapine intramuscular injection
Proprietary / Established name:	ADASUVE [®] <i>Staccato</i> [®] Loxapine Powder for Oral Inhalation
Therapeutic Class	Antipsychotic
Dosage forms / strength:	Combination Drug-Device Product - Single Use Inhalation Device Loxapine 5 mg and 10 mg
Proposed Indications:	1. Acute Agitation associated with Schizophrenia 2. Acute Agitation associated with Bipolar Disorder
Recommendation:	Complete Response

1. Introduction and Summary

ADASUVE (*Staccato*[®] Loxapine powder for oral Inhalation) is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery of loxapine aerosol through absorption in the deep lung. Loxapine is a typical antipsychotic approved in 1975 for the treatment of psychosis. Oral inhalation through the device initiates the controlled, rapid heating (up to 400°C) of a thin film of excipient-free loxapine, resulting in a thermally generated drug vapor, which rapidly condenses into aerosol particles. The particles are of an appropriate size for delivery to the deep lung where the drug is rapidly absorbed.

On 11 December 2009, the sponsor submitted the original NDA for *Staccato*[®] Loxapine in the treatment of acute agitation associated with schizophrenia or bipolar I disorder. The sponsor demonstrated the efficacy of inhaled loxapine in the treatment of acute agitation associated with schizophrenia or bipolar disorder. However, the Division took a Complete Response action on 8 October 2010, because of the risk bronchospasm and related serious outcomes. The sponsor had not submitted an adequate risk evaluation and mitigation strategy (REMS) or adequate product labeling for mitigating the risk of pulmonary toxicity. On 4 August 2011, the sponsor submitted a complete response. There are no new clinical data in the submission. The contents of the submission include a REMS with elements to assure safe (ETASU) use and product labeling. The sponsor has

submitted new data from human factors and usability studies. The sponsor has also submitted a protocol for a postmarketing observational study to assess the risk of bronchospasm when used in clinical practice under the Adasuve REMS.

This review will focus on the risk of bronchospasm and related serious outcomes as well as the REMS and labeling that would be required to mitigate the risk. A multidisciplinary review team worked together closely throughout the review cycle to formulate the Agency's Adasuve REMS and product labeling. We met on numerous occasions to discuss the issues and draft the REMS and labeling. The review team included the Division of Risk Management (DRISK), the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), the Division of Medication Error Prevention and Analysis (DMEPA), the CDRH Division of Anesthesiology, General Hospital, Infection Control, and Dental (CDRH/DAGID), the Study Endpoint and Labeling Division (SEALD), the Division of Pharmacovigilance (DPV), the Division of Epidemiology (DEPI), and the Division of Psychiatry Products (DPP). All of these divisions made major contributions, and their input was critical. The review team also included the Office of New Drugs Quality Assurance (ONDQA), the Office of Clinical Pharmacology (OCP), the Pharmacology-Toxicology in DPP, the Pediatric and Maternal Health Staff (PMHS), Division of Medical Policy Programs (DMPP) – Patient Labeling Team, the CDRH Office of Compliance, and the CDER Office of Compliance. I agree with all of their conclusions and recommendations. I have no disagreements with any of the review teams. Furthermore, the review teams have reached a consensus on all aspects of the REMS and labeling.

During this review cycle, the Agency and the Sponsor had considerable disagreements about the content of the REMS that would be required to mitigate the risk of bronchospasm and serious outcomes such as respiratory arrest and death. The sponsor proposed a minimally restrictive REMS. Under the sponsor's REMS, the use of Adasuve would be limited to facilities that had access to a bronchodilator (via metered-dose inhaler). In essence, under the sponsor's REMS it would be permissible to use Adasuve in a wide range of facilities that did not have immediate access to appropriate personnel and materials required for advanced airway management (including bronchodilator medication via nebulizer, intravenous corticosteroids, intubation, and mechanical ventilation).

In my opinion, the thorough REMS developed by the Agency would substantially mitigate the risk of bronchospasm and related serious outcomes. Under the Agency's Adasuve REMS, lorazepam by oral inhalation may only be administered within facilities that have immediate, on-site access to personnel and materials necessary to deliver advanced airway management (including bronchodilator medication via nebulizer, intravenous corticosteroids, intubation, and mechanical ventilation). As part of the REMS, the Agency has developed detailed full prescribing information and instructions for use that would mitigate the risk of bronchospasm. Labeling includes: 1) contraindications regarding patients at increased risk of developing bronchospasm, 2) a prominent boxed warning and a detailed warning regarding the risk of bronchospasm and measures to mitigate the risk, 3) specific recommendations for thoroughly monitoring

patients following treatment, 4) dosing recommendations that limit treatment to one dose within 24 hours, and 5) detailed instructions for use in the full prescribing information and device packaging that include recommendations for screening and monitoring patients. The REMS requires that enrolled facilities attest to meeting the requirements of the REMS, including providing appropriate training for providers who would administer loxapine. The sponsor is required to develop educational materials for the use of inhaled loxapine. In addition, there are postmarketing requirements for mandatory reporting of bronchospasm and related adverse events.

There are potential limitations for the REMS to eliminate serious outcomes related to bronchospasm. Because of the nature of acute agitation, it will not always be possible to identify patients who have pulmonary disease and are at increased risk of bronchospasm. Thus, it is possible that some patients at increased risk could receive treatment. Also, it is possible that some patients without a history of lung disease could develop their first episode of bronchospasm following treatment with inhaled loxapine. In addition, because bronchospasm can progress quickly, it may not always be possible to prevent serious outcomes even when appropriate personnel and materials are available on-site.

If the product is approved, there will be a postmarketing requirement for the sponsor to conduct a very large observation study to assess the risk of bronchospasm and serious outcomes when loxapine is used in clinical practice under the REMS. The objectives would be to characterize the nature, frequency, and severity of the risks and determine whether the REMS is effective in mitigating the risks.

In my opinion, loxapine by inhalation may have unique benefits compared to other available treatments for acute agitation (i.e., atypical antipsychotics for intramuscular injection). Treatment with inhaled loxapine results in rapid systemic delivery of the drug and rapid onset of action. The effects on acute agitation were apparent within 10 minutes of administration for loxapine 5 mg and 10 mg. It is critically important to control acute agitation as quickly as possible, because acutely agitated patients are at risk for dangerous behavior toward themselves and others, and such behavior can be life-threatening. Although the sponsor did not conduct direct comparisons with products approved for acute agitation, it is apparently widely accepted that antipsychotic injections are typically not effective for at least 30 minutes. Because of this relatively late effect, antipsychotics by injection are often combined with benzodiazepines for intramuscular injection in order to treat acute agitation more quickly. In addition, loxapine by oral inhalation would be a non-invasive option for treatment. It is often necessary to use physical restraint and involuntary injections when treating an acutely agitated patient. Thus, there is a risk of physical injury to the patient and healthcare providers, including the risk of contaminated needle stick injury. Intramuscular injections are often viewed as coercive. Because loxapine by inhalation is a non-invasive treatment and requires a degree of cooperation from the patient, it could provide a relative advantage for patients and staff, compared to other treatments. With this non-invasive treatment option, patients can have a more active role in decisions about treatment, which in itself has the potential to de-escalate acute agitation. In addition, the use of such a therapeutic option has the potential to help foster the therapeutic alliance between the patient and healthcare providers.

The critical issue preventing approval of the NDA is that the sponsor has not responded adequately to concerns outlined by the Center for Devices and Radiologic Health (CDRH), Office of Compliance. There are deficiencies in the device validation processes. According to the CDRH and CDER offices of compliance, there are repeat observations that the sponsor has not addressed fully. The sponsor must respond adequately. In addition, it will be necessary for the CDRH OC to conduct another inspection of the manufacturing facility after the sponsor has submitted adequate data. The CDRH Office of Compliance has made a recommendation of Withhold to CDER OC. CDER OC agrees with the Withhold recommendation. In addition, Dr. Claffey (the CMC reviewer) agrees with the OC recommendations, and he does not support approval of the application.

2. Background and Regulatory History

The key aspects of the regulatory history of the application are outlined below:

- **August 31, 2005:** Alexza submitted an IND application (73-248) for Staccato Loxapine in the treatment of acute agitation associated with schizophrenia or bipolar I disorder.
- **December 11, 2009:** The sponsor submitted the original NDA (22549) for the treatment of acute agitation associated with schizophrenia or bipolar I disorder.
- **October 8, 2010:** The Division took a Complete Response action, identifying pulmonary toxicity (bronchospasm) as the primary issue.
- **December 17, 2010:** The Division and Alexza held an End of Review Meeting to discuss the complete response action and potential means of resolving the issues. The Division stated that it would be reasonable to propose a REMS program to mitigate the risk of pulmonary toxicity.
- **April 29, 2011:** Type C Meeting to discuss the possible components of a REMS, including Elements to Assure Safe Use (ETASU).
- **August 4, 2011:** Alexza submitted a Class 2 Complete Response resubmission. The submission included a REMS with the following components: Elements to Assure Safe Use, revised product labeling, a Medication Guide, a Communication Plan, a Healthcare Facility Certification, an Implementation System, and a timetable for submission of Assessments.
- **October 14, 2011:** REMS Oversight Committee (ROC) meeting: DRISK and DPP presented the review team's minimum requirements for the Adasuve REMS program. The committee agreed that ETASU would be required. They also recommended obtaining input from outside stakeholders (from the Drug Safety Board, for example) during the development of the REMS.

- **November 16, 2011:** Drug Safety Oversight Board (DSB) Meeting – DRISK presented the proposed minimum requirements for the Adasuve REMS. The board commented on the impact the REMS program might have on their healthcare facilities. The discussion did not result in revisions to the Agency’s proposed REMS.
- **December 12, 2011:** Psychopharmacologic Drugs Advisory Committee (PDAC) Meeting. The committee was supplemented with members from the Pulmonary-Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. The committee discussed the potential risks and benefits of treatment with Adasuve, and they considered the REMS programs proposed by FDA and the sponsor. The Advisory Committee members voted 9 to 8 (with one abstention) to approve Adasuve with the FDA-recommended REMS and limiting administration to one dose within a 24-hour period.
- January 10, 2012: Alexza submitted REMS Amendment #2 to align after taking into consideration the Agency’s REMS presented at the PDAC meeting.
- January 19, 2012: The Division decided to extend the review by 3 months, in order to review the REMS (a major amendment to the submission)
- Throughout the review cycle, FDA provided comments to the sponsor about the requirements for the REMS with ETASU. During the 01 March 2012 teleconference with Alexza, the Division clarified that “immediate, on-site access to advanced airway management capabilities” meant that these capabilities must be available within the healthcare facility in which the product would be administered, as opposed to being available by calling emergency response services.

Summary of Cross Discipline Team Leader Review Memo

The following is a summary of my Cross-Discipline Team Leader memo from the first review cycle (October 5, 2010):

The primary safety concern was the pulmonary toxicity associated with loxapine by oral inhalation. Clearly, the toxicity is drug-related. However, an additional component of the toxicity appears to be related to use of the device itself. In the 3 pulmonary safety studies, pulmonary function testing revealed clinically significant decreases in FEV1 that were greater than 10%, 15%, and 20% for individual subjects. A decrease in FEV1 of greater than 10% is considered clinically significant. Furthermore, standard bronchoprovocation tests induce a decrease in FEV1 of 10-20%. Approximately 19% of healthy subjects treated with loxapine and 4% treated with placebo had decreases in FEV1 >15%, and 4% of healthy subjects treated with loxapine had decreases in FEV1 >20%.

In subjects with asthma or COPD, the FEV1 findings were marked. Moreover, a substantial proportion of subjects in the asthma and COPD studies had significant

respiratory signs and symptoms requiring rescue treatment with bronchodilator medication. In asthma subjects, 85%, 62%, and 42% had decreases in FEV1 >10%, >15%, and >20%, respectively. In COPD subjects, 80%, 56%, and 40% had decreases in FEV1 >10%, >15%, and >20%, respectively. A high proportion (40-69%) of asthmatic and COPD subjects had significant respiratory adverse reactions, and a substantial proportion required rescue treatment with bronchodilator medication. Respiratory adverse reactions included bronchospasm, dyspnea, wheezing, chest discomfort and tightness, throat tightness, and cough.

Pulmonary toxicity was dose-related. Subjects treated with a second dose had greater decreases in FEV1 (compared to their first dose) which did not return to baseline at 32 hours post-dose. A significant proportion of asthmatic and COPD subjects were discontinued from the study before receiving the planned second dose, because they had a decreased FEV1 and/or the need for rescue treatment. As a result, one could not determine the true nadir of the FEV1 following treatment with inhaled loxapine.

Additional factors could contribute to an excessive risk of pulmonary toxicity in the intended population. Patients with schizophrenia and bipolar disorder have a high prevalence of tobacco smoking. Thus, many of these patients will have some degree of respiratory disease burden at baseline. Another concern was that acutely agitated patients with schizophrenia or bipolar disorder may be incapable of providing an accurate history of pulmonary disease during the episode of agitation. Similarly, healthcare professionals may not be able to perform an adequate respiratory examination during an acute episode of agitation. Moreover, sedation from loxapine could obscure respiratory signs and symptoms. Finally, the dosage and administration section of proposed labeling stated that inhaled loxapine could be administered every 2 hours up to 3 times, which would allow repeat dosing prior to recovery of FEV1.

We had concluded that labeling would not adequately mitigate the risk of pulmonary toxicity. Furthermore, the sponsor had not submitted a REMS for mitigating the risk.

Foreign Regulatory History and Actions

In October 2011, Alexza submitted a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for marketing authorization via the Centralized Procedure in the European Union. The application is currently under review by EMA. The EMA sent a preliminary list of questions (Day 120 LOQs) which identified several principal deficiencies and concerns. The target submission date for the responses is July 2012. The principal issues are summarized below:

Clinical:

(b) (4)

[REDACTED]

[Redacted] (b) (4)

Safety: [Redacted] (b) (4)

Risk Management Plan: [Redacted] (b) (4)

Quality (CMC): [Redacted] (b) (4)

3. Chemistry Manufacture and Controls, Office of New Drug Quality Assurance (ONDQA)

David Claffey Ph.D. performed the CMC review, and he has filed 3 reviews during the second cycle (15 November 2011, 23 March 2012, and 23 April 2012). Dr. Claffey has stated that he could not recommend approval, because the CDRH and CDER Offices of Compliance have made Withhold recommendations. The sponsor has not responded adequately regarding the deficiencies observed by CDRH. I agree with Dr. Claffey's conclusions and recommendations.

During the first review cycle, the CDER Office of Compliance issued a recommendation of Withhold, based on findings from the inspection at the drug product manufacturing site (Alexza Pharmaceuticals, Mountain View, CA). Dr. Claffey detailed the findings in his original review of the application (filed on 10 September 2010). In July 2011, the sponsor conducted a face-to-face meeting with the District Office to provide an update on corrective actions. Alexza provided a response to the District Office. The Agency issued another 483 in December 2011, and the sponsor subsequently submitted a response in December 2011. After reviewing the response, the Agency communicated deficiencies to the sponsor.

On 23 April 2012, the CDER Office of Compliance issued a Withhold recommendation in the CDER EES Establishment Evaluation Request Detail Report. The decision was based on the Withhold recommendation made by the CDRH Office of Compliance. CDRH OC stated that the sponsor had not provided an adequate response to the 483 issued in December 2011 regarding device deficiencies. Apparently, there were deficiencies in the process validation for the device. (Currently, the details are not available). In addition, CDRH recommends a re-inspection prior to approval of the product.

Regarding the other deficiencies outlined in the CR Letter, Dr. Claffey has concluded that the sponsor has responded adequately. The following is a summary of 1) the deficiencies detailed in the 8 October 2010 Complete Response Letter, 2) the sponsor's responses, and 3) Dr. Claffey's assessment of the sponsor's responses.

1. DMF (b) (4) was not acceptable. The sponsor amended the drug substance specification to include a test and limit for (b) (4). Dr. Claffey concluded that the sponsor responded adequately.
2. The sponsor had not provided adequate data from registration stability lots for the proposed expiry period of (b) (4); they had provided adequate stability data to support only a 6-month expiry period. The sponsor repeated the primary stability program on the product to be marketed, and they provided stability data pertaining to: a) the appearance of the device, b) surface markings on the device, c) device functionality, d) coated dose assay, e) emitted dose, f) primary package leak test, g) seal strength, h) mean aerosol impurities, and i) aerosol particle size. Dr. Claffey has concluded that the sponsor has provided adequate stability data to support the proposed (b) (4) expiry period.
3. Additional data were required on the stability of the heat package. The sponsor conducted a stability study on heat packages in their shipping and storage configuration, as opposed to the initial study on the assembled device. Dr. Claffey has concluded that the revised protocol will control the appropriate parameters regarding the potential for oxidation and compromise of the heat package. The sponsor has provided an adequate response.
4. (b) (4)
Dr. Claffey has concluded that the results are acceptable.
5. (b) (4)
. Dr. Claffey has concluded that the proposed changes and supporting information are acceptable.
6. FDA requested that the sponsor provide information about the change in the thermogram measurement frame. The sponsor stated that the change did not have a significant effect on mean temperature or temperature uniformity specifications. Dr. Claffey concluded that the information provided appears to address the concern adequately.
7. FDA requested information about the in-process weight check method that should include measurements from the lid side and tray side of the product. The sponsor

qualified and implemented a modified testing method to include the measurements. Dr. Claffey concluded that the method appeared to address the issue. They have an in-process control for the amount of drug sprayed onto the heat package for the 10 mg strength.

The CDRH review team had recommended an addition to labeling, which Dr. Claffey and the ONDQA team did not agree with. CDRH recommended that we include in labeling detailed information about the particle size distribution. This would include information about the mass-median aerosol diameter (MMAD), total delivered dose, total respirable dose, respirable fraction, and geometric standard deviation (GSD). Dr. Claffey has stated that CDER typically does not recommend including such information in labeling and that such information would probably not be useful to healthcare professionals. Furthermore, these data are part of the product specification, and such data are generally considered proprietary. The clinical team and I agree that this information would probably not be useful to include in labeling. We held a meeting to discuss these issues with the CDRH team. We agreed that we would include information about the total delivered dose of loxapine and the total respirable dose of loxapine. We agreed that we would not include the other information in labeling.

4. Center for Devices and Radiological Health (CDRH)

The CDRH review team has filed 3 reviews during the second review cycle. are two (actually 3) CDRH reviews for the second cycle. Nayan Patel, Ph.D. filed a review (November 4, 2011) regarding device performing testing. Quynh Nhu Nguyen has filed 2 reviews of the human factors validation studies. (November 1, 2011 and March 23, 2012).

4.1 Nayan Patel, Ph.D. – Device Performance Testing

Nayan Patel, Ph.D., Biomedical Engineer, Anesthesiology and Respiratory Device Branch, Division of Anesthesiology (ARDB), General Hospital, Infection Control, and Dental (DAGID), CDRH reviewed the sponsor's analysis of several aspects of the device performance. There were outstanding issues identified in the CR letter. CDRH made the following requests regarding performance testing on the device: 1) characterize the total mass of the drug delivered to the lungs, and 2) conduct testing of the worst case scenario regarding heat package failure. Dr. Patel has concluded that the sponsor has provided adequate responses.

A. Characterization of Aerosol Properties

CDRH asked whether the pulmonary toxicity observed with following treatment with inhaled loxapine could be related to: 1) the site of deposition of inhaled particles in the lung, or 2) the intrapulmonary dose fraction. CDRH requested that the sponsor perform an analysis of aerosol particle size distribution using data previously collected. Specifically, CDRH requested that the sponsor characterize the total mass of the drug and

ignition products deposited in the lung. In response, the sponsor performed analyses assessing the following factors:

- Effect of varying airflow rates on aerosol properties
- Effect of device orientation on aerosol properties
- Effect of altitude on aerosol properties
- Effect of humidity on aerosol properties
- Effect of ambient temperature on aerosol properties

Effects of varying airflow rates on aerosol properties: The aerosol performance was robust for the 5 mg and 10 mg doses, and the performance results were consistent with results from aerosol characterization studies for other products. The emitted dose was (b) (4) of the mean coated dose for all flow rates tested. The particle sizes fell within the desired range for deep lung deposition of the drug. There were no individual impurities detected at greater than (b) (4) for both doses over the full range of flow rates. The sponsor investigated regional deposition of particles, using a standard mouth/throat/airway model. Over the range of flow rates tested, at least (b) (4) of the emitted dose was deposited in the section of the model corresponding to the bronchial and alveolar regions. The portion of the coated dose left unvaporized on the heat package decreased slightly with increasing flow rate, resulting in a slight increase in the total emitted dose as the flow rate increased.

Effects of device orientation on aerosol properties: The sponsor tested the device in 5 orientations representing the range of possible use orientations. The aerosol properties (emitted dose, aerosol impurities, and aerosol particle size distribution) were measured at each orientation. For all 5 orientations, the emitted dose and particle size distribution were acceptable, indicating the robustness of the product for all potential use orientations tested. There were no aerosol impurities detected at greater than (b) (4) for any of the orientation.

Effects of altitude, humidity, and ambient temperature on aerosol properties: Because the heat package expands during operation, the product was tested in a reduced pressure environment (564 mm Hg) simulating an altitude of 8000 ft. (Federal Aviation Regulation 25). The aerosol properties were acceptable. Aerosol properties were also evaluated in environments having relative humidity in the range of 15% to 90%. The results of aerosol properties were acceptable. The aerosol properties were also acceptable when evaluated in the temperature range of 15°C to 30°C.

B. Worst Case Simulation of Heat Package Failure

CDRH requested that the sponsor conduct more realistic and meaningful testing of worst case scenarios regarding heat package failure than they had previously. The previous worst case was simulated using 1-mm holes in specific areas of the heat package. In the CR letter, we requested that the sponsor evaluate situations in which there is failure of (b) (4) along the seam that holds the tray and lid together, in order to simulate catastrophic heat package failure the could potential cause clinical injury. Alexza conducted testing of the heat package when the weld was missing on the entire side of the heat package. The sponsor conducted testing on 5 types of compromised heat packages

and along with a control (devices with uncompromised heat packages). Dr. Patel has concluded that the sponsor conducted appropriate testing at various temperatures, and he finds the results are acceptable.

4.2 Dr. Nguyen - Human Factors Validation Study

Quynh Nhu Nguyen, Biomedical Engineer/Human Factors Reviewer (CDRH/DAGID) performed 2 second-cycle reviews of the sponsor's human factors validation studies (02 November 2, 2011 and March 23, 2012). Dr. Nguyen has concluded that the sponsor has responded adequately to the Agency's requests regarding the human factors validation studies. The sponsor has implemented the requested changes in the product design, device labeling, pouch labeling, and instructions for use. The changes have resulted in decreased use errors, which has decreased the risk of missed doses, delayed dosing, underdosing, and inappropriate administration of a second dose. I agree with Dr. Nguyen's conclusions.

In the Complete Response Letter, FDA requested that the sponsor conduct a human factors validation study with representative healthcare providers (HCP) and patients, in order to validate that the product can be used safely and effectively. We provided specific comments and requests, and we provided guidance after issuing the Complete Response letter and during the second review cycle. We requested that the sponsor address specific factors in the human use study and provide relevant analyses in the study report, including the following:

1. user performance, use errors, and task failures
2. use-related hazards that could pose a risk to patients and healthcare providers
3. use of the device in a manner that was unintended or unanticipated and management of unanticipated failures
4. proposed risk mitigation strategies (e.g., training, device labeling, or instructions for use) and an evaluation of their effectiveness
5. evaluation of feedback provided by the test participants
6. Discussion of any further mitigation strategies necessary and if further validation is necessary.

The sponsor submitted a Human Factors Validation study report with the Complete Response submission. In her review of the study report, Dr. Nguyen concluded that there were remaining problems with the device and labeling that could impact the use of the product. The Division conveyed additional comments and requests to the sponsor on December 3, 2011.

Dr. Nguyen notes that healthcare professionals will prepare the device for use by the patient, and they will provide instructions to the patient on how to actuate the device and inhale the drug. Patients will only be responsible for following the instructions from the healthcare professional; they will not be responsible for preparing the device, determining when the device is ready to use, determining whether the device has actuated, or determining whether the dose was delivered. No prior training for the healthcare

professional is expected on the instructions for use (IFU). The IFU are presented in the full prescribing information and in the pouch label. The use of Adasuve requires the following operational steps:

- The HCP opens the pouch to remove the device.
- The HCP removes the plastic tab to activate the device for use and observes the illumination of the green LED indicator to confirm that the device is ready for use.
- The HCP provides inhalation instructions to the patient.
- The patient follows the instructions given by the HCP.
- The HCP confirms the delivery of the dose by checking that the LED has turned off.

Dr. Nguyen acknowledged that the sponsor had taken useful measures to reduce the rate of task failures, use errors, close calls, and operational difficulties that were observed in the initial human factors validation study. For example, the sponsor changed the location where the pouch can be opened so the device can be removed safely, and they modified the content of the IFU to clarify instructions and address the difficulties observed in the testing. However, Dr. Nguyen concluded that the modifications were not adequate. There were remaining task failures, use errors, close calls, and operational difficulties that impacted the use of the product, including the delivery of the loxapine dose. For example, HCPs were not aware that they must check the LED light to confirm whether the device had functioned properly upon activation (LED on) or whether the dose was successfully inhaled (LED off). In addition, HCPs did not provide adequate guidance to patients on exhaling before inhaling the dose, inhaling the dose, and holding their breath after inhaling.

Healthcare professionals participating in the study provided comments and recommendations for improving the design of the device and the instructions for use. Some commented that the LED indicator light was inappropriately located; the LED was located on the side opposite the side containing the instructions for use. Some HCPs were uncertain about how long the patient must hold their breath after inhalation, because the IFU did not specify this. The IFU comprehension evaluation test results also indicated that HCPs had uncertainty about this point. HCPs expressed concern that they did not know if the drug was delivered after inhalation. Several stated that the IFU should specify how many times the user should direct the patient to inhale if the green light does not turn off. HCPs stated that the IFU should inform the user that there is a flash of light upon actuation of the device.

Based on these findings, Dr. Nguyen provided additional comments and requests to the sponsor. On 03 December 2011, the Division requested that the sponsor use this guidance to further optimize the device-user interface (including labeling and IFU), in order to minimize the risk of task failures and use errors with intended users of the product. We requested that the sponsor demonstrate improvement through an additional focused human factors/usability validation study. We combined Dr. Nguyen's comments on the human factors study with those of Yalena Maslov (DMEPA reviewer).

1. We requested that the sponsor relocate the product's label containing the proprietary and established name, dosage form, and strength to the side where the LED button is located. This may help minimize technique errors in which participants do not verify whether the LED light is illuminated or that the light is turned off, indicating that the device has been activated or that the dose has been delivered, respectively. In the HF study, there were 31 occasions in which healthcare practitioners did not confirm that the green LED illuminated or turned off and 9 occasions in which healthcare practitioners did not confirm that the green LED illuminated or turned off. One of the root causes for the practitioners not verifying the LED light is that the label and LED light button are located on opposite sides of the device.
2. We recommended adding a label or embossment next to the LED light stating the significance of the LED light when it is lit and when it is turned off (e.g., "when green, inhaler ready to use"). This label/embossment should be prominently displayed to call the HCP's attention.
3. We recommended orienting the device in the pouch so that the LED light and the relocated label containing the proprietary and established names, dosage form, and strength are facing the same side as the IFU on the foil labeling. We recommended this change to ensure easy identification of the label and the LED light on the device, as well as to help eliminate wrong technique errors in which participants do not verify whether LED light is illuminated or turned off. One of the root causes for practitioners not verifying the LED light is that the device is oriented within the foil pouch such that when the IFU label is facing upward, the device's LED light is facing downward. Thus, patients and practitioners overlooked this light.

On 06 March 2012, the sponsor responded to the additional CDRH requests. The sponsor has implemented the requested changes in the product design, device labeling, pouch labeling, and instructions for use. Furthermore, the sponsor has conducted an additional human factors/usability with representative HCPs, in order to validate that the changes in design and labeling have resulted in decreased errors. Dr. Nguyen has concluded that the sponsor has responded adequately and that the changes address the Agency's concerns. I agree with Dr. Nguyen.

5. Nonclinical Pharmacology/Toxicology

There are no unresolved nonclinical issues. No new nonclinical pharmacology or toxicology data were required or submitted in this application. The pharmacology-toxicology reviewers have recommended revisions to the Mechanism of Action and Nonclinical Toxicology sections of labeling.

6. Clinical Pharmacology (OCP)

There are no unresolved clinical pharmacology issues. No new clinical pharmacology data were submitted in this application. The clinical pharmacology reviewers have recommended revisions to the Drug Interactions, Use in Specific Populations, and Clinical Pharmacology sections of labeling.

7. Clinical Review

Francis Becker, M.D. performed two clinical reviews during this review cycle. The first (November 8, 2011) was a review in preparation for the Psychopharmacologic Drugs Advisory Committee (PDAC) meeting, which was held on December 12, 2011. Dr. Becker filed a second review on April 9, 2012. During the first cycle, he performed a detailed review of the efficacy and safety data (September 17, 2010). In the current review, Dr. Becker has focused on the risk of bronchospasm, the proposed REMS for mitigating the risk, and the potential benefits of treatment with inhaled loxapine. He reviewed the sponsor's REMS, labeling, and supporting documents, and he worked closely with reviewers from DRISK and considered their reviews. Dr. Becker has concluded that the sponsor's proposed REMS and labeling are not adequate for mitigating the risk of bronchospasm and related serious outcomes. He has concluded that the REMS developed by the Agency would be adequate for mitigating the risks, and he recommends approval of the application. Furthermore, Dr. Becker has concluded that treatment with loxapine may have unique benefits compared to other available treatments for acute agitation. I agree with Dr. Becker's conclusions and recommendations.

Efficacy Findings

Dr. Becker notes that the pivotal trials clearly demonstrated the efficacy of inhaled loxapine in the treatment of acute agitation in patients with schizophrenia or bipolar I disorder. There were 2 virtually identically designed trials (one in schizophrenia and one in bipolar I disorder). These were randomized, double-blind, placebo-controlled, parallel-group, fixed-dose trials of loxapine 5 mg or 10 mg. The only significant difference between the trials was the length of the screening period: up to 2 weeks in the schizophrenia trial and up to 3 days in the bipolar disorder study. The primary endpoint was the Positive and Negative Syndrome Scale-Excited Component Scale (PEC). The PEC is a valid and reliable measure of acute agitation in these populations. The primary endpoint was the change in PEC score at 2 hours after dosing. In both studies and for both doses, loxapine was superior to placebo. The differences in treatment effects were statistically and clinically significant; there was substantial reduction in the severity of agitation. Moreover, the treatment effects were apparent at all time points assessed, beginning at 10 minutes after dosing.

Safety Findings:

In the clinical trials in acutely agitated patients, 524 patients were treated with loxapine, and 263 received placebo. In the loxapine group (5 mg or 10 mg), 63% of patients

received a single dose, 31% received 2 doses, and 7% received 3 doses. In the 3 pulmonary safety studies, 26 asthmatic patients were treated with 1 or 2 doses of loxapine 10 mg, 26 COPD patients were treated with 1 or 2 doses of loxapine 10 mg, and 30 healthy volunteers were treated with two doses of loxapine 10 mg. In the pivotal trials in acute agitation, loxapine 5 mg or 10 mg was generally safe and well tolerated when administered in 1, 2, or 3 doses. The most common adverse reaction was sedation (12% of the loxapine group and 10% of the placebo group), which is a common effect of loxapine when administered orally or intramuscularly. Other relatively common reactions were dysgeusia and throat irritation, which were related to the route of administration (oral inhalation). Dysgeusia was reported by 14% of the loxapine 10 mg group, 11% of the 5 mg group, and 5% of the placebo group. Throat irritation was reported by 3% of the 10 mg group, 1% of the 5 mg group, and none of the placebo group. A small proportion of patients had extrapyramidal symptoms such as dystonia, akathisia, and tremor ($\leq 0.4\%$ for each).

In the pivotal efficacy studies, there was one case of bronchospasm. A 59 year-old woman in the schizophrenia study developed labored breathing and wheezing that was audible without a stethoscope approximately 5 minutes after the first dose of loxapine 10 mg. She responded to treatment with albuterol by metered dose inhaler and oxygen. This patient did not have a history of pulmonary disease. There were two (0.4%) cases of wheezing in the loxapine group in the pivotal trials that occurred on the day following treatment with loxapine. There were no cases in the placebo group. A 32 year-old male without a history of pulmonary disease had wheezing on the day following treatment with a single dose of loxapine 5 mg. The wheezing resolved after 2 days and did not require treatment. A 42 year-old female without a history of pulmonary disease developed wheezing the day following treatment with loxapine 5 mg. The wheezing resolved after one day and did not require treatment.

The sponsor conducted pulmonary safety studies in patients with asthma or COPD and in healthy volunteers. Spirometry was performed. The sponsor's definition of notable respiratory signs or symptoms included: 1) a decrease in forced expiratory volume in the first second (FEV1) $\geq 20\%$, 2) an airway adverse event, or 3) use of rescue medication (bronchodilator via metered dose inhaler or nebulizer). In the asthma study, 69% of the loxapine group and 12% of the placebo group had significant respiratory signs or symptoms. Approximately 54% of patients in the loxapine group had an airway adverse event, compared to 12% of the placebo group. These adverse events included bronchospasm (27% of the loxapine group and 4% of the placebo group), chest discomfort (23% of the loxapine group and 8% of the placebo group), wheezing (15% of the loxapine group and none of the placebo group), and dyspnea (12% of the loxapine group and none of the placebo group), cough (4% of the loxapine group and none of the placebo group), and throat tightness 4% of the loxapine group and none of the placebo group). In asthma patients, FEV1 decreases of $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$ occurred much more frequently in the loxapine group (85%, 62%, and 42%, respectively) than in the placebo group (11.5%, 3.8%, and 3.8%, respectively). In addition, 54% of the patients in the loxapine group required bronchodilator treatment, compared to 12% in the placebo group.

In the COPD study, 58% of the loxapine group and 22% of the placebo group had notable respiratory signs or symptoms. Approximately 19% of the loxapine group and 11% of the placebo group had airway adverse events: dyspnea (12% of the loxapine group and 4% of the placebo group), cough (12% of the placebo group and none of the placebo group), wheezing (8% of the loxapine group and none of the placebo group), pulmonary congestion (4% of the loxapine group and none of the placebo group), and bronchospasm (none of the loxapine group and 4% of the placebo group). FEV1 decreases $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$ were more common in the loxapine group (80%, 56%, and 40%, respectively) than in the placebo group (67%, 33%, and 11%, respectively). In the loxapine group, 23% of patients required bronchodilator treatment, compare to 15% in the placebo group.

Dr. Becker has discussed his assessment of the Agency' REMS in detail. He agrees with DRISK on all of the elements of the REMS. He has concluded that the risk of pulmonary toxicity would not be acceptable without implementation of the REMS. The REMS would limit the use of loxapine to facilities that have immediate, on-site access to appropriate personnel and equipment necessary for delivery of advanced airway management. This component is critical, because bronchospasm can progress rapidly and lead to serious outcomes including respiratory arrest and death. The REMS would require that facilities to conduct careful screening to prevent patients at increased risk for bronchospasm from being treated with the product. The REMS would also require that facilities perform close monitoring following treatment with inhaled loxapine. In addition, treatment would be limited to one dose within a 24-hour period.

The REMS can substantially reduce the risk of bronchospasm and serious outcomes. However, Dr. Becker acknowledges that there are potential limitations for the REMS to completely eliminate risks. In an acute setting, it may not always be possible to perform ideal screening. In an acutely agitated state, patients may not be able to provide a reliable medical history, and it may not be possible to perform an adequate physical examination to rule out the presence of respiratory signs. In addition, it is possible that patients could develop bronchospasm after treatment with loxapine even if they do not have any history of pulmonary disease.

Dr. Becker has concluded that there are potential advantages of inhaled loxapine, compared to other available treatments for acute agitation associated with schizophrenia or bipolar I disorder (atypical antipsychotics for intramuscular injection). Dr. Becker notes that orally inhaled loxapine has a relatively rapid onset of action; in the clinical trials, significant improvement in symptoms was apparent 10 minutes after dosing. Although the sponsor did not conduct direct comparisons with antipsychotic injections, it is widely accepted that IM antipsychotics often require up to 30 minutes for a significant effect. In practice, it is common to combine an antipsychotic and a benzodiazepine in a single injection in order to achieve rapid control of agitation. In addition, loxapine by oral administration is a non-invasive treatment, and its use requires some degree of cooperation from the patient. Administration of intramuscular injections often requires the use of physical restraint. Thus, there are risks of injury, including contaminated needle stick injuries. In addition, intramuscular injections are often viewed as coercive.

Patients and providers may prefer to have a non-invasive treatment option available, such as loxapine for inhalation. Furthermore, by involving the patient as an active participant in treatment decisions, it is possible that using such an option can strengthen the therapeutic alliance between the patient and provider.

8. Biostatistics Review

There are no unresolved statistical issues. No new clinical efficacy data were submitted in this application. The biostatistics team has recommended revisions for the Clinical Studies section of labeling.

9. Pulmonary, Allergy, and Rheumatology Products (DPARP)

Theresa Michele, M.D. (clinical team leader in the Pulmonary, Allergy, and Rheumatology Products) performed the DPARP consultation review. Dr. Michele and Sally Seymour, M.D. (Deputy Director for Safety, DPARP) have provided expert advice throughout the first and second review cycles. There were no new clinical data submitted during the second cycle. Dr. Michele's analysis of the pulmonary safety findings are based on previously reviewed data from the three pulmonary safety studies in asthmatic patients, COPD patients, and healthy subjects, as well as safety data from the pivotal clinical trials in patients with acute agitation associated with schizophrenia or bipolar I disorder. Dr. Michele performed a detailed review of the safety data in her memo for the advisory committee meeting (November 2, 2011). In the current review (30 March 2012), Dr. Michele has summarized the findings. In addition, she has reviewed the sponsor's proposed REMS and labeling, and she has worked closely with DPP and DRISK to develop the Agency's proposed Adasuve REMS and product labeling.

Dr. Michele has concluded that there is a significant risk of bronchospasm following administration of inhaled loxapine. The risk is particularly high in patients with underlying airway hyperresponsiveness caused by conditions such as asthma and COPD. In addition, the risk of bronchospasm is dose-related. Dr. Michele has also concluded that the sponsor's proposed REMS and product labeling are not adequate to mitigate the risk of bronchospasm and related serious outcomes (i.e., respiratory decompensation, respiratory arrest, and death). Dr. Michele would support approval of loxapine for oral administration only if the sponsor implemented the REMS and labeling that the Agency has formulated. I agree with all of Dr. Michele's conclusions regarding the serious risk of bronchospasm caused by treatment with loxapine by oral inhalation. I also agree with all of her recommendations for the Agency's proposed REMS and product labeling for mitigating the risk of bronchospasm and related serious outcomes.

The asthma and COPD pulmonary studies had the identical design. These were randomized, double-blind, placebo-controlled, parallel-group studies of inhaled loxapine 10 mg administered as 2 single doses separated by 10 hours. In the healthy volunteer, crossover study, each subject received a single dose of loxapine 10 mg and placebo. The objectives were to assess pulmonary function test parameters by spirometry and to assess respiratory adverse reactions. The protocol specified that patients would be discontinued

from the study if they had a significant decrease in forced expiratory volume in one second (FEV1) or significant respiratory adverse events. In addition, they would be treated with rescue medication (bronchodilator) as needed.

Treatment with inhaled loxapine caused bronchospasm in the pulmonary studies, as demonstrated by substantial FEV1 changes and respiratory adverse events (wheezing, dyspnea, chest tightness, cough, and throat tightness). In patients with asthma or COPD, bronchospasm was relatively common. Per protocol, a number of subjects did not receive the second planned dose and were discontinued from the studies, because they developed decreases in FEV1 or they experienced respiratory adverse reactions. A high proportion of these subjects required rescue treatment with a bronchodilator (administered by a metered dose inhaler or nebulizer). Dr. Michele notes that the magnitude of FEV1 decreases was greater after the second dose than the first dose. Moreover, in patients with asthma, pulmonary function did not return to baseline for at least 24 hours following the second dose of inhaled loxapine.

In the asthma study, there were marked decreases in FEV1 that occurred immediately after dosing with loxapine. The majority of respiratory reactions occurred within the first hour after dosing, but the time of onset ranged from 0 to 2.1 hours. The mean FEV1 decrease after the first dose was 303 mL, and the mean decrease after the second dose was 537 mL. After the first dose, the maximum decrease in FEV1 for individual patients was 32%. The maximal decrease in FEV1 after the second dose was 50%. Approximately 85% of patients treated with loxapine had FEV1 decreases $\geq 10\%$, and 42% had FEV1 decreases $\geq 20\%$. These are clinically significant changes. Dr. Michele notes that standard bronchoprovocation agents cause FEV1 decreases of approximately 10% to 20%. Dr. Michele also notes that the true FEV1 nadir following loxapine treatment is unknown, because all patients with an FEV1 decrease $\geq 20\%$ were discontinued from the study and many required treatment with albuterol. Nine of 26 patients in the loxapine group did not receive the second dose, because they had an FEV1 decrease $\geq 20\%$ or respiratory symptoms after the first dose. Two of these patients had only a decrease in FEV1, two had only respiratory symptoms, and 5 had both. Rescue treatment with albuterol was administered to 54% of patients in the loxapine group and 12% of patients in the placebo group. There were no serious adverse events requiring hospitalization or intubation.

In the COPD study, there were FEV1 decreases following dosing. The decreases were greater in the loxapine group. The greatest mean decrease occurred after the second dose. The mean decrease in FEV1 was 0.125L (8.0%) in the loxapine group and 0.051L (3.2%) in the placebo group. The magnitude of the change was smaller than in the asthma study. Dr. Michele notes that this is typical of bronchoreactive effects in a COPD population, in which there is a greater degree of fixed obstruction and less of a reactive component. In addition, this population has a lower baseline lung function than the asthma population; thus, smaller changes are expected.

Approximately 80% of loxapine-treated patients had a decrease in FEV1 of $\geq 10\%$, and 40% had a decrease of $\geq 20\%$. The true FEV1 nadir was not determined, because some patients with a $\geq 20\%$ decrease in FEV1 were treated with albuterol. Several patients in

the placebo group had decreases in FEV1, suggesting that COPD patients may be more susceptible to changes in lung function resulting from inhalation of hot air from the device. There were no differences in FEV1 changes when the data were analyzed by smoking status (current smoker versus former smokers). Seven of 25 in the loxapine group did not receive the second dose, because they had FEV1 decreases $\geq 20\%$ or respiratory events after the first dose. Four patients in the loxapine group and 3 patients in the placebo group had respiratory adverse events (bronchospasm, wheezing, dyspnea, cough, pulmonary congestion). The majority of these events occurred within the first hour after dosing. Rescue bronchodilator medication was administered to 23% of patients in the loxapine group and 15% in the placebo group. There were no serious respiratory adverse events requiring hospitalization or intubation. Respiratory adverse events included

In the pivotal trials in acutely agitated patients, there were 524 patients exposed to loxapine and 263 exposed to placebo. Approximately 63% received a single dose. Dr. Michele note that patients were excluded from the trials if they had “clinically significant acute or chronic pulmonary disease (e.g., clinically apparent asthma, chronic bronchitis, or emphysema).” She also notes that the screening period was up to 2 weeks in the schizophrenia study and up to 3 days in the bipolar disorder study. It was not possible to conduct spirometry in these patients with acute agitation. Four patients (0.8%) in the loxapine group and one (0.4%) in the placebo group had airway-related adverse events. Two patients in the loxapine 5 mg group had wheezing, and one patient in the 10 mg group had cough, all of which resolved without treatment. In addition, one patient in the 10 mg group developed bronchospasm. A 59 year-old female patient with schizophrenia developed labored breathing and wheezing audible without a stethoscope approximately 5 minutes after the first dose of loxapine. She responded to treatment with albuterol and oxygen. This patient apparently did not have a history of pulmonary disease

Dr. Michele has concluded that the risk of bronchospasm from inhaled loxapine is increased in the intended population, because of several factors. There is a very high prevalence of smoking (70% to 90%) in this population of patients with chronic psychiatric illness. In addition, such patients have a relatively high burden of medical conditions, and they commonly do not have routine medical care. Dr. Michele notes that risk factors for death from asthma include low socioeconomic status, inner-city residence, illicit drug use, major psychosocial problems, other chronic lung disease, and chronic psychiatric disease. Dr. Michele notes that acutely agitated patients might not be able to provide a reliable medical history, which could lead to inadequate screening of patients with lung disease and risk factors for bronchospasm. In addition, providers may not have immediate access to medical records, and it might not be feasible to obtain a pulmonary history or perform a pertinent physical examination (auscultation of the chest and assessing respiratory rate and other vital signs). Dr. Michele also notes that loxapine can cause sedation, which could mask respiratory signs and symptoms. Finally, Dr. Michele notes that while there were no cases of serious outcomes such as hospitalization, intubation or death related to brochospasm, the safety database and exposure to inhaled loxapine is limited. Thus, it is possible that the experience in the clinical program cannot be fully extrapolated to the intended population.

Dr. Michele has reviewed the sponsor's proposed REMS for mitigating the risk of bronchospasm, and she has concluded that it is inadequate. In the sponsor's proposed REMS, the use of loxapine would be restricted to facilities that had access to an albuterol metered dose inhaler. In effect, this would allow the use of the product in a wide range of settings, including free-standing psychiatric units, outpatient clinics, and outpatient solo practitioner's offices. Dr. Michele notes that many inpatient psychiatric units or outpatient psychiatry clinics do not routinely have appropriate personnel or materials for treating acute bronchospasm and performing advanced airway management (e.g., albuterol nebulization, intravenous corticosteroids, intubation, and mechanical ventilation). Such conditions would increase the risk of a serious outcome if a patient developed bronchospasm. Dr. Michele states that serious outcomes can occur rapidly in patients with bronchospasm; thus, it is critical to have available a complete repertoire of respiratory treatment options.

Dr. Michele and Dr. Seymour have worked closely with DRISK and DPP to develop the Agency's proposed REMS. They would support approval of inhaled loxapine only if the sponsor implemented the REMS proposed by the Agency. Under this REMS, the product may be used only in facilities in which there is immediate access to appropriately trained personnel and equipment necessary for providing advanced airway management (i.e., intubation and mechanical ventilation). Dr. Michele states that early treatment of respiratory distress is critical. This requires recognition of early signs and taking prompt action, such as the use of inhaled short-acting beta agonists (via MDI or in more severe cases nebulization). It is important to remove the environmental factor causing bronchospasm (i.e. avoiding additional doses of inhaled loxapine). In moderate to severe cases, standard treatment includes oxygen and short acting beta-agonists with the addition of ipratropium bromide in severe bronchospasm (repetitive or continuous administration, usually via nebulization). Treatment should include systemic corticosteroids (oral or IV) in patients who do not respond promptly to bronchodilators. Additional treatments could include intravenous magnesium sulfate or heliox in severe bronchospasm. Intubation and mechanical ventilation would be required in patients with evidence of poor response or impending respiratory failure (patients generally do not wheeze on physical examination due to poor airflow, and are drowsy and confused).

Based on these treatment guidelines and the known risk profile of inhaled loxapine, Dr. Michele has recommended a REMS with elements to ensure safe use. The elements include screening patients for underlying respiratory conditions, acute respiratory signs or symptoms, or use of medications to treat respiratory conditions. These conditions should be contraindications to inhaled loxapine administration. Inhaled loxapine should be administered only in a healthcare setting that is equipped to handle bronchospasm and the potential for respiratory decompensation. This includes the availability of nebulized albuterol, oxygen, and staff trained to treat bronchospasm and perform advanced airway management, including intubation and mechanical ventilation. Providers must monitor patients frequently following administration of inhaled loxapine. Monitoring should include vital sign assessment and physical examination, including chest auscultation, every 15 minutes for at least one hour following administration. Dr. Michele also recommends limiting the administration of inhaled loxapine to one dose in a 24-hour period. In addition, there should be controls at an institutional level (i.e., pharmacy) to

permit administration of only a single dose within a 24-hour period. The REMS should also require that facilities provide a training program for healthcare professionals who would administer loxapine by inhalation.

Dr. Michele states that the restrictions and conditions of the REMS likely will limit, but may not completely eliminate, potentially severe adverse airway events that may occur with inhaled loxapine. She recommends that, if the product is approved, the sponsor should be required to conduct a postmarketing, large observational study assess the risk of bronchospasm and evaluate the safety of loxapine when used in clinical practice using the REMS and labeling developed by the Agency. I agree with all of Dr. Michele's conclusions and recommendations regarding the risk of bronchospasm and the REMS and product labeling that would be necessary for the Agency to approve the application.

10. Division of Risk Management (DRISK)

Kimberly Lehrfeld, Pharm.D. and Megan Moncur, M.S. from DRISK worked closely with the Division and the DPARP review team to develop the Agency's Adasuve REMS. Dr. Moncur filed the DRISK review on April 2, 2012. The DRISK team reviewed the sponsor's proposed REMS and concluded that it was not adequate to ensure the safe use of inhaled loxapine. The review teams agreed on the minimum REMS requirements (described below), and DRISK presented these requirements to the REMS Oversight Committee (ROC) on October 14, 2011, the Drug Safety (DSB) on November 17, 2011, and the Psychopharmacologic Drug Advisory Committee (PDAC) on December 12, 2011. The elements of the REMS included ETASU B- HCF Certification with the Communication Plan components integrated into the ETASU requirements.

Dr. Moncur notes that the attestations under ETASU B for HCF certification are more comprehensive than those proposed by the sponsor. (b) (4)
(b) (4) the HCF would have to attest to having immediate access on-site to advanced airway management abilities including the ability to intubate a patient, thereby, significantly limiting the HCFs that would be eligible for enrollment. In addition, (b) (4)
(b) (4) were enhanced and are mandatory as part of the policies, procedures or order sets at certified HCFs. The mandatory screening and monitoring requirements must include not only visual assessments but also a physical examination including chest auscultation to detect underlying pulmonary disease and early bronchospasm. (b) (4) *ADASUVE Education Program* would become mandatory training for certified HCF practitioners involved in prescribing, dispensing, and administering Adasuve, as well as for the HCF practitioners monitoring patients after treatment. This training would be the responsibility of the HCF representative to ensure and document.

As Dr. Moncur states in her review, the goal of the Agency's REMS is to mitigate the negative outcomes associated with loxapine-induced bronchospasm by:

- Ensuring that ADASUVE is dispensed only in certified health care settings that have immediate access on-site to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation.
- Informing healthcare professionals in these settings that ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest.
- Informing healthcare professionals in these settings about the safe use of ADASUVE, including appropriate patient selection, monitoring, and management.

Elements to Assure Safe Use (ETASU)

The elements to assure safe use include the following:



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Under the implementation system for the REMS, the sponsor must ensure that wholesalers and distributors who distribute Adasuve are enrolled in the ADASUVE REMS program. The DRISK team has described in detail the wholesalers/distributor

enrollment process and the steps that must be completed by the distributor's authorized representative prior to receiving Adasuve for distribution.

The DRISK team has also described the timetable for submission of REMS assessments. The sponsor will submit REMS assessments to the Agency at 6 and 12 months from the date of the REMS approval, and annually thereafter. At the time of the DRISK review, the Assessment Plan was undergoing review.

11. Division of Medication Errors Prevention and Analysis DMEPA)

Yalena Maslov, Pharm.D, performed two reviews during the second review cycle (November 10, 2011 and March 12, 2012). Dr. Maslov reviewed the human factors validation study (in collaboration with the CDRH reviewer, Dr. Quynh Nguyen). Dr. Maslov also reviewed product labeling. This included a review of the full prescribing information, the instructions for use (IFU), labeling on the device, pouch labeling, and carton labeling. Dr. Maslov made a number of recommendations to the sponsor during the review cycle regarding the human factors study and labeling. Dr. Maslov has concluded that the sponsor has responded adequately to our requests. The results of the human factors studies are acceptable. The sponsor has incorporated all requested changes in the design of the product and in all aspects of labeling for the product. I agree with Dr. Maslov's conclusions.

Dr. Maslov reviewed the design of the device, the results of the sponsor's initial usability study, and labeling (full prescribing information, instructions for use, and labeling on the device, the foil pouch, and the carton). Following the Complete Response action (October 8, 2010), the DMEPA and CDRH review teams provided detailed guidance to the sponsor on the design of the usability studies.

Dr. Maslov analyzed the use failures experienced by patients and healthcare professionals. Dr. Maslov concluded that the use errors could pose risks such as inadequate inhalation, underdosing, dose omissions, and failure to recognize the LED button status. The LED "On" (green light on) indicates that the device has been activated and is ready for use. The LED "OFF" (no light) indicates that the device has emitted the vaporized dose of loxapine.

The observed use errors by healthcare professionals included the following:

1. did not determine that a non-actuated device was unusable.
2. did not confirm that the green LED illuminated to indicate that the device was functioning properly
3. did not direct the patient to exhale prior to inhaling
4. did not direct the patient to hold his/her breath after inhaling
5. inadvertently pulled the tab when removing the device from the pouch
6. did not check that the LED light turned off after inhalation

The use errors by patients included:

1. did not inhale fully with a steady breath

2. did not exhale prior to inhaling
3. did not hold breath after inhaling

Dr. Maslov concluded that the factors that contributed to use errors included the following: 1) the position of the device in the foil pouch, 2) the location of the LED button on the side of the device opposite that of the device label containing the instructions, 3) inconspicuous placement of important information in the instructions for use (IFU), forgetfulness, inattention, anxiety, and distractions. The distractions included a) a prominent flash of bright light upon inhalation through the device, which occurs with normal use, b) a clicking sound upon inhalation, and c) a temperature rise during inhalation that patients sense at their mouth.

Dr. Maslov had a number of observations and comments regarding the instructions for use. The IFU uses the word “product” instead of “inhaler.” The use of the word “inhaler” could improve the user’s comprehension of the IFU. The IFU does not inform the HCP or patient that there is a flash of light, clicking sound, or temperature increase during normal use of the product. This information could reduce the risk of startle and fear responses, distractions, and lack of information or incomplete inhalation during use of the product. These phenomena occur in all instances of normal use. The IFU lacks information. The IFU does not inform the HCP that the LED light will turn off after the medication has been emitted. The IFU image of the patient holding their breath does not look as if he is holding the breath; the image does not depict puffed cheeks or pursed lips. The IFU does not state how long the patient should hold the breath after inhaling the medication from the inhaler; they must be instructed to hold the breath for 10 seconds. The IFU does not state how many times certain steps can be repeated. The IFU does not state what steps the HCP can take if the device malfunctions and is not usable.

Dr. Maslov also made important observations and recommendations regarding deficiencies in the full prescribing information, the device labels, and the pouch and carton labels. The FPI did not state that the initial dose is 10 mg. (b) (4)

The device labels did not include the dosage form and dosage strengths. In addition, they did not include the name of the manufacturer, packer, or distributor. The pouch and carton labels did not include information about dosages, the route of administration, and the instruction to discard the inhaler a single use. There were other technical and formatting problems with the pouch and carton labels.

In summary, Dr. Maslov concluded in her first 2nd cycle review that there were numerous significant deficiencies with the design and labeling for the product that contributed to substantial use errors by the patient and the HCP. These errors pose risks regarding the safe and effective use of the product. Medication errors could include missed doses, underdosing, and unintentional overdosing. Dr. Maslov recommended that the sponsor modify the design of the product and various aspects of the IFU and product labels. In addition, Dr. Maslov and the CDRH review team recommended that the sponsor conduct another human factors/usability study with HCPs using the modified product, IFU, and product labels. The DMEPA and CDRH teams provided detailed comments and requests

to the sponsor in a letter from the Division (December 3, 2011), and they provided additional guidance throughout the review cycle.

In a telephone conversation on 22 March 2011, Dr. Maslov stated that she has reviewed the sponsor's second human factors validation/usability study, and she has concluded that the sponsor's study and results are acceptable. The sponsor has accepted all of our requests; they have modified the design of the product, and they have revised the instructions for use and other labeling. The results of the human factors study indicate that the modifications of the design and labeling have significantly reduced the risk of use errors to an acceptable level. Dr. Maslov has concluded that no further modifications of the device or labeling are necessary at this point. I agree with Dr. Maslov's conclusions.

12. Division of Medical Policy Programs (DMPP) – Patient Labeling Review

Shawna Hutchins, MPH, BSN, RN performed the review of Patient Labeling (medication guide). Dr. Hutchins filed the review on March 16, 2012. Dr. Hutchins revised the sponsor's proposed medication guide considerably in all sections, in order to be consistent with the full prescribing information. The multidisciplinary review team has made substantial revisions to the full prescribing information. These are discussed in the labeling review below (Section 17). Dr. Hutchins met with the review team on several occasions to discuss the revised medication guide. The review team has accepted all of the recommended revisions. I agree with all of Dr. Hutchins' proposed revisions to patient labeling.

13. Postmarketing Observational Study - Division of Epidemiology I (DEPI)

The Division had requested that the sponsor submit a protocol for a postmarketing, large, observational study to assess the risk of loxapine when used in clinical practice under the REMS. At the beginning of the review cycle, the sponsor had submitted a brief synopsis of a protocol. Cary Parker, M.P.H. reviewed the limited synopsis (November 3, 2011) and provided high-level comments which we sent to the sponsor (December 3, 2011) to provide guidance on developing a full protocol for the observational study. Dr. Parker and the Division agreed that the synopsis had numerous limitations.

Initial Protocol Synopsis

The proposed study is a multi-center, non-randomized, prospective observational cohort study to be conducted at approximately 50 medical or psychiatry emergency settings in the U.S. The study population will be acutely agitated patients with a diagnosis of schizophrenia or bipolar disorder. Study treatments would include inhaled loxapine, intramuscular atypical antipsychotics, and intramuscular benzodiazepines. The investigator would decide on the particular treatment for an individual patient. Outcome data on safety would be collected for up to 24 hours following treatment or discharge/transfer from the emergency department, whichever comes first. Outcomes of interest include: respiratory adverse events (e.g., respiratory signs and symptoms such as coughing, wheezing, or shortness of breath), 2) use of short-acting bronchodilator or

other medication to treat emergent symptoms (e.g. bronchospasm, extrapyramidal symptoms), 3) adverse events such as sedation/somnolence, extrapyramidal symptoms), 4) serious adverse events (requiring hospitalization, intubation, and mechanical ventilation. The sponsor also proposes assessments of treatment patterns and effectiveness. The efficacy endpoint would be the change PANSS-EC scores for patients treated loxapine compared to other treatments for acute agitation medications.

Dr. Parker thought that the safety objectives were reasonable. She had numerous suggestions regarding the patient selection criteria, methods for obtaining medical information at baseline and during follow-up, case definitions of adverse events and operational definitions for respiratory outcomes, and sample size calculations. The Division conveyed the comments to the sponsor on December 3, 2011.

In addition, the Division held a teleconference with the sponsor to provide additional comments regarding a more complete protocol for the observational study. We emphasized that the study must be very large (approximately 10,000 patients) so that the sponsor could adequately assess the risk of bronchospasm and related outcomes in the intended population, using inhaled loxapine in clinical practice under the REMS. We requested that the study not include active comparators. The outcomes of interest include bronchospasm and related adverse respiratory events, the need for rescue medications, serious adverse events such as hospitalization, intubation, or mechanical ventilation to treat bronchospasm. We requested that the sponsor conduct detailed follow-up of patients and describe important factors such as the ability to screen as intended, availability of medical records, ability to monitor as directed in labeling, pulmonary and other baseline medical conditions, smoking, and use of concomitant medications.

Complete Protocol for the Observational Study

Late in the review cycle, the sponsor submitted a complete protocol for the observational study. Dr. Parker and I have performed a preliminary review of the protocol. We agree that the protocol is generally acceptable; the sponsor has adequately addressed most of the issues that we had raised. However, we will need to reach agreement with the sponsor on a number of details.

This will be a large (N = 10,000), non-randomized, non-controlled, multicenter (150 U.S. sites) observational study to assess the risk of bronchospasm and related outcomes in acutely agitated adult patients with schizophrenia or bipolar disorder who present to an emergency department. The study would assess the relevant factors when the product is used in clinical practice under the REMS proposed by the Agency. The primary safety objectives are to assess the frequency and severity of bronchospasm and related serious adverse events and serious outcomes (i.e., the need for rescue medication, hospitalization, intubation, and mechanical ventilation to manage bronchospasm). The clinicians at the clinical site would decide on the particular treatment for an individual patient. The proposed exclusion criteria include patients with current respiratory symptoms or those who are currently treated for asthma or COPD.

The sponsor proposes [REDACTED] (b) (4)

The sponsor proposes [REDACTED] (b) (4)

[REDACTED] We must consider this point further and reach agreement with the sponsor. The proposed types of safety data and baseline data appear acceptable, but we will need to consider this in more detail. Generally, the proposed safety outcomes of interest appear acceptable; however, we must carefully develop case definitions.

In my opinion, the critical aspects that we must work out are the required methods for follow-up and the required duration for follow-up. There is a considerable risk that there will be a substantial amount of missing data that could markedly impact the interpretability of findings from the study. Not all cases of bronchospasm and related events in the trials occurred within the first 1 to 2 hours following treatment. Furthermore, pulmonary function test parameters often did not return to baseline within 24 hours following treatment. In addition, we must develop specific adverse event reporting requirements.

14. Pediatric Use, PREA waivers or deferrals, Pediatric Plan

The use of loxapine for oral inhalation has not been studied in pediatric patients. The sponsor has submitted a pediatric plan for studies in pediatric patients [REDACTED] (b) (4) years old in schizophrenia and ≥ 10 in bipolar I disorder). The sponsor plans to conduct a pediatric PK study of single, ascending doses of inhaled loxapine in non-agitated pediatric patients with schizophrenia or bipolar disorder. The general study design and planned doses are reasonable. The initial dose would be [REDACTED] (b) (4). The sponsor also plans [REDACTED] (b) (4)

[REDACTED] pediatric patients with schizophrenia or bipolar I disorder. The study will use fixed-doses which will be selected based on the results of the pediatric PK study. Generally, the study design appears reasonable. However, we should consider whether the [REDACTED] (b) (4) of the study design is reasonable. Probably, the sponsor has proposed this in order to meet the requirements of the E.M.A.

The Division presented the pediatric plan to PeRC. The sponsor requested a partial waiver for studies in patients 0-10 years-old, because it is extremely difficult to make a diagnosis of schizophrenia or bipolar disorder in this age group. Thus, such studies would be impractical. The Division supported this request. The sponsor has requested a deferral for studies in acute agitation in pediatric patients with schizophrenia or bipolar disorder

The Division thinks that an efficacy study in this population is reasonable, because the product may provide a meaningful benefit compared to currently available atypical antipsychotics for intramuscular injection. The comparative benefits could include the same as for adults; this would be a non-invasive treatment that could provide rapid control of acute agitation, with a lower risk of physical injury. Furthermore, treatment with this product would be less likely to be perceived as being coercive; thus the use of this option could assist in strengthening the therapeutic alliance between the patient and healthcare providers.

PeRC agreed to grant a waiver for studies in patients below the age of 10 years old. PeRC agreed to grant a deferral for studies in patients with schizophrenia (b) (4) old and in patients with bipolar I disorder \geq 10 years old.

PeRC had several recommendations: (b) (4)

(b) (4)
3) we should request that the sponsor submit the complete efficacy and PK protocols in a PPSR, 4) the sponsor should not initiate the studies until the Agency has issued a pediatric written request, and 5) the Agency should state in the written request that we would partially rely on efficacy data from the adult studies. We will follow through on these recommendations.

[Reviewer's note: (b) (4)

15. Pediatric and Maternal Health Staff Consult

Erica Radden, M.D., performed the consult review for the Pediatric and Maternal Health Staff. Dr. Radden notes that this application has triggered PREA, because the application is for a new indication and involves a new dosage form and route of administration trigger PREA. Loxapine for inhalation has not been evaluated in pediatric patients. In accordance with the PREA, the sponsor has submitted a request for a partial waiver in children under age 10 with bipolar disorder and children under (b) (4) with schizophrenia. It is difficult to make these diagnoses in these age groups; studies in these age groups are impossible or highly impractical, because the number of pediatric patients in this age group is very small (section 505B(a)(4)(B)(i) of the Act). (b) (4)

(b) (4). Dr. has concluded that the Agency can grant a partial waiver, because the necessary studies are impossible or highly impracticable. Dr. Radden also agrees that the Agency should grant a deferral for studies in schizophrenia (in patients (b) (4)) and in bipolar I disorder (in patients \geq 10 years old). The product could provide a meaningful benefit over existing therapies.

Dr. Radden agrees with the proposed labeling in the Specific Populations – Pediatric Use section:

The safety and effectiveness of ADASUVE in pediatric patients have not been established.

16. Labeling Review

The multidisciplinary review team worked throughout the review cycle to develop product labeling. We reached a consensus on all aspects of labeling. The main focus of labeling was to describe and mitigate the risk of bronchospasm and related serious outcomes, consistent with the Agency’s REMS. The sponsor’s proposed labeling was not adequate in addressing these risks. The sections below present the language from the critical sections of labeling that address the risk of bronchospasm. These include Dosage and Administration and Instructions for Use, the Boxed Warning, Contraindications, Warnings, and Adverse Reactions.

A. Boxed Warning and Warnings and Precautions – Bronchospasm:

The boxed warning clearly states that treatment with inhaled loxapine can cause bronchospasm, which can lead to respiratory arrest and death. The warning states that the product may be used only in facilities that have immediate access on-site to advanced airway management capabilities. It also highlights the requirement for screening out patients at increased risk of bronchospasm; the use of the product is contraindicated in such patients. The warning also discusses the monitoring required after dosing. Finally, the warning discusses the restricted use and the REMS necessary for the use of the product.

(b) (4)



B. Dosage and Administration:

The section includes a number of critical points that are elements of the REMS with ETASU. The use of the product is restricted to facilities that have all necessary components to manage acute bronchospasm and related serious outcomes. Administration is limited to one dose within a 24-hour period, because the rate and severity of bronchospasm was dose-related in the pulmonary safety studies, and bronchospasm did not always resolve within 24 hours following a single dose. Labeling states the requirements for screening and physical examination before dosing and for specific monitoring after dosing. The Instructions for Use provide detailed instructions for the healthcare professional using the product. The IFU includes instructions that the provider must give to the patient before administration. In addition, the IFU contains detailed figures for each step of administration (the figures are not included below).

2.1 Dosing Information

ADASUVE must be administered only by a healthcare professional. ADASUVE is administered by oral inhalation only. The recommended dose for acute agitation is 10 mg administered by oral inhalation, using a single-use inhaler. (b) (4) Administer only a single dose within a 24-hour period [see *Warnings and Precautions (5.1)*].

2.2 Required Examination Prior to Dosing

Prior to administering ADASUVE, screen all patients for a history of asthma, COPD, or other pulmonary disease and examine patients (including chest auscultation) for respiratory signs (e.g. wheezing) [see *Warnings and Precautions (5.1)*].

2.3 Important Administration Instructions (Instructions for Use)

Read all of these instructions prior to administering ADASUVE.

Step 1. Open the Pouch

When ready to use, tear open the foil pouch and remove the inhaler from the package (see Figure 1).

When the ADASUVE inhaler is removed from the pouch, the indicator light is off (see Figure 2).

Step 2. Pull Tab

Firmly pull the plastic tab from the rear of the inhaler (see Figure 3). Check that the green light turns on. This indicates that the inhaler is ready for use. Use the inhaler within 15 minutes after removing the tab to prevent automatic deactivation of the inhaler. The green light will turn off, indicating that the inhaler is not usable. Discard the inhaler after one use

Step 3. Explain Procedures to the Patient

Explain the administration procedures to the patient prior to use, and advise the patient that it is important to follow the instructions. Inform the patient that the inhaler may produce a flash of light and a clicking sound, and it may become warm during use. These are normal.

Step 4. Instruct the Patient to Exhale

Instruct the patient to hold the inhaler away from the mouth and breathe out fully to empty the lungs (see Figure 4).

Step 5. Instruct the Patient to Inhale

Instruct the patient to put the mouthpiece of the inhaler between the lips, close the lips, and inhale through the mouthpiece with a steady deep breath (see Figure 5). Check that the green light turns off indicating that the dose has been delivered.

Step 6. Instruct the Patient to Hold Breath

Instruct the patient to remove the mouthpiece from the mouth and hold the breath for as long as possible, up to 10 seconds (see Figure 6).

Important: If the green light remains on after the patient inhales, the dose of ADASUVE has NOT been delivered. Instruct the patient to repeat Step 4, Step 5, and Step 6 up to 2 additional times. If the green light still does not turn off, discard the inhaler and use a new one.

2.4 Monitoring to Assess Safety

Monitor the patient for signs and symptoms of bronchospasm after ADASUVE administration. Perform a physical examination, including chest auscultation, at least every 15 minutes for at least one hour after ADASUVE administration [*see Warnings and Precautions (5.1)*].

C. Contraindications:

ADASUVE is contraindicated in patients with the following:

- Current diagnosis or history of asthma, COPD, or other lung disease associated with bronchospasm
- Acute respiratory symptoms or signs (e.g., wheezing)
- Current use of medications to treat airways disease, such as asthma or COPD [*see History of bronchospasm following ADASUVE treatment*]
- Known hypersensitivity to loxapine or amoxapine (e.g., serious skin reaction).

D. Adverse Reactions:

The Adverse Reactions section includes a specific section on Bronchospasm and Respiratory Adverse Reactions. The section provides detailed information on the spirometry findings and respiratory reactions from the three pulmonary safety studies (in asthma, COPD, and healthy volunteers) and the pivotal clinical efficacy trials. There is a discussion of the rescue medications that were required in the studies.

17. Conclusions and Recommendations

Recommended Regulatory Action

I recommend that the Division take a Complete Response action. The critical issues preventing approval are the device deficiencies identified by the CDRH and CDER Offices of Compliance. These offices have made a recommendation of Withhold. The inspection of facilities and review of the CMC data revealed that there are deficiencies in the process validation for the device. The Agency has detailed the deficiencies and communicated these to the sponsor on several occasions. The sponsor has not provided adequate data. The sponsor is required to submit adequate data to resolve the issues. In addition, CDRH OC would require an additional inspection after the sponsor has provided adequate data for review.

I would support approval of the application if there were no outstanding device and compliance issues. In my opinion, the Agency's REMS and product labeling would be adequate to mitigate the risk of bronchospasm and serious related outcomes. Under the REMS, use of the product would be restricted to facilities that immediate, on-site access to appropriate personnel and equipment required for advanced airway management (including bronchodilator medication via nebulization, intravenous corticosteroids, intubation, and mechanical ventilation). In addition, the REMS provides requirements for appropriate screening to identify patients at increased risk of bronchospasm who would not be eligible for treatment with the product. Labeling includes clear contraindications and a prominent boxed warning regarding the risk of bronchospasm and requirements for screening and monitoring. The REMS and labeling also limit dosing to a single dose within a 24-hour period, and the REMS has requirements for controls within the facility to ensure that a patient receives only one dose within 24 hours. The REMS also includes requirements for the facilities to provide training to staff who would administer the product.

However, there are potential limitations to the REMS in preventing and mitigating the risks bronchospasm and related serious outcomes. There is a risk that the screening process will not always be ideal. Because of the nature of acute agitation in the intended population, it will not always be possible to obtain a reliable medical history, obtain medical records promptly, or perform an adequate physical examination to determine if a patient is at increased risk of bronchospasm. In addition, patients may be potentially at risk for developing bronchospasm after treatment with inhaled loxapine, even if they do not have a history of pulmonary disease; it is possible that they could develop their first

episode of bronchospasm following treatment with the product. In addition, it is possible that patients will not always be monitored thoroughly, and they could develop respiratory problems which could go unnoticed. This risk could be increased if the patient becomes sedated. Also, as demonstrated in the pulmonary safety studies and the efficacy trials, some patients developed significant respiratory adverse reactions after the first 1 to 2 hours following treatment. Thus, it is possible that patients could be discharged and develop complications relatively late. Finally, because bronchospasm can progress rapidly, there is a potential risk that even in a facility with on-site access to full capabilities for advanced airway management, the response to an event might not be immediate, or proper management might not be fully successful.

In my opinion, loxapine for oral inhalation may offer unique benefits compared to other available treatments for this indication (i.e., atypical antipsychotics for intramuscular injections). The two pivotal trials clearly demonstrated the efficacy of inhaled loxapine in the treatment of acute agitation associated with schizophrenia or bipolar disorder. The onset of efficacy was relatively rapid; significant reductions in the severity of agitation were apparent as early as 10 minutes after dosing with loxapine 5 mg or 10 mg. Although the sponsor did not conduct direct comparisons with such treatments, it is widely accepted that there is a significant delay in clinical response with antipsychotic injections. Clinicians often combine the IM antipsychotic with an IM injection of benzodiazepine in a single injection in order to achieve rapid control of agitation. It would be a significant public health benefit to have a treatment available that could provide rapid control of acute agitation; acute agitation can be severely debilitating and it can lead to violence, physical injury, and death. Furthermore, a non-invasive treatment such as this product could offer distinct advantages. The use of intramuscular injections often requires physical restraint and some degree of coercion. During restraint and injection, there is a risk of physical injury, including contaminated needle stick injury. With a non-invasive treatment option, there could be a reduced risk of injury. Patients and providers could view this as a significant benefit. In addition, with this treatment option, patients could have a more active role in making decisions about treatment. This, in itself, has the potential to de-escalate acute agitation and dangerous behavior, and it has the potential to strengthen the therapeutic alliance between the patient and healthcare provider.

Recommended Postmarketing Requirements and Commitments

If we were to approve the application, I would recommend a PMR for a postmarketing, large observational study to assess the risk of bronchospasm when the product is used in clinical practice under the Agency's REMS. The primary objectives would be to assess the frequency and severity of bronchospasm and related serious outcomes (e.g., respiratory events that require rescue medication, intubation or mechanical ventilation, and events such as respiratory arrest and death). One of the main objectives would be to assess how well the REMS mitigates these risks.

Recommended Comments to the Applicant in the Regulatory Action Letter

I recommend that we request a safety update in case there are ongoing IND studies with loxapine for oral inhalation.

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

/s/

ROBERT L LEVIN
04/25/2012

CLINICAL REVIEW
Cycle 2 Addendum

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Priority Designation Standard

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1. Recommendations/Risk Benefit Assessment

1.1 Recommendations on Regulatory Action

I recommend an approval action be taken for Staccato loxapine for Inhalation (Adasuve) for the treatment of acute agitation associated with schizophrenia or bipolar disorder. However, approval should only be granted after agreement on appropriate REMS as recommended by the Agency in conjunction with the Division of Risk Management. At the time of this writing, CDRH is still considering a withhold recommendation for device deficiencies at an Alexza site. Therefore, my recommendation is also contingent upon the final recommendations of other divisions involved in review of this NDA.

Agreement with the sponsor to limit dosing to a single dose in 24 hours in conjunction with appropriate REMS should decrease the likelihood of serious respiratory adverse events. Furthermore, the REMS proposed by FDA will facilitate safer and more effective management of serious respiratory adverse events should they occur.

1.2 Risk/Benefit Assessment

Staccato Loxapine for Inhalation (Adasuve) provides a non-invasive, rapid treatment of acute agitation associated with schizophrenia or bipolar disorder. It will provide an alternative to current medications approved for this indication which are either invasive (eg, intramuscular) or may have a slower onset (eg, oral medications).

Acute agitation is a severe, disruptive complication of schizophrenia and mania. It may progress from inner distress (nervousness, restlessness, panic) to an outwardly apparent dysfunctional state with cursing, hostility, difficulty controlling impulses, uncooperative behavior, and increased potential for violence. The rapid onset and proven efficacy of Adasuve will quickly prevent this escalation of agitation symptoms, decreasing the likelihood of injuries to the patient or medical personnel associated with having to physically restrain the patient. The fact that Adasuve is noninvasive is important because use of Adasuve could avoid injuries associated with needle sticks, especially in an acutely agitated patient.

Another clinically significant benefit of Adasuve is that the therapeutic alliance between an agitated patient and the treatment team can be strengthened by allowing the patient to be more involved in treatment decisions. By presenting the options of the inhalable product, injections, or orals, the patient can have some choice, and the healthcare provider can avoid coercion and the danger of wrestling with patients and forcibly injecting them. In fact, establishing a better relationship with the patient can, in itself, help de-escalate agitation and violent behavior.

There is a significant risk of bronchospasm associated with Adasuve use, especially in patients with asthma or COPD. The severity of airway obstruction is worse after a second dose. However, the sponsor's agreement with FDA to limit dosing to once in 24 hours will decrease the risk of severe bronchospasm. In addition the REMS proposed by FDA will provide adequate screening for patients at risk for Adasuve-induced bronchospasm (eg, history of asthma or COPD) who should not receive Adasuve.

Despite adequate screening, it is likely that some patients who receive Adasuve will develop respiratory adverse events. In the pivotal trials, one subject who had no history of pulmonary disease developed bronchospasm requiring treatment with albuterol. However, the REMS proposed by FDA will ensure that all patients who receive Adasuve are carefully monitored for respiratory signs and symptoms post-dosing and should result in early detection of respiratory adverse events if they develop.

Although all the respiratory adverse events in clinical trials were mild to moderate, it should not be assumed that there is no risk of severe respiratory compromise in all patients who receive Adasuve post-approval. In the pulmonary safety trials, frequent monitoring of FEV1 and use of rescue bronchodilators for decreases in FEV1 \geq 20% may have prevented further respiratory decompensation. Patients with decreases in FEV1 are frequently not aware of respiratory symptoms until later. Furthermore, in the pivotal trials, patients were screened for up to 2 weeks. In an emergency setting, this is not practical, and obtaining accurate history and performing adequate physical examination on acutely agitated and, in some cases, psychotic patients may be challenging. Considering this and considering the high rate of smoking in the intended treatment population, the possibility of serious respiratory compromise exists. However, the REMS will ensure that capabilities for full respiratory treatment and support, including intubation and ventilation, are available on-site. Thus, respiratory adverse events will be rapidly and effectively managed if they develop.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Based on the data provided, several conclusions can be made which are relevant to development of an appropriate REMS. First, as noted above, limiting Adasuve to a single dose in 24 hours will decrease, but not eliminate, the risk of respiratory adverse events (AEs). Second, since a few subjects in the pivotal trials developed respiratory AEs despite exclusion of subjects with acute or chronic pulmonary disease, it is apparent that some patients may develop respiratory AEs despite adequate screening. Therefore, careful monitoring of patients post-dose and availability of full respiratory treatment and support capabilities on site is imperative. Third, in the pulmonary safety trials, most of the respiratory adverse events which occurred after a first dose of Adasuve (7 of the 8 asthma subjects and all 4 COPD subjects) occurred within 25 minutes of dosing. Therefore, it is especially important to monitor patients carefully during this time period. Fourth, since sedation is a common AE associated with Adasuve, healthcare practitioners should not rely on patient reported symptoms alone for monitoring for pulmonary toxicity post-dose.

The sponsor's revised REMS takes into account the agreement at the Psychopharmacologic Drugs Advisory Committee (PDAC; see **Section 4** below) to limit treatment with Adasuve to 1 dose per 24 hour period and includes language notifying healthcare practitioners that patients should be monitored every 15 minutes for at least one hour post-dose. This is acceptable.

However, the sponsor's proposed REMS is inadequate for the following reasons:

[REDACTED] (b) (4)

1.5 Recommendations for Postmarket Requirements and Commitments

I recommend that the sponsor conduct a postmarketing study with the primary goal to assess the safety of Adasuve. All adverse events in the study should be reported with particular attention to respiratory adverse events. All treatments and patient outcomes should be included. In addition, data on device failures and demographics of the patient population treated with Adasuve should be obtained. This study will need to be sufficiently powered to provide accurate information and therefore will of necessity enroll large numbers of patients. Therefore, it would be impractical to conduct this study pre-approval.

2. Introduction

ADASUVE (loxapine) inhalation powder (*Staccato* Loxapine) is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery by inhalation of a thermally generated aerosol of loxapine. *Staccato* Loxapine represents a new dosage form for loxapine, an antipsychotic with dopamine D₂ blocking activity that has been available in the United States (US) since 1975. *Staccato* Loxapine (5-mg and 10-mg dose levels) has been developed by the sponsor for the treatment of agitation in patients with schizophrenia or bipolar disorder. Since agitation in these psychiatric populations is an acute and intermittent condition, it is expected that patients will be treated with *Staccato* Loxapine on an infrequent basis.

This review is an addendum to this reviewer's Cycle 2 Clinical Review which was submitted prior to the Psychopharmacologic Drugs Advisory Committee (PDAC) Meeting of December 12, 2011. Therefore, this review will focus on issues raised at the PDAC Meeting as well as information resubmitted by the sponsor post-PDAC Meeting and remaining issues which need to be addressed. For a complete clinical review, the reader is referred to this reviewer's **Cycle 1 Clinical Review** (September 17, 2010) and **Cycle 2 Clinical Review** (November 8, 2011).

3. Brief Regulatory History

The sponsor submitted NDA 22549 on December 11, 2009 to support the approval of *Staccato* Loxapine as a prescription drug product for the rapid treatment of agitation associated with Schizophrenia or Bipolar Disorder in adults. On October 8, 2010, a Complete Response (CR) action was taken by the Division, identifying pulmonary toxicity, specifically bronchospasm, as the primary issue.

The sponsor met with the Division on December 17, 2010 (*End of Review Meeting*) to discuss the issues raised in the CR letter and how they should be resolved. Further conceptual guidance on the content of product labeling and the components of a Risk Evaluation and Mitigation Strategy (REMS) to manage the risk of bronchospasm was discussed with the sponsor at a *Type C Meeting* on April 29, 2011.

On August 4, 2011, the sponsor resubmitted NDA 22549 with proposed REMS. A Psychopharmacologic Drugs Advisory Committee (PDAC) Meeting was held on December 12, 2011. At the PDAC Meeting, agreements were reached with the sponsor to revise the proposed REMS based on Agency recommendations. As a result, the sponsor submitted a revised REMS

proposal on January 10, 2012. Updated proposed labeling was submitted by the sponsor on January 12, 2012. On January 19, 2012, the sponsor was notified that FDA was extending the user fee goal date by three months to provide time for full review of the submission.

4. Psychopharmacologic Drugs Advisory Committee (PDAC) Meeting

At the PDAC Meeting of December 12, 2011, the sponsor's presentation included an overview of the clinical development program for Adasuve with presentation of efficacy and safety data. The sponsor clarified that use of Adasuve was anticipated to be in three places: psychiatry emergency rooms, medical emergency rooms, and psychiatric inpatient units.

FDA presentation included a brief clinical overview by this reviewer with focus on specific aspects of the clinical trials that are important from FDA perspective. This was followed by a presentation by Theresa Michele, M. D. from the Division of Pulmonary, Allergy and Rheumatology products (DPAAP). Dr. Michele discussed the pulmonary safety of Adasuve including the data from the three dedicated pulmonary trials and the pulmonary safety data from the phase 2 and phase 3 trials in agitated patients. Lastly, Kimberly Lehrfeld, Pharm. D., from the Division of Risk Management discussed the Risk Evaluation and Mitigation Strategy for Adasuve.

The FDA pointed out that in studying agitated patients with schizophrenia or bipolar disease, the conditions necessary for recruiting and screening patients, obtaining informed consent, and performing a well-designed study may influence the type and severity of agitated patients studied. Specifically, the FDA noted potential limitations of the efficacy trials which may limit the generalizability of the results from the study population to the intended patient population.

First, very few patients were recruited from emergency rooms, yet emergency rooms would likely be a common setting for use of Adasuve if it is approved. Over half of the study patients presented directly to the study site for treatment. It is possible that patients presenting directly to the study site who were referred from healthcare practitioners in the community may be more cooperative, may be more likely to have an established relationship with a healthcare provider, and may have medical records more readily available compared to patients presenting directly to an emergency room. Second, the screening period for the efficacy trials was up to two weeks in the schizophrenia trial and up to 24 hours in the bipolar trial. This allowed for ample time for obtaining medical history and performing physical examinations to screen for active pulmonary disease, which may not be the case in an acute clinical setting. Third, subjects were screened for their ability to perform the inhalation maneuver necessary for Adasuve administration and underwent some device training, which may not be practical in an acute setting.

Dr. Michele discussed the data from the pulmonary safety studies outlining a significant risk of bronchospasm with *Staccato* Loxapine treatment, particularly in patients with underlying airway hyper-responsiveness. The severity of bronchospasm is greater with a second dose and does not return to baseline for at least 14 hours following that dose. Importantly, Dr. Michele noted that there was limited safety data in patients dosed every two hours, a frequency permitted in the proposed label. Dr. Michele concluded that, based on NIH asthma treatment guidelines and what we know about the safety profile of *Staccato* Loxapine, minimum risk

mitigation should include the following components: 1) screen and do not administer *Staccato* loxapine to patients with an underlying respiratory condition, 2) give *Staccato* Loxapine only in healthcare settings with advanced airway management capabilities, and 3) monitor patients frequently with vital signs and physical examinations. Furthermore, given the sedative nature of the drug and the characteristics of the intended patient population, it would be important not to rely solely on patient-reported symptoms.

Dr. Lehrfeld's presentation concluded that the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS) for Adasuve will not sufficiently mitigate the serious patient outcomes that could result from loxapine inhalation and included the FDA's recommendations regarding REMS. The FDA's minimum requirements would include observation of patients for acute respiratory signs and symptoms pre-dose with specific inquiry as to whether the patient is taking any medication to treat lung disease. Monitoring should include physical examination, including vital signs and pulmonary examination. Post-dose, FDA recommended monitoring every 15 minutes for the first hour and every 30 minutes thereafter. The exact period of time for monitoring remains up for discussion. The sponsor has proposed that a short-acting beta agonist metered dose inhaler (MDI) be available at the treatment site. However, Dr. Lehrfeld pointed out that a metered-dose inhaler can be difficult to use, especially in a patient who has no experience with using a metered-dose inhaler, is agitated, or is sedated. Therefore, the FDA's minimum proposal is to ensure the availability of an inhaled short-acting beta agonist bronchodilator in a metered-dose inhaler as well as in a nebulized form. In addition, the FDA proposal would ensure that the treatment center has immediate access to advanced airway management capabilities, including intubation and ventilators.

Overall, the Advisory Committee felt that one of the advantages to Adasuve would be that it is a non-invasive treatment. Another potential advantage would be a more rapid onset of efficacy compared to other medications available for the same indication, but the Committee agreed that, in the absence of head-to-head comparisons, a judgment cannot be reached about relative time of onset based just on pharmacokinetic data. In addition, there was general agreement that the sponsor's proposed REMS was inadequate, and the Committee favored the REMS program proposed by the FDA.

Regarding the sponsor's proposed post-marketing observational study, the committee questioned the value of a non-randomized comparator study, and the FDA clarified that the primary interest was in getting additional safety data as opposed to getting comparative data. The sponsor stated that they would be agreeable to changing the study design to assess the safety of Adasuve alone. The Committee was unable to reach a consensus as to whether the observational study should be done pre- or post-marketing.

The Committee agreed that Adasuve had been shown to be effective as a treatment for agitation in patients with schizophrenia or bipolar mania. However, the Committee expressed major concern over the lack of pulmonary safety data after a second dose of Adasuve when dosing is every two hours as proposed in the sponsor's labeling. Concern was expressed about potential serious outcomes for at-risk patients who are not identified at screening and receive a second dose of Adasuve. However, the majority of Committee members agreed that, if Adasuve was limited to a single dose in 24 hours, it would be acceptably safe when used in conjunction with the REMS proposed by FDA. By a close final vote of 9 to 8 with 1 abstention, the Committee concluded that Adasuve should be approved for use as a single dose in 24 hours when used with the FDA-proposed REMS as a treatment for agitation in patients

with schizophrenia or bipolar mania. A prevalent concern among the 8 Committee members who voted “no” was the belief that some type of observational study to obtain more real-world data was necessary pre-approval.

5. Sponsor’s Revised Risk Evaluation and Mitigation Strategy (REMS) Proposal

Based on the PDAC and FDA recommendations, the sponsor submitted a revised REMS proposal to the FDA on January 6, 2012. According to the sponsor, the goals of the Adasuve REMS are to:



The sponsor’s proposed REMS includes a Medication Guide, Communication Plan, and Elements to Assure Safe Use (ETASU) which the sponsor believes will ensure that Adasuve is only available in healthcare facilities where there is ready access to a short-acting bronchodilator (eg, albuterol) and emergency response services capable of providing advanced airway management. Enrolled healthcare facilities will also attest to having or establishing procedures, protocols, and/or order sets to ensure screening of patients prior to treatment with Adasuve, observing and monitoring following treatment, and managing patients in the event that bronchospasm occurs; and that relevant staff is trained on the safe use of Adasuve.

The revised REMS takes into account the agreement at the PDAC to limit treatment with Adasuve to 1 dose per 24 hour period and includes expansion of ETASU with additional healthcare facility attestations based on the pertinent text in the Relprevv REMS.

5.1 Management of the Risks of ADASUVE

The sponsor proposes that this risk can be mitigated by the product labeling and the proposed REMS. Through the labeling and the REMS, Alexza will communicate the risk of bronchospasm and educate healthcare professionals to (i) identify and select only appropriate patients for treatment, (ii) observe patients for respiratory signs and symptoms for one hour after each treatment, and (iii) have a short-acting beta-agonist bronchodilator (eg, albuterol) readily accessible to manage bronchospasm, if it occurs. The sponsor notes that, in the cases of bronchospasm seen in the clinical program, the bronchospasm symptoms began within 25 minutes of treatment in the significant majority of cases. The sponsor believes an appropriately

conservative, but not unduly burdensome, goal is to have healthcare professionals observe and monitor patients for bronchospasm for at least one hour after treatment.

Prior to the PDAC meeting, the sponsor also proposed that healthcare facilities be enrolled in a distribution program whereby product is only made available in facilities ensuring there is a short-acting beta-agonist bronchodilator readily accessible in the treatment settings. Based on feedback from the FDA and the PDAC, the healthcare facility requirements for enrollment in the distribution program have been expanded. The sponsor is now proposing that healthcare facilities be enrolled in a distribution program whereby product is only made available in facilities ensuring there is a short-acting beta-agonist bronchodilator readily accessible in the treatment settings *and* that there is ready access to emergency response services capable of providing advanced airway management. Under the sponsor's revised proposal, enrolled healthcare facilities will also attest to having or establishing procedures, protocols and/or order sets to ensure screening of patients prior to treatment with Adasuve, observation and monitoring following treatment, and managing of patients in the event that bronchospasm occurs; and that relevant staff is trained on the safe use of Adasuve.

5.2 Prescribing Information

The sponsor proposes that a **Boxed Warning** will be included in the Full Prescribing Information that will highlight for prescribers the following information:

WARNING: BRONCHOSPASM IN PATIENTS WITH ACTIVE AIRWAYS DISEASE AND INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

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 healthcare facilities where there is ready access to an inhaled short-acting beta-agonist bronchodilator (eg, albuterol) and to emergency response services capable of providing advanced airway management; and where the patient can be observed and monitored every 15 minutes for at least one hour after treatment.

The language in the revised **Boxed Warning** is identical to the language in the **Boxed Warning** proposed by the sponsor prior to the PDAC meeting except that the last sentence has been changed from, "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 1 hour after treatment" to "Adasuve should be administered only in healthcare facilities where there is ready access to an inhaled short-acting beta-agonist bronchodilator (eg, albuterol) and *to emergency response services capable of providing advanced airway management; and where the patient can be observed and monitored every 15 minutes for at least one hour after treatment.*" [Bold italics added by this reviewer.]

The Full Prescribing Information will also include the following contraindication, which is identical to the sponsor's proposed language prior to the PDAC meeting:

4. CONTRAINDICATIONS

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 be made clearly visible on the primary packaging (product pouch) as follows:

ADASUVE™ (loxapine) Inhalation Powder
For oral inhalation only

WARNING: Do not use in patients with acute respiratory signs/symptoms (eg, wheezing) or who are taking medications to treat asthma or COPD

See ADASUVE Medication Guide

Additionally, the full prescribing information will include the following information related to bronchospasm in the **Warnings and Precautions** sections. These sections have been modified by the sponsor in the revised REMS. In the previous submission, these sections contained information on respiratory adverse events in the pulmonary safety studies without differentiating adverse event incidence after a single-dose of Adasuve from adverse event incidence after multiple dosing. Since the sponsor has now agreed to limit treatment with Adasuve to 1 dose per 24 hour period, this differentiation has been added. In addition, the language has been revised to reflect the sponsor's proposed requirements for administration of Adasuve only where there is "ready access" to "emergency response services capable of providing advanced airway management" and for the more specific observation and monitoring of patients "every 15 minutes for at least one hour after treatment with Adasuve for signs and symptoms of bronchospasm." Thus, the proposed **Warnings and Precautions** section is as follows:

5. WARNINGS AND PRECAUTIONS

5.1 Bronchospasm

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. After a first dose of ADASUVE only, bronchospasm was reported in 8 of 26 asthma subjects (30.8%), and in 4 of 26 COPD subjects (15.4%). These events occurred within 25 minutes of dosing in 7 of the 8 asthma subjects (median 4 minutes for all 8 subjects) and in all 4 of the COPD subjects (median 10 minutes). 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 receiving 1 or 2 doses of ADASUVE. 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 that have ready access to an inhaled short-acting beta-agonist bronchodilator (eg, albuterol) and emergency response services capable of providing advanced airway management. Patients should be observed and monitored every 15 minutes for at least one hour after treatment with ADASUVE for signs and symptoms of bronchospasm. If bronchospasm occurs, it should be treated with a short-acting beta-agonist bronchodilator and other measures as clinically indicated, and ADASUVE should not be given again to the patient.

Patients should be advised of the risk of bronchospasm if they have active airways disease (eg, asthma or COPD) and to inform their healthcare professionals 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)].

As noted above, an agreement was reached at the PDAC meeting to limit treatment with Adasuve to 1 dose per 24 hour period. Therefore, the sponsor's proposed language in the **Dosing and Administration** section of the Full Prescribing Information pertaining to dosing frequency now states:

2. Dosage and Administration

*The recommended dose of ADASUVE is 10 mg. [REDACTED] (b) (4)
[REDACTED] Only a single dose should be administered in any 24-hour period.*

The sponsor's Full Prescribing Information will also include a Medication Guide that will be affixed to the product pouch.

5.3 Medication Guide

The sponsor proposes the use of a Medication Guide as part of the REMS. The Medication Guide will accompany the Prescribing Information and will be affixed to the outside of the pouch that is the primary package for each unit. In addition to providing instructions for successful use of Adasuve, the Medication Guide will explain the risks of Adasuve to patients and caregivers and ask patients and their caregivers to inform their doctors if they develop any of the symptoms of bronchospasm.

The sponsor acknowledges that, while the Medication Guide is directed to the patient, it may be impractical in an urgent situation to review the Medication Guide with the patient before treatment. However, the sponsor believes that the Medication Guide will also serve as a reminder to healthcare professionals of the steps for safe use of Adasuve. The Adasuve Medication Guide has been designed to provide useful information to the healthcare professionals who prescribe and/or administer the product about the risk of bronchospasm,

proper patient selection, the need to observe the patient for at least one hour after treatment with Adasuve, and how to manage bronchospasm should it occurs.

5.4 Communication Plan

In addition to the Prescribing Information and Medication Guide, the sponsor proposes a multi-prong Communication Plan for healthcare providers. The key communication messages of the Adasuve REMS that inform healthcare professionals how to mitigate the risk of bronchospasm are to:

1. Screen to identify appropriate patients for treatment,
2. Observe and monitor patients for bronchospasm for at least one hour after treatment, and
3. Manage bronchospasm if it occurs

The sponsor argues that through a healthcare facility enrollment requirement, a short-acting beta-agonist bronchodilator (eg, albuterol) and emergency response services capable of providing advanced airway management will be readily accessible.

5.4.1 Screening to Identify and Select Appropriate Patients

The first message of the proposed REMS informs of the risk of bronchospasm and instructs the healthcare provider to screen patients to identify and select appropriate patients for treatment with Adasuve. Under the proposed REMS, the healthcare provider will need to determine if the patient has active airways disease and/or is taking medications to treat such a condition. The sponsor argues that the prescribing clinician's obligation to screen patients for active airways disease can be accomplished by 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 sponsor believes that this is consistent with current medical practice in the proposed institutional treatment settings.

5.4.2 Post Treatment Observation and Monitoring for Bronchospasm

The sponsor believes that the REMS anticipates the possibility that even with a medical screening protocol, some patients with active airways disease may receive Adasuve. Through the communication and education aspect of the REMS, the healthcare provider is instructed to observe and monitor all patients for at least one hour after dosing with Adasuve. Since, as previously noted, a high percentage of the asthma and COPD subjects who experienced bronchospasm did so within 25 minutes after administration, a minimum one-hour observation period following treatment has been proposed. The sponsor reports that consultation with 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, the sponsor believes that that this component of the REMS is also readily accomplished because it is consistent with established medical practices.

5.4.3 Managing Bronchospasm

The sponsor's final REMS message addresses the ability of the clinician to treat bronchospasm if it occurs by ensuring that there is ready access to a short-acting beta-agonist bronchodilator

(eg, albuterol) and emergency response services capable of providing advanced airway management. The sponsor considers the ready access to a short-acting beta-agonist bronchodilator and emergency response services capable of providing advanced airway management to be key components of the risk mitigation strategy for Adasuve. Therefore, through the ETASU 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. In addition, to assure that severe bronchospasm is appropriately treated, the healthcare facility representative will also attest that emergency response services capable of providing advanced airway management are also readily accessible.

5.4.4 Materials

The proposed Communication Plan will comprise the materials listed below:

1. Dear Healthcare Professional Letter
2. Prescriber Brochure
3. Adasuve Safe Use Checklist
4. Order Set/Protocol Template
5. Adasuve Education Program
6. Adasuve REMS Website

5.4.4.1 Dear Healthcare Professional Letter

A Dear Healthcare Professional Letter will inform healthcare professionals of the risk of bronchospasm in patients with active airways disease, such as asthma or COPD. The letter will be accompanied by the Full Prescribing Information, Medication Guide and the additional Communication Plan components described below.

5.4.4.2 Prescriber Brochure

The Prescriber Brochure will provide information related to the risk of bronchospasm. The brochure will also provide guidance to prescribers on how to communicate both the risk of and the signs and symptoms of bronchospasm to patients.

5.4.4.3 Adasuve Safe Use Checklist

The checklist will provide the healthcare professional with steps to follow to ensure safe use before, during, and after treatment with ADASUVE. The checklist will be included in the Prescriber Brochure, integrated into the Order Set / Protocol Template and will also be made available as a stand-alone tool.

5.4.4.4 Order Set/Protocol Template

The Order Set / Protocol Template will outline the important clinical practices related to use of ADASUVE, and will be made available to healthcare facilities to customize for their own use.

5.4.4.5 Adasuve Education Program

The sponsor will provide an Adasuve Education Program to train relevant staff. The training records will be kept by the healthcare facility and will be auditable as part of the healthcare facility enrollment process. Via a slide presentation, the program will describe:

1. How Adasuve works and its proper administration
2. Appropriate patient screening and patient selection for Adasuve, including pertinent clinical risk factors for bronchospasm:
 - Screening patient prior to treating with ADASUVE for acute respiratory signs and symptoms by physical exam (including, for example, taking vital signs, respiratory assessment)
 - Conducting additional screening (ie, take medical history to identify other risk factors, inquiring if patient is taking medication to treat asthma or COPD)
3. Appropriate monitoring of patients following Adasuve treatment
4. Important safety information, including:
 - Dosage and administration
 - Characterization of bronchospasm seen in clinical trials
 - Ready-access to a short-acting, beta-agonist bronchodilator (eg, albuterol) to manage bronchospasm if it occurs
 - Ready access to emergency response services capable of providing advanced airway management, if needed

The Education Program will be offered and delivered in person in the healthcare facilities as part of required training mandated by the ETASU attestation requirement.

5.4.4.6 Adasuve REMS Website

A website (www.adasuverems.com) dedicated to the Adasuve REMS components will be available as a resource for healthcare providers. The content of the web pages will be reflective of the REMS components and will be updated accordingly.

5.4.5 Distribution of Materials

Prior to product launch, the Adasuve REMS components and the Full Prescribing Information will be sent via direct mail to member lists of professional psychiatric and emergency medicine organizations whose members are likely to prescribe Adasuve for the treatment of agitation. These include, for example, the American Psychiatric Association, American Association for Emergency Psychiatry, and the American Academy of Emergency Medicine. Other healthcare professionals who will either dispense or administer Adasuve will also receive this information.

The Communication Plan materials, Medication Guide and Full Prescribing Information will be available at the Adasuve REMS website, by request through the sponsor's toll-free information number, and through Alexza sales representatives and field-based medical personnel.

The Adasuve Education Program will be offered to healthcare professionals by Alexza prior to product launch through various channels (eg, mail, field force). Once the product is launched, healthcare facilities that place an order for Adasuve following enrollment in the Distribution Program, will be offered an in-service education program (if they have not already completed one). The program will be scheduled via the facility contact person (eg, pharmacy director), will be conducted by a clinical educator (eg, nurse consultant, medical science liaison) and will also be available on-line at the Adasuve REMS website. The Education Program will train healthcare professionals working in the enrolled facility who may prescribe, dispense, administer and/or monitor patients receiving Adasuve.

5.5 Elements to Assure Safe Use (ETASU)

The sponsor also proposes to include an ETASU in the Adasuve REMS with the goal of ensuring that Adasuve is only available in healthcare facilities where there is a short-acting beta-agonist bronchodilator readily accessible to manage bronchospasm if it occurs and that there is ready access to emergency response services capable of providing advanced airway management if medically necessary. Enrolled healthcare facilities will also attest to having or establishing procedures, protocols, and/or order sets to ensure screening of patients prior to treatment with Adasuve, observation and monitoring following treatment, and managing patients in the event that bronchospasm occurs; and that relevant staff is trained on the safe use of Adasuve.

Before Adasuve may be dispensed and administered in a healthcare facility, an authorized healthcare facility representative must complete and sign the Healthcare Facility Enrollment Form. In signing the form, the representative attests to the following:



(b) (4)

This attestation is done at the healthcare facility level and as a result the enrollment has been completed prior to any patient's need for Adasuve. The sponsor argues that this places no significant burden on the healthcare professionals treating the patient and ensures that there will be no delay in patient treatment.

5.6 Implementation System

The sponsor's proposed Implementation System will include the following:

(b) (4)

5.7 REMS Assessment Plan

The sponsor's proposed REMS Assessment Plan will include Healthcare Professional Assessments, Patient Assessments, Periodic Audits of the Distribution Database, and Periodic Training Record Audits.

5.7.1 Timetable for Submission of Assessment of the REMS

The sponsor proposes to submit REMS assessments to the FDA at [redacted] (b) (4) [redacted] after the REMS is initially approved.

(b) (4)

6. Sponsor's Proposed Labeling Amendment

On January 10, 2012, the sponsor submitted updates to the components of the draft labeling section of the NDA. The updates are based on agreements reached with the FDA at the Psychopharmacologic Drugs Advisory Committee Meeting on December 12, 2012 to revise the proposed REMS and to limit treatment with Adasuve to 1 dose per 24 hour period.

In addition, the sponsor references an Information Request from the Agency dated December 3, 2011 which recommended a number of changes to the *Instructions for Use* (and to product design), with a recommendation to conduct a Human Factors Validation on these changes. The changes to the *Instructions for Use* that are included in this updated version represent those recommendations from the Agency that the sponsor believes should be implemented without additional Human Factors Validation. However, the sponsor commits to conducting a Human Factors Validation study with the broader set of recommendations from the Agency.

Elements of proposed labeling (**Boxed Warning, Contraindications, Warnings and Precautions**, and **Dosage and Administration**) that relate to the sponsor's proposed REMS have been discussed above (see Section 4.2 *Prescribing Information*). Other important elements of the proposed labeling are summarized below:

5 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

7. Clinical Communications with Sponsor

7.1 Clinical Labeling Request

On February 2, 2012, a clinical labeling request was sent to the sponsor. The clinical request was as follows:

We are currently reviewing your submission and we have the following request:

(b) (4)

7.2 Sponsor' Response

(b) (4)

8. Significant Efficacy/Safety Issues Related to Other Review Disciplines

8.1 CDRH

On January 27, 2012, CDRH compliance determined that they would be temporarily recommending a withhold (WH) action for an Alexza site for device deficiencies. CDRH Compliance found that process validation was not complete. At the time of this writing, CDRH is still completing their review of the device portion of the Establishment Inspection Report (EIR) from the previous inspection which is leaning towards Official Action Indicated (OAI) and withhold. At this point, a Complete Response is possible unless CDRH determines that a re-inspection of the facility prior to the PDUFA date could resolve the outstanding issues preventing approval.

In a Response to Consult Request, Nayan Patel, Biomedical Engineer, Anesthesia and Respiratory Device Branch, Division of Anesthesia (ARDB), CDRH, reviewed updated labeling information submitted by the sponsor on January 12, 2012 pertaining to the device component. Dr. Patel concluded that the labeling test provided has been updated to incorporate changes to the REMS, dosing recommendations, and Instructions for Use and is in agreement with Agency recommendations after the PDAC. However, Dr. Patel recommended that the sponsor provide additional information regarding the device performance specifications in the device labeling. Response from the sponsor to this recommendation is pending at the time of this writing.

In a letter dated March 6, 2012, the sponsor indicated that they have implemented changes to the product design, device labeling, pouch labeling, and instructions for use. In addition, the sponsor submitted results of additional human factors testing to demonstrate how the revisions support safe and effective use. The data was reviewed by QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, who concluded that the sequential Human Factors studies showed that the use errors have decreased significantly which were attributed to the device and IFU changes that the sponsor implemented. Many of the use errors that were originally observed have been eliminated, and the only errors remaining (forgetting to check the status of

the green LED light turning on, providing incomplete inhalation instructions) are effectively minimized. Feedback from representative users has improved. The root cause analyses of the residual use errors show that additional changes to the device or IFU would likely not affect the usability or use-safety of the product.

The Human Factors Reviewer concludes, “The remaining risks associated with the use of the device are acceptable, and further mitigations are not necessary. The sequential Human Factors study demonstrated that use-related risks have been effectively minimized through design and IFU/labeling changes. The study results were found acceptable.”

8.2 Chemistry Manufacturing and Controls

On March 19, 2012, David Claffey, Ph.D., ONDQA provided an update on outstanding CMC-related issues impacting final recommendation and referenced the recommendations of CDRH.

Dr. Claffey noted that a recommendation was made in CMC Review #2 (November 15, 2011) to approve this application from a CMC-perspective pending an acceptable recommendation from CDRH ODE and CDRH Office of Compliance. Furthermore, at the time there was insufficient data to support the proposed (b) (4) drug product expiry period.

CDRH ODE has found that the sponsor’s response has adequately addressed the “device engineering related issues” (Review date: November 4, 2011).

A CDRH ODE review of product labeling (Review date: March 5, 2012) recommended that labeling include detailed information on drug product particle size distribution. ONDQA recommends that these data not be included in product labeling as it has not been CDER practice to do so and it is unclear how Health Care Professionals or patients could use these data. Further, as these data are part of the drug product specification, they are generally considered proprietary in nature.

Updated stability data were provided in an amendment dated January 13, 2012. These were evaluated and were found to support the proposed (b) (4) expiry period.

A final CDER Office of Compliance recommendation remains pending, and Dr. Claffey concludes that a final recommendation from a CMC perspective will be made on receipt of the CDER Office of Compliance recommendation.

8.3 Division of Medical Policy Programs (DMPP)

On March 16, 2012, DMPP submitted a Patient Labeling Review in response to DPP request for DMPP to review the sponsor’s proposed Medication Guide (MG) and Instructions for Use (IFU) for Adasuve. DMPP stated that, in their review of the MG, they have:

- Simplified wording and clarified concepts where possible
- Ensured that the MG is consistent with the prescribing information
- Ensured that the MG meets the Regulations as specified in 21 CFR 208.2.
- Ensured that the MG meets the criteria as specified in FDA’s Guidance for Useful Written Consumer medication Information (published July, 2006)

DMPP further stated, “We acknowledge the submission of an IFU; however the IFU is intended for use as a reference document for the provider who will be administering Adasuve (loxapine) and consequently the IFU was not reviewed by DMPP.”

DMPP concluded, “The MG is acceptable with our recommended changes.”

8.4 Division of Medication Error Prevention and Analysis (DMEPA)

On January 12, 2012, DMEPA completed a Proprietary Name Review. The review was in response to a request from Alexza Pharmaceuticals, Inc. for re-assessment of the proposed proprietary name, Adasuve, regarding potential name confusion with other proprietary or established drug names in the usual practice setting. The proposed proprietary name was previously found acceptable on May 6, 2010 in OSE Review #2010-371. In the review of January 12, 2012, DMEPA noted that the Office of Prescription Drug Promotion (OPDP) had determined that the proposed name is acceptable from a promotional perspective. DMEPA concurred with OPDP and concluded that the proposed proprietary name is acceptable from both a promotional and safety perspective.

On February 16, 2012, comments were emailed to the sponsor based on DMEPA review of the sponsor’s submission. The comments specifically addressed issues related to the device label. DMEPA advised the sponsor that the dosage form should immediately follow the established name, followed by the strength [i.e. (loxapine) inhalation powder, 10 mg]. The proprietary and established names, dosage form and strength should be relocated to the side of the device that has the LED light. Furthermore, the sponsor was advised to include the name of the manufacturer, packer, or distributor on the opposite side of the side with the product’s name and LED light and include the route of administration if space permits.

8.5 Division of Pediatric and Maternal Health

A pediatric labeling review by Erica Radden, M.D. was completed on March 12, 2012. PMHS concurs that due to the low prevalence of schizophrenia or bipolar disorder in children, a partial waiver is indicated. Regarding labeling, the current proposed labeling dated January 12, 2012, states:

8.4 Pediatric Use

The safety and effectiveness of ADASUVE in pediatric patients have not been established.

Dr. Radden states, “If a partial waiver is granted due to impracticability of studies or the studies are deferred, rather than a complete waiver due to safety concerns, the current proposed language for the Pediatric Use subsection is appropriate since loxapine has not been studied and is not approved for use in the pediatric population.”

The Maternal Health Team (MHT) Review by Tammie Howard, RN, MSN was completed on March 26, 2012. The proposed labeling from the Maternal Health Team utilized the Proposed Pregnancy and Lactation Labeling Rule published in May, 2008.

The Pregnancy section was restructured and sub-headers (Risk Summary, Animal Data) were added to provide an organized presentation of data. The Risk Summary paragraph provides the appropriate regulatory language and a summary of risks, based on the available data, followed by the animal data. The FDA required labeling language regarding the use of antipsychotics during pregnancy and the risks to neonates appears under the Human Data sub-header. After discussion with the Division, agreement was reached on labeling as follows:

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of ADASUVE use in pregnant women. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Loxapine, the active ingredient in ADASUVE, has demonstrated increased embryofetal toxicity and death in rat fetuses and offspring exposed to doses approximately 0.5-fold the maximum recommended human dose (MRHD) on a mg/m² basis. ADASUVE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Animal Data

In rats, embryofetal toxicity (increased fetal resorptions, reduced weights, and hydronephrosis with hydroureter) was observed following oral administration of loxapine during the period of organogenesis at a dose of 1 mg/kg/day. This dose is equivalent to the MRHD of 10 mg/day on a mg/m² basis. In addition, fetal toxicity (increased prenatal death, decreased postnatal survival, reduced fetal weights, delayed ossification, and/or distended renal pelvis with reduced or absent papillae) was observed following oral administration of loxapine from mid-pregnancy through weaning at doses of 0.6 mg/kg and higher. This dose is approximately 0.5-fold the MRHD of 10 mg/day on a mg/m² basis.

No teratogenicity was observed in the rat, rabbit, or dog following oral administration of loxapine during the period of organogenesis at doses up to 12, 60, and 10 mg/kg, respectively. These doses are approximately 12-, 120-, and 32-fold the maximum recommended human dose (MRHD) of 10 mg/day on a mg/m² basis, respectively.

The Nursing Mothers section was restructured, providing appropriate regulatory language, stating that it is not known if Adasuve is present in human milk, however, because of the potential risk if present, a decision to discontinue drug or discontinue breastfeeding should be made. As this formulation of loxapine is indicated as an acute treatment, it may be acceptable

to provide instructions regarding pumping and discarding breast milk, should a breastfeeding mother wish to continue breastfeeding. The MHT discussed this option with the Division. Agreement was reached on the following language:

8.3 Nursing Mothers

It is not known whether ADASUVE is present in human milk. Loxapine and its metabolites are present in the milk of lactating dogs. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ADASUVE, a decision should be made whether to discontinue nursing or discontinue ADASUVE, taking into account the importance of the drug to the mother.

8.6 Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

In a Consult Review dated March 16, 2012, Theresa Michele, M.D. of the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) provided labeling recommendations. The intent of the DPARP proposed labeling is to strengthen the warnings regarding bronchospasm. In addition, the Adasuve contraindications have been broadened. Specifically, the proposed labeling makes it clear that Adasuve has the potential to lead to respiratory arrest. Furthermore, the labeling clarifies that Adasuve may only be administered in a facility that has immediate on-site access to equipment and personnel trained to manage acute bronchospasm, including advanced airway management. The sponsor has proposed that ADASUVE should be administered only in enrolled healthcare facilities that have ready access to an inhaled short-acting beta-agonist bronchodilator (eg, albuterol) and emergency response services capable of providing advanced airway management. This implies that all that is needed is a short-acting beta-agonist on-site, and it may be interpreted that off-site emergency response services are acceptable. This is not adequate from DPARP viewpoint.

In addition, a history of asthma, COPD, or other lung disease associated with bronchospasm has been added to contraindications. The DPARP rationale is that this broadening of the contraindications would provide a broader safety margin in a real-world scenario.

Thus, the DPARP proposed labeling would read as follows:

WARNING: BRONCHOSPASM

ADASUVE can cause severe bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. Administer ADASUVE only in an enrolled healthcare facility that has immediate access on site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation). Patients with asthma or other pulmonary diseases, such as chronic obstructive pulmonary disease (COPD) are at increased risk of bronchospasm, and ADASUVE is contraindicated in these patients. Prior to administering ADASUVE, screen and examine patients. Monitor patients for signs and symptoms of bronchospasm following treatment with ADASUVE.

5 WARNINGS AND PRECAUTIONS

5.1 WARNING: BRONCHOSPASM

ADASUVE can cause bronchospasm that can lead to respiratory distress and respiratory arrest. Administer ADASUVE only in an enrolled healthcare facility that has immediate access on site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation).

Clinical trials showed that patients with asthma or other pulmonary diseases, such as chronic obstructive pulmonary disease (COPD) are at increased risk of bronchospasm. ADASUVE is contraindicated in patients with the following conditions:

- A history of asthma, COPD or other lung disease associated with bronchospasm
- Acute respiratory signs or symptoms (e.g., wheezing)
- Use of medications to treat asthma or COPD
- A history of bronchospasm following ADASUVE treatment

Prior to administering ADASUVE, screen patients for a history of asthma, COPD, or other pulmonary disease and examine patients (including chest auscultation) for respiratory signs and symptoms (e.g. wheezing). Monitor patients (e.g. vital signs and chest auscultation) for signs and symptoms of bronchospasm at least every 15 minutes for a minimum of one hour following treatment with ADASUVE. ADASUVE causes sedation, which could mask the symptoms of bronchospasm.

Because clinical trials in patients with asthma or COPD demonstrated that the degree of bronchospasm was greater following a second dose of ADASUVE, limit ADASUVE use to a single dose (either 5 or 10mg) in a 24 hour period.

Advise all patients of the risk of bronchospasm. Advise them to inform the healthcare professional if they develop any breathing problems such as wheezing, shortness of breath, or other symptoms of bronchospasm following treatment with ADASUVE.

In conclusion, Dr, Michele wrote:

“There is a significant risk of post-inhalation bronchospasm following administration of inhaled loxapine, particularly in patients with underlying airway hyperresponsiveness caused by conditions such as asthma and COPD. The severity of obstruction is greater following a second dose and does not return to baseline for 24 hours or more following repeat dosing. Characteristics of the patient population, including a high prevalence of smoking and inability to give a reliable history, increase the risk of bronchospasm following inhaled loxapine administration.

The FDA-proposed REMS and labeling is intended to both limit administration in patients at highest risk of bronchospasm and monitor patients following use of inhaled loxapine so that developing bronchospasm can be treated early. These restrictions likely will limit, but may not completely eliminate, potentially severe adverse airway events that may occur with inhaled loxapine. This risk must be weighed against the clinical need for a rapidly acting, non-

invasive treatment of acute agitation and potential benefit in this patient population. If approved, additional post-marketing surveillance including a post-marketing requirement for a clinical trial to evaluate safety in a real-world setting using the REMS and labeling would be beneficial.”

8.7 Division of Risk Management (DRISK)

On February 16, 2012, a revised REMS, based on DRISK review of the sponsor’s proposed REMS, was sent to the sponsor. The sponsor was advised that the Communication Plan, described in the sponsor’s REMS received January 10, 2012, has been removed as a separate element of the REMS and will be included under the ETASU section. In addition, the changes provided by DRISK emphasized the following:

1. Enrolled healthcare facilities must have immediate access on site to equipment and personnel needed to provide advanced airway management.
2. Availability of a short-acting beta-agonist should include a nebulizer in addition to an MDI.
3. Adasuve should be limited to one dose per patient within 24 hours.
4. Adasuve is contraindicated in patients with a history of asthma, COPD, or other lung disease associated with bronchospasm.

Under **Section I, Goal**, the following changes were made (DRISK changes in blue):

The goal of the ADASUVE REMS is to mitigate the negative outcomes associated with ADASUVE-induced bronchospasm by:

(b) (4)

Under **Section II, REMS Elements**, the following changes were made (DRISK changes in blue):

A. Elements To Assure Safe Use

(b) (4)



On February 21, 2012, the sponsor provided comments regarding the revised REMS proposed by DRISK on February 12, 2012. DRISK responded to the sponsor's comments on March 2,

2012. The sponsor's comments of February 21, followed by DRISK response (in blue) of March 2 are as follows:

Alexza Comment 1 – Section I.1

Original text:

[Redacted text block] (b) (4)

Change to (sponsor's proposed changes in red):

[Redacted text block] (b) (4)

Rationale for Change:

[Redacted text block] (b) (4)

FDA Response to Comment 1:

We disagree that your proposed revised text above will sufficiently mitigate the risk of the negative outcomes associated with ADASUVE-induced bronchospasm. Management of Post-injection Delirium Sedation Syndrome (PDSS) is not equivalent to management of bronchospasm. PDSS is a slowly progressing, sedation syndrome. Bronchospasm could progress quickly to respiratory arrest, potentially more rapidly than emergency response services can respond. If Adasuve is approved, certified health care facilities, which dispense and administer Adasuve, must have immediate access, on-site, to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation.

Alexza Comment 2 – Section I.2

Original text:

[Redacted text block] (b) (4)

Change to (sponsor's proposed changes in red):

“Informing healthcare professionals in these settings that ADASUVE can cause (b) (4) bronchospasm that has the potential to (b) (4) lead to respiratory distress and respiratory arrest.”

Rationale for Change:

In the ADASUVE clinical development program, there were no observed cases of severe bronchospasm nor did any patient require medication beyond albuterol to resolve the adverse event. All events were categorized as either mild or moderate. In addition, the proposed new wording in this section is consistent with wording the Agency used in Section II.A.1.k.i.

FDA Response to Comment 2:

We agree with your proposed change to align with other language in the REMS document.

Alexza Comment 3 – Section II.A.1.c

Original text:

(b) (4)

Change to (sponsor’s proposed changes in red):

(b) (4)

Rationale for Change:

The new wording is consistent with the proposed changes to the wording in Section I.1; please refer to the rationale provided above.

FDA Response to Comment 3:

We disagree with the revised text above. Refer to FDA response to Comment 1.

Alexza Comment 4 – Section II.A.1.d

Original text:

(b) (4)

Change to (sponsor's proposed changes in red):

(b) (4)

Rationale for Change:

(b) (4)

FDA Response to Comment 4:

We disagree. If Adasuve is approved, a nebulizer must be available at certified health care facilities. First, per National Heart Lung and Blood Institute (NHLBI) guidelines, a nebulizer is required to manage severe bronchospasm. Second, there is no evidence that a given spacer works with a given MDI. Therefore there is no currently labeled approved inhaler and spacer combination which could be substituted for a nebulizer.

Alexza Comment 5 – Section II.A.1.e, Bullet 3 and Section II.A.1.f

Original text:

(b) (4)

Change to:

(b) (4)

Rationale for Change:

(b) (4)

FDA Response to Comment 5:

We disagree. If Adasuve is approved, certified health care facilities must be responsible for having controls in place to limit the dispensing of more than one dose of Adasuve in 24 hours. This product is expected to be utilized in emergency departments which have frequent staff turnover (i.e. shift changes, staff reallocated due to emergency situations) during the course of an individual patient’s care. Therefore, limiting the dispensing of the product at the institution or pharmacy level will provide added assurance that a patient does not receive more than one dose. Since pharmacy dispensing is managed by the institution and not the prescribers of the drug, this health care facility attestation must be included.

Alexza Comment 6 – Section II.A.1.k.ii

Original text:

[Redacted text block] (b) (4)

Change to (sponsor’s proposed changes in red):

[Redacted text block] (b) (4)

Rationale for Change:

[Redacted text block] (b) (4)

FDA Response to Comment 6:

We disagree. (b) (4) is too broad and not adequate. Patients with history of asthma are our main concern. We acknowledge that “history of asthma” is broad and conservative, but we are trying to prevent adverse outcomes. We may consider alternative language, if you have language you would like to propose.

On March 8, 2012, the sponsor submitted a response to DRISK comments of March 2. The sponsor agreed to DRISK Comments 1 through 5, but proposed the following in response to Comment 6:

Current Language:

(b) (4)

Alexza’s Proposed Language:

(b) (4)

On March 16, 2012, DRISK issued the following response to the sponsor regarding the sponsor’s proposed change of March 8:

FDA Response:

After discussing your proposal, we have determined that the term "history" should be maintained because there is no rationale for providing a particular cut off period and we want to assure that we are covering a broad range of patients who may have a bronchospastic event from the drug. We do agree to one edit, which was suggested in your response document dated February 22, 2012, (b) (4)

Thus, we propose the following language:

The representative understands that ADASUVE is contraindicated in patients with a (b) (4) history of asthma, COPD or other lung disease associated with bronchospasm, and patients with acute respiratory signs/symptoms (e.g., wheezing) or who are taking medications to treat (b) (4) airways disease, such as asthma or chronic obstructive pulmonary disease (COPD).”

On March 27, 2012, the sponsor submitted a REMS amendment which incorporated the changes recommended by DRISK and discussed in this section.

On April 2, 2012, the Final Risk Evaluation and Mitigation Strategy (REMS) Review was submitted by Dr. Lehrfeld of DRISK. Dr. Lehrfeld concluded that, “the appended REMS for Adasuve submitted on March 27, 2012, contains all revisions to the REMS that have been

communicated to date.” Furthermore, Dr. Lehrfeld wrote, “The REMS submitted on March 27, 2012 includes the required major elements: DRISK finds it to be generally acceptable. However, additional revisions to the REMS will be required as labeling is negotiated and/or as a result of the REMS clearance process. DRISK’s final approval, along with any additional revisions, will be documented in an addendum to this review.”

Regarding REMS tools, DRISK noted the following:

1. DRISK recommended that the medication guide be removed from the REMS. The intended patient population of acutely agitated patients may not be capable of reading or understanding the information due to their level of agitation. In addition, the medication guide will not help them make an informed decision about whether to take Adasuve.
2. The *Safe Use Checklist* was changed to a document titled *Steps for the Safe Use of Adasuve*, which can be potentially handed out or posted in appropriate treatment locations for healthcare professionals to reference during administration of Adasuve. In addition, DRISK recommended making the components of the *Steps for Safe Use of ADASUVE* mandatory under the Element to Assure Safe Use as noted above. The healthcare facility representative will have to assure that prior to ordering Adasuve the healthcare facility will have policies, procedures and/or order sets (e.g., components of the Steps for Safe Use of Adasuve) in place to assure the proper screening and monitoring of patients who will receive Adasuve. To facilitate development of these policies, the ADASUVE REMS includes an *Order Set/Protocol Template*. This document includes all screening and monitoring required by the ADASUVE REMS.
3. *ADASUVE REMS Education Program*: In order to assure healthcare facility staff is educated about the ADASUVE REMS program requirements and how to use Adasuve safely, education is mandatory under ETASU B.
4. *Dear Healthcare Professional Letter*: In order to inform psychiatrists and emergency medicine health care practitioners about the risk of bronchospasm associated with Adasuve and the ADASUVE REMS program, *Dear Healthcare Professional Letters* will be distributed at least 2 weeks prior to product launch and in the event of any substantial safety update.

8.8 Office of Clinical Pharmacology (OCP)

On January 27, 2012, OCP submitted comments to the sponsor.

In the first comment, OCP noted that the current Section 8.8 (original section is under Section 12.3) of the sponsor’s proposed labeling reads as follows:



OCP requested that the sponsor construct a Forest plot to represent the data for AUC_{0-2h} , AUC_{inf} , and C_{max} . It is OCP'S determination that using Forest plots in drug labeling may communicate more effectively extrinsic factors effects on pharmacokinetics than using texts. In addition, OCP requested that the sponsor provide a table for the original PK information in Section 8 in the label associated with Forest plots for the label in the following format:

Factor (e.g. smoking)	Moiety	PK (C_{max} , AUC_{0-2h} , AUC_{inf})	Geometric Mean Ratio	90% CI		Recommendation
				Lratio	Uratio	

OCP also noted that the current Section 12.3 of the label contains the following graph related to multiple dose administration:



OCP requested that, since the sponsor has agreed that dosing will be limited to a single dose in a 24-hour period, this graph be replaced by one representing a single dose administration.

In a response dated January 31, 2012, the sponsor provided the following text, tables, and figures as proposed revision to labeling:

Special Populations (original section 12.3):



8.9 Office of Compliance (OC)

The Office of Compliance (OC) reviewed the sponsor’s proposed REMS. In REMS Memorandum dated March 30, 2012, OC made the following important comments regarding the Adasuve REMS with the goal of improving the enforceability of the Adasuve REMS document (bold italics added by OC to highlight points of interest):

1. Section II.A.1.f states:

[Redacted]

(b) (4)

OC Comments: If facilities are required to train relevant staff (“must train relevant staff”), then documentation of training needs to also be required. The language used [Redacted] (b) (4) leaves the documentation of the training as optional. As a result, if Alexza audits a facility and finds there is no record of staff training, Alexza cannot require the facility to retrain and document the training, or take any other corrective action. Unless documentation of training is required, the Office of Compliance will be unable to enforce the REMS requirement that health care facilities train their staff.

2. Item II.A.1.j states:

(b) (4)

OC Comments: Unlike the requirements for wholesalers and distributors found in Section II.B.1.1, this section does not require that Alexza audit for documentation and implementation of procedures, protocols and/or order sets. If Alexza either does not audit health care facilities for procedures, protocols and/or order sets, or does not require corrective action in cases where health care facilities lack them, the Office of Compliance will be unable to enforce the REMS requirement that health care facilities establish procedures, protocol and/or order sets.

3. Item II.A.1.k.iii states:

(b) (4)

OC Comments: This language does not require health care facilities to meet the REMS requirements before they receive shipments of Adasuve, and makes it appear that FDA will be satisfied if each health care facility waits until a fatality has occurred before meeting the REMS requirements. Unless health care facilities are required to meet the REMS requirements before receiving shipments of Adasuve, the Office of Compliance will be unable to enforce the requirement that the Division of Psychiatry Products clearly enunciated during REMS development meetings; healthcare facilities must have immediate access on-site to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation.

4. Section II.B.1. (Implementation System) states:

(b) (4)

OC Comments: Wholesalers and distributors must meet the REMS requirements before receiving Adasuve, but are not required to document staff training. As a result, if Alexza audits

a wholesaler/distributor and finds there is no record of staff training, Alexza cannot require that facility to retrain and document the training or take any other corrective action. Unless wholesalers and distributors are required to document staff training on REMS requirements, FDA will be unable to enforce the REMS requirement that wholesalers and distributors train their staff on REMS requirements.

Therefore, OC recommended the following modifications (OC changes are underlined):

1. Modify Section II.A.1.f to read as follows:

Each health care facility must train relevant staff (e.g., staff involved in prescribing, dispensing or administering ADASUVE and monitoring patients after ADASUVE administration) on the safe use of ADASUVE, as described in the ADASUVE REMS Education Program. This training must be documented and is subject to audit.

2. Modify section II.A.1.j to read as follows:

Each health care facility must establish procedures, protocols and/or order sets to help ensure compliance with the safe use conditions required in the ADASUVE REMS, and as described II.A.1.b through i., above. These procedures, protocols and/or order sets must be documented and are subject to audit.

3. Modify section II. A.1.k.iii to read as follows:

The health care facility will meet the requirements in b. through j. above prior to certification.

4. Modify Section 2.B.1.1.i. to read as follows:

The Wholesaler/Distributor will ensure that relevant staff are adequately trained on the Adasuve REMS program procedures and will follow the requirements of the Adasuve REMS program. This training must be documented and is subject to audit.

8.10 Office of Prescription Drug Promotion (OPDP)

OPDP reviewed the proposed product labeling and provided extensive editing and formatting recommendations to the proposed labeling.

9. Conclusions

The data provided by the sponsor support the sponsor's claim for efficacy of Adasuve in the treatment of acute agitation associated with schizophrenia or bipolar disorder. In two pivotal trials, *Staccato* Loxapine (Adasuve) demonstrated efficacy in the acute treatment of agitation associated with schizophrenia (Trial **004-301**) and bipolar disorder (Trial **004-302**). Both the 5- and 10-mg doses met the primary efficacy endpoint (change in PEC score from baseline to 2 hours after Dose 1, active vs. placebo) and key secondary endpoint (CGI-I score 2 hours after Dose 1, active vs. placebo). In both trials, the effect size was larger in the 10-mg group compared to the 5-mg group, providing evidence for a dose-response pattern.

For the 10 mg dose, efficacy was demonstrated as early as ten minutes after dosing, and pharmacokinetic data demonstrated IV-like kinetics. In schizophrenic and bipolar patients, rapid control of acute agitation is important to prevent escalation of agitation symptoms which may lead to self-injury and violence. Thus, although it is difficult to draw firm conclusions in the absence of head-to-head studies with intramuscular antipsychotics approved for the same indication, the rapid onset of effect may prove beneficial.

Another benefit of Adasuve is that it is noninvasive. In the pivotal trials, device failure rates were very low. It is possible that careful screening of patients entering the trials and device training may have contributed to these low rates. In an emergency room setting, patients may be less cooperative and device training may be less practical. However, extensive REMS training of healthcare practitioners on how to administer the drug as well as DMEPA recommendations on Instructions for Use and exterior design of the Adasuve inhaler may improve successful administration of the device under emergency conditions. For example, DMEPA has recommended placement of the green light on the device in a location where it is more easily seen. Thus, if the light fails to turn off after an inhalation attempt, the practitioner will know that the drug has not been successfully administered. The practitioner may then either administer again or use another medication. Thus, the likelihood of harm to the patient is reduced.

In general, the adverse events (AEs) associated with *Staccato* Loxapine were either expected from the known adverse event profile of loxapine or related to the method of loxapine administration (inhalation). In the pivotal trials, the most frequently reported AEs in patients treated with *Staccato* Loxapine were dysgeusia (~13%) and sedation (10.5%). Most AEs (96.3%) were mild to moderate. Dysgeusia, sedation (including sedation combined with somnolence), fatigue, and throat irritation were identified as potential adverse reactions associated with *Staccato* Loxapine (incidence rate $\geq 2\%$ and greater than placebo in either the 5-mg or 10-mg *Staccato* Loxapine groups). Dysgeusia and throat irritation exhibited evidence for dose-dependency. Akathisia and tremor were observed rarely, each occurring in 2 patients (0.4%), and there was one report of neck dystonia combined with oculogyration.

However, significant pulmonary adverse events, particularly in subjects with asthma or COPD, were reported and are a major safety concern. In subjects with asthma (Trial **004-105**), eighteen (69%) loxapine-treated subjects and 3 (12%) placebo-treated subjects had notable respiratory signs or symptoms, defined as FEV1 decrease from baseline of $\geq 20\%$, an airway AE, or use of rescue medication. The most common airway adverse events in subjects with asthma were bronchospasm (~27%), chest discomfort (~23%), wheezing (~15%), and dyspnea (11.5%). In subjects with COPD (Trial **004-108**), fifteen (~58%) loxapine-treated subjects had notable respiratory signs or symptoms compared to six (~22%) placebo-treated patients. Airway AEs that occurred in more than a single loxapine-treated subject in Trial **004-108** were dyspnea (3 subjects, 11.5%), cough (3 subjects, 11.5%), and wheezing (2 subjects, ~8%). No airway AEs occurred in more than a single placebo-treated subject in this trial.

In both the asthma and COPD trials, dosing was performed every 10 hours for 2 doses, and there was evidence of worsened airflow obstruction after the second dose. After a first dose of Adasuve only, bronchospasm was reported in ~31% of asthma subjects and ~15% of COPD subjects. In subjects who received 1 or 2 doses of Adasuve, reports of bronchospasm increased

to ~54% of asthma subjects and ~19% of COPD subjects. In the asthma trial, FEV1 did not return to baseline as late as 14 hours after the second dose. In both the asthma and COPD trials, patients who had a decrease in FEV1 $\geq 20\%$, developed significant respiratory adverse events, or received rescue albuterol after the first dose were excluded from receiving the second dose. Thus, the true FEV1 nadir is unknown, particularly after a second dose. As noted by the PDAC, there is insufficient data to adequately assess the respiratory risks from the sponsor's originally proposed dosing interval of every 2 hours. Thus, the sponsor's agreement with FDA to revise labeling to limit dosing to a single dose in 24 hours will significantly decrease, but not eliminate, the risk of pulmonary toxicity associated with use of *Staccato* Loxapine.

In the pivotal trials, the most frequently reported respiratory system AEs in loxapine-treated subjects versus placebo-treated subjects were throat irritation (~2% vs. 0.4%), pharyngeal hypoaesthesia (0.6% vs. 0%), and wheezing (0.4% vs. 0%). Patients with clinically significant acute or chronic pulmonary disease were excluded from the pivotal trials, yet two subjects developed wheezing and one subject developed bronchospasm. The two subjects with AEs of wheezing did not require treatment. Bronchospasm was reported for one subject in the *Staccato* Loxapine 10 mg group in Trial **004-301**, resulted in early discontinuation, and required treatment with a bronchodilator. It is noteworthy that this patient had no history of pulmonary disease. Thus, it is apparent that the exclusion of patients with clinically significant acute and chronic pulmonary disease did not completely eliminate the risk of respiratory AEs, although all the respiratory AEs in the pivotal trials were classified as mild to moderate.

In conclusion, Adasuve will be beneficial in the treatment of acute agitation associated with schizophrenia or bipolar disorder. Adasuve is noninvasive, and a 10 mg dose demonstrated efficacy as early as 10 minutes post-dose. This may be of significant benefit to patients, in whom a noninvasive means of prevention of escalation of agitation to verbal or physical aggression to objects or persons is extremely important. There is a risk of pulmonary toxicity after treatment with Adasuve. However, limiting dosing to a single inhalation in a 24-hour period and institution of an effective REMS as proposed by the FDA will substantially mitigate this risk.

Francis E. Becker, M.D., F.A.C.P.
Medical Officer,
FDA CDER ODE1 DPP HFD 130

cc: NDA 22549
HFD 130
T Laughren
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FRANCIS E BECKER
04/09/2012

ROBERT L LEVIN
04/09/2012
See team leader memo to follow.

**DIVISION OF PULMONARY, ALLERGY, and RHEUMATOLOGY PRODUCTS
BRIEFING PACKAGE REVIEW**

Date: March 16, 2011
To: Thomas Laughren, MD
Director, Division of Psychiatry Products
From: Theresa M. Michele, MD
Clinical Team Leader, Division of Pulmonary, Allergy, and
Rheumatology Products
Through: Sally Seymour, MD
Deputy Director for Safety, Division of Pulmonary, Allergy, and
Rheumatology Products
Through: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary, Allergy, and Rheumatology Products
Subject: Pulmonary safety evaluation of Adasuve (loxapine) inhalation powder for
New Drug Application (NDA) 22-549 at a dose of 5 mg or 10 mg every 2
hours as needed to a maximum dose of 30 mg per day for the treatment of
agitation associated with schizophrenia or bipolar disorder in adults

General Information

NDA#: 22-549
Sponsor: Alexza Pharmaceuticals
Drug Product: Adasuve (loxapine) inhalation powder
Materials Reviewed: NDA 22-549 SD#1, original submission dated December 11, 2009;
NDA 22-549 SD#28, complete response dated August 4, 2011

1. Executive Summary

This is a consult review from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) regarding the complete response for NDA 22-549. The purpose of this review is to summarize the pulmonary safety of loxapine inhalational powder, proposed for treatment of adult patients with agitation associated with schizophrenia and bipolar disorder. Loxapine is a typical first generation antipsychotic drug, similar to haloperidol. It was approved as an oral formulation in 1975 and an intramuscular formulation in 1979, although only the oral dosage form is currently marketed.

Pulmonary safety trials conducted with loxapine inhalational powder in healthy volunteers, patients with asthma, and patients with COPD demonstrate that inhaled loxapine can cause bronchospasm. This risk is increased in patients with underlying airway hyperresponsiveness, including asthma and chronic obstructive pulmonary disease (COPD), and is dose related, with greater decreases in lung function, as measured by forced expiratory volume in 1 second (FEV1), after a second dose.

Due to issues with pulmonary safety, NDA 22-549 for inhaled loxapine was not approved in the first cycle, and the sponsor submitted a complete response to address the clinical deficiencies. No new clinical data were provided in the complete response. As such, this review provides an overview of previous pulmonary safety data, supplemented by review of the sponsor's response and proposal for mitigation of pulmonary safety issues in a Risk Evaluation and Mitigation Strategy (REMS). Detailed review of the pulmonary safety from the initial submission may be found in the consultation by Dr. Anya Harry (DPARP) dated August 20, 2010.

In the Complete Response, the Applicant provided a REMS with a restricted access program limiting administration of the product to facilities that had an albuterol metered dose inhaler (MDI) available for use. The risk benefit assessment of inhaled loxapine and proposed REMS were discussed at a Psychopharmacologic Drugs Advisory Committee (PDAC) meeting on December 12, 2011. PDAC membership was supplemented by members of the Pulmonary Allergy Drug Advisory Committee and the Drug Safety and Risk Management Committee. Discussion focused on the risk of acute bronchospasm with inhaled loxapine. Recommendations from the committee were to limit loxapine to a single dose in a 24 hour period and that the sponsor's proposed REMS was not sufficient to assure safety. The committee favored a more restrictive REMS as proposed by the FDA. Even with FDA's proposed REMS and limiting administration to a single dose, there was a split vote regarding whether inhaled loxapine should be approved, with a narrow margin favoring approval (9 Yes, 8 No, 1 Abstain).

From a pulmonary standpoint, the risk of acute bronchospasm with inhaled loxapine is clear, particularly in patients with underlying airway hyperresponsiveness such as those with asthma and COPD. DPARP has concerns for bronchospasm and the potential for respiratory decompensation, including respiratory arrest, with inhaled loxapine. Although bronchospasm did not lead to serious outcomes such as hospitalization, intubation, or death in the clinical trials performed with inhaled loxapine, the safety database is limited in size and there are a number of factors related to the proposed patient population and therapeutic effects of the drug that raise concerns of increased risk of serious events. Because patients with agitation and schizophrenia or bipolar disorder have a high prevalence of smoking and may not be able to provide a reliable medical history, screening may not be sufficient to ensure that patients with airway hyper-responsiveness do not receive inhaled loxapine. In addition, since inhaled loxapine is a sedative, patients may be less likely to report symptoms of bronchospasm.

The potential risk of bronchospasm must be weighed against the clinical need for a rapidly acting, non-invasive treatment of acute agitation and potential benefit in this patient population. This review is focused on the pulmonary safety, and the risk-benefit assessment is deferred to the Division of Psychiatry Products (DPP). From a pulmonary standpoint, if inhaled loxapine is approved, recommendations regarding labeling and REMS are provided to try to prevent use of inhaled loxapine in patients at high risk of bronchospasm, ensure patients treated with inhaled loxapine are monitored for bronchospasm, and ensure that appropriate personnel and treatment are available for patients that develop bronchospasm. A summary of the recommendations are provided below and in more detail in Sections 5 and 6.

- Limit the administration of inhaled loxapine to a single dose in a 24 hour period. Studies in patients with asthma and COPD clearly demonstrate a larger decrease in FEV1 following a second dose of inhaled loxapine. In patients with asthma the FEV1 in asthmatics the FEV1 did not return to baseline for at least 24 hours following a second dose of inhaled loxapine.
- Include the risk of bronchospasm in labeling (Boxed Warning) and contraindicate inhaled loxapine in patients: 1) with a history of asthma, COPD, or other lung disease associated with bronchospasm, 2) with acute respiratory signs or symptoms, 3) using medications to treat asthma or COPD, or 4) with a history of bronchospasm following inhaled loxapine treatment. Detailed labeling comments are discussed in Section 6.
- Require a REMS with Elements to Assure Safe Use (ETASU) to screen patients and avoid use of inhaled loxapine in patients at highest risk of bronchospasm, monitor patients following use of inhaled loxapine, and ensure appropriate personnel and equipment are available to treat bronchospasm. Inhaled loxapine should only be administered in health care facilities with immediate on-site access to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation. The REMS should include a training program for healthcare professionals administering inhaled loxapine, a monitoring plan following dosing, and institutional-level (i.e. pharmacy) controls permitting administration of only a single dose in 24 hours. The REMS will limit, but may not completely eliminate, potentially severe adverse airway events that may occur with inhaled loxapine. Details of the recommended REMS are discussed in Section 5.4.
- Obtain additional safety information through a post-marketing requirement (PMR) for a clinical trial to evaluate safety in a real-world setting using the approved REMS and labeling.

2. Background

2.1. Regulatory history

In NDA 22-549, Alexza Pharmaceuticals is seeking approval for loxapine inhalation powder, at a dose of 5 mg or 10 mg as frequently as every 2 hours as needed to a maximum dose of 30 mg per day for the treatment of agitation associated with schizophrenia or bipolar disorder in adults. The proposed trade name for the product is Adasuve. Alexza initially submitted this application to the Agency on December 11, 2009. FDA took a complete response action on the original submission on October 8, 2010, because of clinical deficiencies related to pulmonary safety. Specific deficiencies identified are as follows.

The primary clinical safety concern is the pulmonary toxicity associated with the use of loxapine inhalation powder. Clearly, the toxicity is drug-related. However, an additional component of the toxicity appears to be related to use of the device itself, as demonstrated by the responses in the placebo group. In the 3 pulmonary safety studies, pulmonary function testing revealed clinically significant decreases in FEV1 that were

greater than 10%, 15%, and 20% for individual subjects. A decrease in FEV1 of greater than 10% is considered clinically significant. To place these findings in perspective, one should note that the standard bronchoprovocation tests cause a decrease in FEV1 of 10-20%. In healthy subjects, 27% of the loxapine group and 27% of the placebo group had a decrease in FEV1 of >10%. Approximately 19% of healthy subjects treated with loxapine and 4% treated with placebo had decreases in FEV1 >15%. In addition, 4% of healthy subjects treated with loxapine had decreases in FEV1 >20%. The decreases in FEV1 observed above occurred in the 8 hours after either dosing.

In subjects with asthma or COPD, the FEV1 findings were marked. In asthma subjects, 85%, 62%, and 42% had decreases in FEV1 >10%, >15%, and >20%, respectively. In COPD subjects, 80%, 56%, and 40% had decreases in FEV1 >10%, >15%, and >20%, respectively. Furthermore, a high proportion (58-69%) of asthmatic and COPD subjects had significant respiratory signs/symptoms or required rescue treatment with bronchodilator medication. Respiratory signs and symptoms included bronchospasm, dyspnea, wheezing, chest discomfort, and cough.

Pulmonary toxicity was dose-related in the safety studies. Subjects treated with a second dose of loxapine inhalation powder had greater decreases in FEV1 (compared to their first dose), which did not return to baseline at 24 hours post-dose. A significant proportion of asthmatic and COPD subjects discontinued from the study before receiving the second dose, due to a decreased FEV1 and/or the need for rescue treatment of respiratory signs and symptoms. As a result, one cannot determine the true nadir of the FEV1 following treatment with loxapine inhalation powder in the pulmonary safety studies.

Additional factors could contribute to an unacceptable risk of pulmonary toxicity in the intended population. Patients with schizophrenia and bipolar disorder have a high prevalence of tobacco smoking. Thus, many of these patients will have some degree of respiratory disease burden at baseline. As noted above, exposure to loxapine inhalation powder can result in acute obstructive exacerbations requiring rescue bronchodilator treatment in patients with baseline obstructive disease. Another concern is that acutely agitated patients with schizophrenia or bipolar disorder may be incapable of providing an accurate history of pulmonary disease during the episode. Similarly, healthcare professionals may not be able to perform an adequate respiratory examination during an acute episode of agitation. Furthermore, rescue treatment may not be readily available in some settings in which patients would be treated with loxapine inhalation powder. Moreover, sedation from loxapine inhalation powder could obscure respiratory signs and symptoms. Finally, the dosage and administration section of proposed labeling states that loxapine inhalation powder could be administered every 2 hours up to 3 times, which would allow repeat dosing prior to recovery of FEV1 or respiratory symptoms.

Alexza submitted a complete response to these deficiencies on August 4, 2011, including: 1) justification that the Phase 3 studies included patients representative of the intended population, 2) Risk Evaluation and Mitigation Strategy proposal of labeling, medication guide, communication plan, and elements to assure safe use, and 3) a post-marketing observational trial. No new safety data were provided in the complete response.

2.2. Background data from other disciplines

2.2.1. Chemistry, Manufacturing, and Controls

Loxapine inhalational powder is a combination product, consisting of the drug loxapine and a single use Staccato device. There are no excipients in the drug product. The Staccato device is a novel inhaler that delivers a thermally generated aerosol of loxapine. The device consists of a sealed stainless steel heat package that generates heat to vaporize the drug and produce the aerosol, an excipient-free drug coating, a breath sensor activation mechanism, and a plastic housing that directs the airflow over the vaporizing drug.

After removal of the activation tab, battery power is delivered to a printed circuit board assembly as shown by a green indicator light. The inhalation maneuver of the patient activates a mechanical flow switch and a capacitor charged by the battery ignites the starter assembly on the heat pack. Thermal reactants in the heat pack ignite to 420°C, which quickly vaporizes the loxapine coating on the outside of the stainless steel surfaces of the heat pack. The resultant loxapine vapor is entrained in the inhalation airstream where it is then inhaled by the patient for delivery to the systemic circulation via the lungs. The maximum temperature of the inhaled product is approximately 37°C. A loud noise and visible spark can be observed when the device is activated. See Figure 1 for a diagram of the Staccato device, and Figure 2 for a device schematic.

Figure 1: Staccato single use device

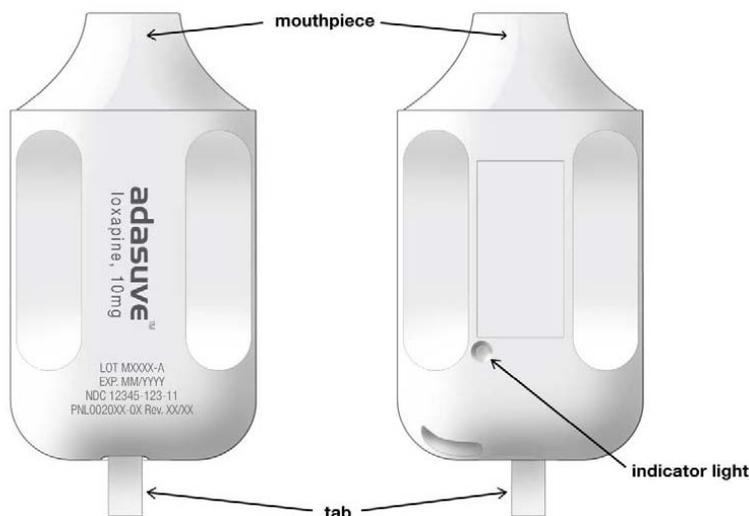
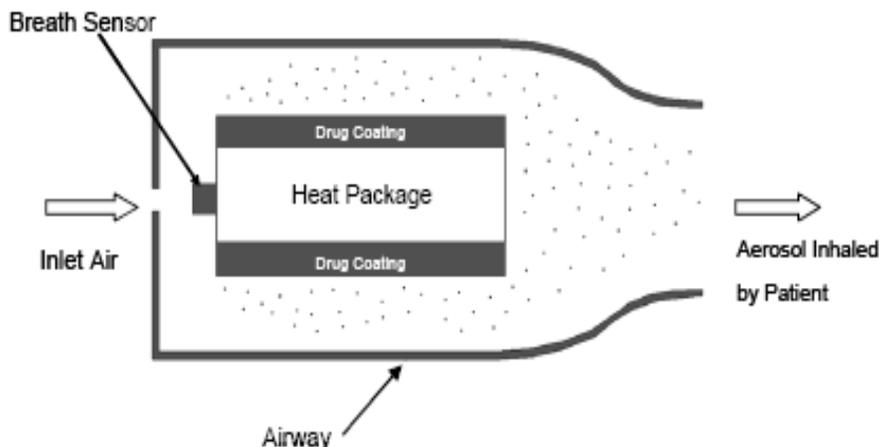


Figure 2: Staccato single use device schematic side view



2.2.2. Toxicology

Toxicology studies to support the safety of inhalation delivery of loxapine included single and repeat dose inhalational toxicology and toxicokinetic studies in rats and dogs, a cardiovascular and respiratory safety pharmacology study in dogs, pharmacokinetic studies in rats and dogs, and *in vitro* metabolism studies. Genotoxicity studies were also completed.

The respiratory safety study in dogs showed no effect of loxapine on respiratory parameters following IV bolus doses of 0.15 and 0.5 mg/kg. Fourteen day nose-only inhalation studies (not using the Staccato device) in rats showed dose-related CNS clinical signs consistent with the pharmacology of loxapine. The only respiratory finding was squamous metaplasia of the larynx, likely related to particle impaction from the route of administration. The NOAEL was considered to be 1.7 mg/kg/day based on persistence of clinical CNS signs and body weight changes. In dogs administered loxapine by oral inhalation for 5 and 28 days, primary findings were again CNS related, consistent with the action of the drug. No respiratory findings were observed. Similar to the rat studies, the Staccato device was not used for administration, according to standard practice for toxicology trials of inhalational products. The NOAEL in dogs was considered to be 1.8 mg/kg/day.

2.2.3. Clinical Pharmacology

Four Phase 1 clinical pharmacology studies were conducted, including 1) 004-101: dose escalation study in healthy volunteers, 2) 004-102: multidose trial in patients on chronic, stable antipsychotic regimens, 3) 004-103: four period crossover to assess bioequivalence of two different device designs, and 4) 004-106: single dose trial comparing PK in smokers versus non-smokers. These studies demonstrated that systemic exposure to loxapine is dose proportional with linear kinetics. Study 004-106 showed that the pharmacokinetics of inhaled loxapine in smokers and nonsmokers were the same.

2.3. Overview of clinical program for pulmonary safety

The clinical program for inhaled loxapine consisted of a total of 11 clinical trials, including five Phase 1 trials, three Phase 2/3 pivotal efficacy and safety trials in agitated patients, and three dedicated pulmonary safety trials. In addition, data were provided from two trials in patients with migraine headache. Dedicated pulmonary safety trials included one trial in healthy volunteers (Trial 004-104), one in patients with asthma (Trial 004-105), and one in patients with COPD (Trial 004-108). Pulmonary safety trials were all conducted in the United States. See Table 1.

Table 1: Efficacy and safety trials

Study #	Study design	Patient population	Treatment groups	N
Pulmonary safety trials				
004-104	2 period crossover (2 doses 8 hr apart)	Healthy volunteers	10 mg/placebo	30
004-105	Parallel group (2 doses 10hr apart)	Mild-moderate persistent asthma	10 mg Placebo	26 26
004-108	Parallel group (2 doses 10 hr apart)	Mild-severe COPD	10 mg Placebo	26 27
Safety and efficacy trials in proposed population				
004-301	Ph 3 efficacy and safety (1-3 doses)	Schizophrenia	5 mg 10 mg Placebo	116 113 115
004-302	Ph 3 efficacy and safety (1-3 doses)	Bipolar I disorder	5 mg 10 mg Placebo	104 105 105
004-201	Ph 2 single dose	Schizophrenia or schizoaffective disorder	5 mg 10 mg Placebo	45 41 43

The focus of this review and the attached consult is the dedicated pulmonary safety studies; however, information relevant to pulmonary safety (e.g., pulmonary adverse events) from other parts of the program will be included when appropriate.

3. Specific Pulmonary Safety Trials

3.1. Pulmonary Safety in Healthy Subjects (Protocol 004-104)

Trial 004-104 was a single center, randomized, placebo controlled, 2-period cross-over trial assessing the pulmonary safety of 10 mg inhaled loxapine, administered as 2 doses 8 hours apart on the same day, in healthy subjects. A total of 30 healthy non-smoking subjects aged 18-65 years of age were administered placebo or inhaled loxapine with a washout of at least 4 days in between treatments. Subjects were required to have normal pulmonary function at baseline, defined as FEV1 and FVC \geq 85% predicted and room air oxygen saturation \geq 95% by pulse oximetry, and no history of asthma, COPD, or other

pulmonary disease. Assessments (spirometry, SpO₂, respiratory rate, heart rate, and sedation) in each period were performed in the hour before the first dose and at 0.25, 0.5, 1, 2, 4, 6, 8, 8.25, 8.5, 9, 10, 12, 14, 16, 24 and 32 hours after the first dose.

If a subject's FEV₁ decreased by $\geq 20\%$ from the same-period baseline after any dose, or if there were any AEs of wheezing, dyspnea, or bronchospasm, the subject was not to receive additional doses of study treatment. Albuterol via metered-dose inhaler or nebulizer could be administered as clinically indicated as was required for any subject with a FEV₁ decrease of $\geq 20\%$. Subjects were to be followed with repeat spirometry testing every 0.5 hour until the FEV₁ returned to within 10% of same-period baseline, at which time spirometry testing continued on the routine schedule.

Subjects enrolled in the trial were primarily Caucasian (93.3%) males (66.7%). Four patients (13.3%) had a smoking history, ranging from <1 pack year to 34 pack years. The remaining 26 subjects were never smokers.

Thirty patients were randomized into the trial and 25 completed. Of note, one patient withdrew consent after 2 doses of inhaled loxapine; however, she would have been discontinued due to a drop in FEV₁ of 24%.

Subjects receiving both placebo and inhaled loxapine had a decrease in baseline FEV₁ immediately following dosing, with a mean decrease of -0.062L (1.5%) in the placebo group and -0.075L (1.8%) in the loxapine group 15 minutes post-dose. While this change is generally considered within the variability of the test, if the results are evaluated by maximal FEV₁ decrease (responder analysis), approximately one third of patients in the safety population had clinically important FEV₁ decreases of $\geq 10\%$ (Table 2), suggesting that both inhaled loxapine and placebo given via the Staccato device may cause some degree of bronchospasm, even in healthy subjects. Of note, in all of the 6 subjects in the loxapine group with $\geq 15\%$ drop in FEV₁, the maximum decrease occurred after the second dose, three within the first hour after dosing. No patients in this trial had airway-related adverse events (cough, wheezing, chest tightness, dyspnea).

Table 2: Protocol 004-104: Maximum FEV₁ decrease from same period baseline after either dose (safety population)

Maximum FEV₁ decrease	Placebo N=29 n (%)	Loxapine 10 mg N=27 n (%)
$\geq 10\%$	10 (34.5)	9 (33.3)
$\geq 15\%$	1 (3.4)	6 (22.2)
$\geq 20\%$	0	2 (7.4)

FEV₁ categories are cumulative; i.e. a subject with a maximum decrease of 21% is included in all 3 categories

CSR 004-104; Table 12, page 63

The sponsor explains these decreases as sedative effects, normal variability, and incomplete effort on the part of the subjects. The FEV₁/FVC ratio was inconsistently decreased from baseline, and did not decrease out of the normal range, arguing against bronchospasm. However, in normal subjects, early obstructive changes may be represented by changes in the small airways that do not affect this ratio. Further, while some degree of variability and diurnal variation is expected, changes $>15\%$ are unusual.

The effects seen in the placebo group are unexpected since the product contains no excipients. However, airway reactivity due to hot or cold air is a known phenomenon and may be a contributing effect.

3.2. Pulmonary Safety in Subjects with Asthma (Protocol 004-105)

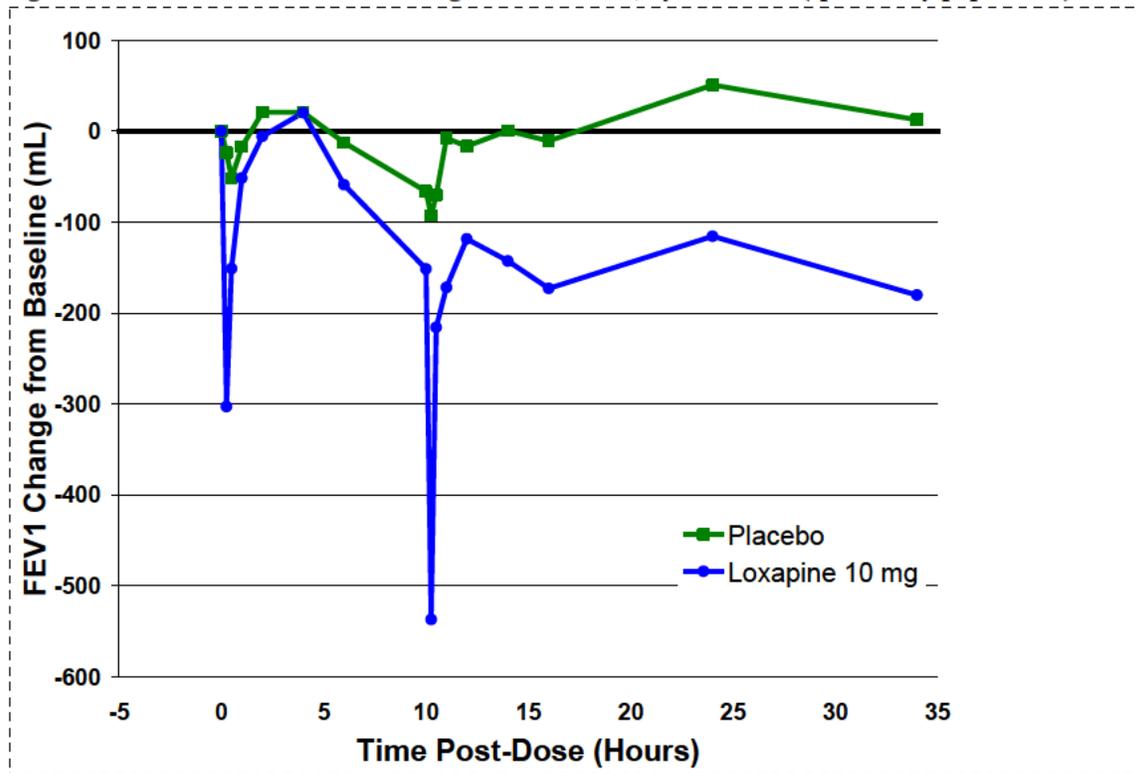
Trial 004-105 was a multicenter, randomized, placebo controlled, parallel group trial assessing the pulmonary safety of 10 mg inhaled loxapine, administered as 2 doses 10 hours apart on the same day, in 52 patients with mild to moderate persistent asthma. Patients were required to have a pre-bronchodilator FEV1 \geq 60% predicted, a history of FEV1 reversibility, and be on a stable asthma drug regimen for at least 2 weeks prior to dosing. Patients with \geq 10 pack year smoking history were excluded. Controller medications, including long-acting beta-agonists were continued during the trial, but short acting bronchodilators were held from 6 hours before study medication until 24 hours after the last study treatment. Assessments (spirometry, SpO₂, respiratory rate, heart rate, and sedation) in each period were performed in the hour before the first dose and at 0.25, 0.5, 1, 2, 4, 6, 10, 10.5, 11, 12, 14, 16, 24 and 32 hours after the first dose. Patients with respiratory symptoms or FEV1 decrease of \geq 20% were given albuterol (metered dose inhaler or nebulizer) and were not eligible for a second dose, but continued to be followed with spirometry. The spirometry population is defined as all patients who received study medication, had a baseline FEV1 measurement, and had at least one post-baseline FEV1 measurement that was obtained before the use of rescue medication.

Subjects enrolled in the trial were primarily Caucasian (78.8%) and were equally balanced between genders. Approximately two thirds (67.3%) had mild asthma (baseline FEV1 \geq 80%), while the remaining patients had moderate asthma (FEV1 60-80%). Nine patients (17.3%) were former smokers.

Fifty-two patients were randomized into the trial and 51 completed. Of the 52 treated patients, only 42 received both planned doses of study treatment. Ten patients (9 in the loxapine group and 1 in the placebo group) received only 1 dose, primarily due to a decrease in FEV1 \geq 20% and respiratory AEs. A total of only 10/26 (38%) patients in the loxapine group and 23/26 (88%) in the placebo group were able to complete both doses and spirometry assessments to 36 hours, providing a very limited sample size of asthmatics who received multiple doses of inhaled loxapine.

Marked decreases in FEV1 were observed immediately after dosing, particularly in the inhaled loxapine treated group. The secondary decrease in FEV1 observed at 4 hours after initial recovery is consistent with a late asthmatic response. Decreases were greater after the second dose given 10 hours after the first dose, and the group mean did not return to baseline after the second dose. The mean decrease after the first dose was -303 mL, with a maximal decrease for an individual patient of -0.99 L (31.8% decline); the mean decrease after the second dose was -537 mL, with the maximal decrease for an individual patient of -1.71 L (50.2% decline). Of note, patients with a \geq 20% decrease after the first dose did not receive a second dose and are not included in the curves beyond hour 10. See Figure 3, shown without error bars to provide clearest visualization of the curves.

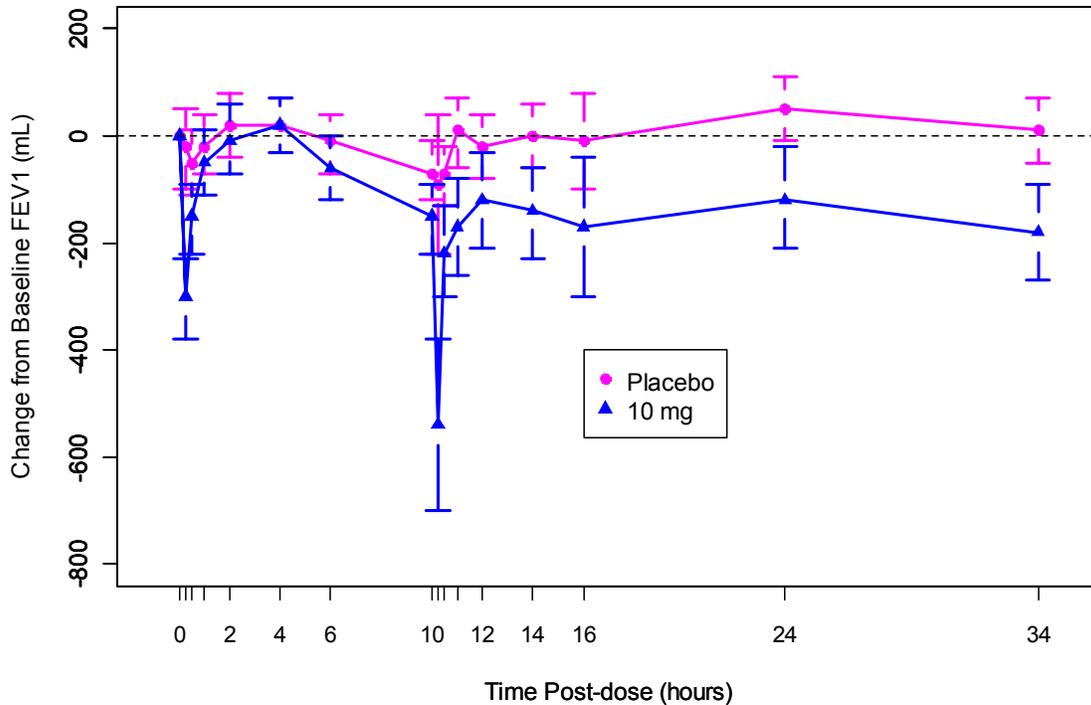
Figure 3: Protocol 004-105: FEV1 change from baseline, by treatment (spirometry population)



Note: Patients with a $\geq 20\%$ decrease in FEV1 did not receive a second dose of study drug and are not included in the curves beyond hour 10. Graph generated by reviewer from CSR Trial 004-105, Post-text data table 3.15.1, p. 246-253.

Figure 4 shows the same curve, including 95% confidence intervals. Non-overlapping confidence intervals between loxapine and placebo demonstrate a statistically significant difference between points at 15 minutes, 10.25 hours, 10.5 hours, 24 hours, and 34 hours after the initial dose.

Figure 4: Protocol 004-105: FEV1 change from baseline and 95% Confidence Intervals, by treatment (spirometry population)



Note: Patients with a $\geq 20\%$ decrease in FEV1 did not receive a second dose of study drug and are not included in the curves beyond hour 10. Graph generated by Dr. Yeh-Fong Chen, FDA statistical reviewer, from CSR Trial 004-105, Post-text data table 3.15.1, p. 246-253.

Results from the responder analysis show that 85% of loxapine treated patients had a decrease in FEV1 of $\geq 10\%$, and 42% had a decrease of $\geq 20\%$. See Table 3. Results for the safety population were similar (not shown). The true FEV1 nadir is unknown because all patients with a $\geq 20\%$ decrease in FEV1 received albuterol. The maximum FEV1 decrease from baseline after the first dose occurred within the first 2 hours. Results were more variable after the second dose. Again, the true time of nadir is unknown due to per-protocol rescue medication use.

Table 3: Protocol 004-105: Maximum FEV1 decrease from baseline (spirometry population)¹

Maximum % FEV1 Decrease	Placebo n (%)	Loxapine 10 mg n (%)
After either dose	N=26	N=26
≥10%	3 (11.5)	22 (84.6)
≥15%	1 (3.8)	16 (61.5)
≥20%	1 (3.8)	11 (42.3)
After Dose 1	N=26	N=26
≥10%	2 (7.7)	16 (61.5)
≥15%	1 (3.8)	8 (30.8)
≥20%	1 (3.8)	6 (23.1)
After Dose 2	N=25	N=17
≥10%	3 (11.5)	12 (70.6)
≥15%	1 (3.8)	9 (52.9)
≥20%	1 (3.8)	5 (29.4)

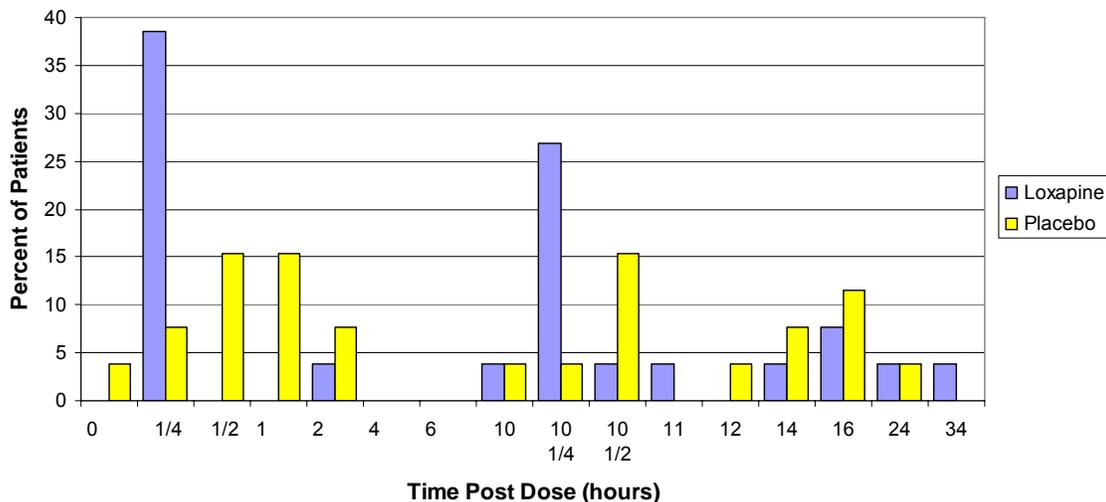
FEV1 categories are cumulative; i.e. a subject with a maximum decrease of 21% is included in all 3 categories

CSR 004-105; Table 13, page 76

¹ The spirometry population rather than the safety population is shown in order to better illustrate the percentage of patients who had a FEV1 decrease after Dose 2.

The timepoint at which each patient had his or her minimum FEV1 is shown in Figure 5 below. After the first dose, the minimum FEV1 occurred at 2 hours or earlier in all patients. After the second dose, the time after dosing to minimum FEV1 showed greater distribution, although the greatest frequency was still in the first hour after dosing.

Figure 5: Protocol 004-105: Timepoint of Minimum FEV1



Graph generated by reviewer from CSR Trial 004-105, Post-text Table 3.21.1., p. 334.

In asthmatics, FVC and FEV1/FVC ratio also decreased immediately after dosing, providing substantive evidence of airway obstruction due to bronchospasm. Nine of 26 patients in the loxapine group did not receive the second dose due to either a $\geq 20\%$

decrease in FEV1 or respiratory symptoms after the first dose; 2 had only a FEV1 decrease, 2 had only respiratory symptoms, and 5 had both. See Table 4 for a summary of respiratory adverse events (AEs) after either dose.

Table 4: Protocol 004-105: Respiratory adverse events (safety population)

Adverse event	Placebo N=26 n (%)	Loxapine 10 mg N=26 n (%)	Total N=52 n (%)
Respiratory, Thoracic and Mediastinal Disorders	3 (11.5)	14 (53.8)	17 (32.7)
Bronchospasm	1 (3.8)	7 (26.9)	8 (15.4)
Chest discomfort	2 (7.7)	6 (23.1)	8 (15.4)
Cough	0	1 (3.8)	1 (1.9)
Dyspnea	0	3 (11.5)	3 (5.8)
Throat tightness	0	1 (3.8)	1 (1.9)
Wheezing	0	4 (15.4)	4 (7.7)

CSR 004-105; post-text Table 3.2.1, page 140-143

The majority of respiratory AEs occurred within the first hour after dosing, ranging from 0 to 2.08 hours. Although there were no respiratory SAEs, rescue medication (albuterol via MDI or nebulizer) was given to 53.8% of patients in the loxapine group and 11.5% in the placebo group. After the first dose, 7 patients (27%) in the loxapine group and 1 patient (4%) in the placebo group received rescue. After the second dose, an additional 7 patients (41% of the 17 patients who received a second dose) in the loxapine group and 2 patients (8%) in the placebo group received rescue.

3.3. Pulmonary Safety in Subjects with Chronic Obstructive Pulmonary Disease

Trial 004-108 was a multicenter, randomized, placebo controlled, parallel group trial assessing the pulmonary safety of 10 mg inhaled loxapine, administered as 2 doses 10 hours apart on the same day, in 53 patients with COPD. Patients were required to have a >15 pack year history of smoking, a post-bronchodilator FEV1 \geq 40% predicted, a FEV1/FVC ratio of <0.70, and be on a stable COPD drug regimen for at least 2 weeks prior to dosing. Patients using supplemental oxygen were excluded. Controller medications, including long-acting beta-agonists and anticholinergics were continued during the trial, but short acting bronchodilators were held from 6 hours before study medication until 24 hours after the last study treatment. Assessments (spirometry, SpO2, respiratory rate, heart rate, and sedation) in each period were performed in the hour before the first dose and at 0.25, 0.5, 1, 2, 4, 6, 10, 10.5, 11, 12, 14, 16, 24 and 34 hours after the first dose. Patients with respiratory symptoms or FEV1 decrease of \geq 20% were given albuterol (metered dose inhaler or nebulizer) at the investigator's discretion and were not eligible for a second dose, but continued to be followed with spirometry. The spirometry population is defined as all patients who received study medication, had a

baseline FEV1 measurement, and had at least one post-baseline FEV1 measurement that was obtained before the use of rescue medication.

Subjects enrolled in the trial were primarily Caucasian (83.0%), with a slight predominance of males (56.6%). About two thirds were current smokers and one third were former smokers. In general, the population was milder than that seen in typical COPD trials. A little over half of patients had moderate COPD (57%, GOLD Stage II)¹, a third had severe disease (32%, GOLD Stage III), and 11% had mild disease (GOLD Stage I). In addition, there were 3 patients who did not meet enrollment criteria for obstruction (FEV1/FVC ratio <70%). See review by Dr. Harry for details.

Fifty-three patients were randomized into the trial and 52 completed. Of the 52 treated patients, 45 received both planned doses of study treatment. Eight patients (7 in the loxapine group and 1 in the placebo group) received only 1 dose, primarily due to a decrease in FEV1 \geq 20% and respiratory AEs.

Similar to the asthma patient population, there was a FEV1 decrease following dosing, particularly in the loxapine treated group, with the greatest decrease seen after the second dose [LS mean decrease of 0.125L (8.0%) in the loxapine group and 0.051L (3.2%) in the placebo group]. However, the amount of change was less than in asthma. This is typical for bronchoreactive effects in a COPD population, in which there is a greater degree of fixed obstruction and less reactive component. In addition, this population has a lower baseline lung function than the asthma population, so smaller changes are expected.

Results from the responder analysis show that 80% of loxapine treated patients had a decrease in FEV1 of \geq 10%, and 40% had a decrease of \geq 20%. See Table 5. Results for the safety population were similar (not shown). The true FEV1 nadir is unknown because some patients with a \geq 20% decrease in FEV1 received albuterol. There were also a large number of patients with decreases in the placebo group, suggesting that COPD patients may be more susceptible to changes in lung function due to the hot air from the device. There was no difference in percentage of patients with FEV1 drops when analyzed by smoking status (current versus former smokers). See review by Dr. Harry for details.

¹ Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2009 (<http://www.goldcopd.org>)

Table 5: Protocol 004-108: Maximum FEV1 decrease from baseline (spirometry population¹)

Maximum % FEV1 Decrease	Placebo n (%)	Loxapine 10 mg n (%)
After either dose	N=27	N=25
≥10%	18 (66.7)	20 (80.0)
≥15%	9 (33.3)	14 (56.0)
≥20%	3 (11.1)	10 (40.0)
After Dose 1	N=27	N=25
≥10%	8 (29.6)	16 (64.0)
≥15%	4 (14.8)	10 (40.0)
≥20%	2 (7.4)	9 (36.0)
After Dose 2	N=26	N=19
≥10%	15 (57.7)	12 (63.2)
≥15%	6 (23.1)	10 (52.6)
≥20%	1 (3.8)	5 (26.3)

FEV1 categories are cumulative; i.e. a subject with a maximum decrease of 21% is included in all 3 categories

CSR 004-108; Table 12, page 74

¹The spirometry population rather than the safety population is shown in order to better illustrate the percentage of patients who had a FEV1 decrease after Dose 2.

There were decreases in FVC at most time points following dosing. The FEV1/FVC ratio did not show a systematic pattern, consistent with the more fixed deficits seen in COPD patients. Seven of 25 in the loxapine group did not receive the second dose due to either a ≥20% decrease in FEV1 or respiratory symptoms after the first dose. Note that numbers do not match Table 5 due to protocol violations in which 7 patients were given the second dose despite having FEV1 decreases or symptoms. A total of 4 patients in the loxapine group compared with 3 in the placebo group reported respiratory AEs. See Table 6.

Table 6: Protocol 004-108: Respiratory adverse events (safety population)

Adverse event	Placebo N=27 n (%)	Loxapine 10 mg N=26 n (%)	Total N=53 n (%)
Respiratory, Thoracic and Mediastinal Disorders	3 (11.1)	4 (15.4)	7 (13.2)
Bronchospasm	1 (3.7)	0	1 (1.9)
Cough ¹	1 (3.7)	3 (11.5)	4 (7.5)
Dyspnea	1 (3.7)	3 (11.5)	4 (7.5)
Pulmonary congestion	0	1 (3.8)	1 (1.9)
Sinus headache	1 (3.7)	0	1 (1.9)
Throat irritation	1 (3.7)	0	1 (1.9)
Wheezing	0	2 (7.7)	2 (3.8)

¹includes terms of cough and productive cough

Modified from CSR 004-108; post-text Table 3.2.1, page 143-146

There were no respiratory SAEs. The majority of these adverse events occurred within the first hour after dosing. Overall, rescue medication (albuterol via MDI or nebulizer) was given to 23% of patients in the loxapine group and 12% in the placebo group. After the first dose, 2 patients (8%) in the loxapine group and 1 patient (4%) in the placebo group received rescue medication. After the second dose, an additional 4 patients (21% of the 19 patients who received a second dose) in the loxapine group received rescue medication. Three patients (11%) of the placebo group received rescue medication after the second dose, one of whom also received rescue after the first dose. Per protocol, this patient should not have received the second dose of study medication (considered a protocol violation).

4. Pulmonary Safety in Agitated Patients

There were three Phase 2 and 3 efficacy and safety trials in agitated patients with schizophrenia or bipolar disorder, enrolling a total of 787 patients, 524 of whom received inhaled loxapine. Of these, 328 (62.6%) received a single dose. Given the clinical scenario of an agitated patient, it was not possible to obtain spirometry in these clinical trials. In these 3 trials, there were 4 patients (0.8%) with airway related adverse events in the combined loxapine groups, compared to none in placebo. Two patients in the loxapine 5 mg dose group had wheezing and one patient in the loxapine 10 mg group had cough, all of which resolved without treatment. One patient in the loxapine 10 mg group was discontinued from the trial due to bronchospasm. This was a 59 year old female with schizophrenia who developed labored breathing and wheezing audible without a stethoscope approximately 5 minutes after her first dose of inhaled loxapine. She did not complain of shortness of breath. She responded to albuterol MDI and oxygen via nasal cannula. Of note, patients who had “clinically significant acute or chronic pulmonary disease (e.g. clinically apparent asthma, chronic bronchitis, emphysema)” were excluded from these trials.

Counting only the patient who required treatment for bronchospasm, the risk of clinically important acute bronchospasm was 1/524 (0.2%) in a known and carefully screened population [i.e. number needed to harm (NNH) =524]. Counting all 4 events, the NNH is 131.

5. Risk/Benefit Assessment

5.1. Pulmonary risks

From a pulmonary standpoint, the risk of acute bronchospasm with inhaled loxapine is clear, particularly in patients with underlying airway hyperresponsiveness such as those with asthma and COPD. Although bronchospasm did not lead to serious outcomes such as hospitalization, intubation, or death in the clinical trials performed with inhaled loxapine, the safety database is limited in size and there are a number of factors related to the proposed patient population and therapeutic effects of the drug that raise concerns of increased risk of serious events. These include:

- Patients with schizophrenia and bipolar disorder have a high prevalence of smoking², which increases the risk of airway disease.
- Patients with acute agitation may be unable to give a reliable history of airway disease and be uncooperative with physical examination, making screening these patients out prior to administration difficult. In the Phase 2 and 3 clinical trials, patients with clinically apparent asthma and COPD were ineligible for the trial and were screened up to two weeks prior to enrollment for schizophrenia patients and up to 24 hours prior to enrollment for bipolar patients. Patients were not necessarily in an agitated state during screening. Even so, four patients had clinical symptoms of bronchospasm, and one was discontinued due to acute wheezing that required albuterol.
- Patients with acute agitation may be seen in an emergency setting in which practitioners familiar with the patient's history and healthcare records are unavailable. This also limits the ability to screen out patients with underlying airway disease.
- Many healthcare facilities in which patients with acute agitation are cared for, such as psychiatry clinics or inpatient psychiatric facilities, do not routinely keep materials or staff on hand to treat acute bronchospasm (albuterol nebulization, IV corticosteroids) or perform advanced airway management (intubation and mechanical ventilation). This increases the risk of a serious outcome for the individual patient if a respiratory adverse event occurs.
- Risk factors for death from asthma include low socioeconomic status or inner-city residence, illicit drug use, major psychosocial problems, other chronic lung disease, and chronic psychiatric disease.³
- Inhaled loxapine is a sedative. Patients who are sedated may be less likely to report symptoms of bronchospasm and may have less evidence of wheezing on physical examination due to more shallow breathing.
- Not all patients may recognize symptoms of bronchospasm. Even patients with known asthma may perceive the severity of airflow obstruction poorly.³ This was evidenced in clinical trials with inhaled loxapine in which some patients with a FEV1 decrease of >20% were asymptomatic.
- Monitoring for acute bronchospasm with pulse oximetry is unlikely to be helpful because oxygenation is generally maintained until respiratory failure ensues.
- The proposed dosing for inhaled loxapine is as frequently as every 2 hours for up to three 10 mg doses. No spirometry safety data are available at this dosing frequency or number of doses. Pulmonary safety trials in asthma and COPD patients were performed with dosing every 10 hours for 2 doses, and there was evidence of worsened airflow obstruction after the second dose. Further, in the asthma trial, FEV1 did not return to baseline as late as 24 hours after the second

² Hughes et al. *American Journal of Psychiatry* 143:993-7, 1986.

³ National Asthma Education and Prevention Program, National Heart, Lung, and Blood Institute. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007.

dose, increasing the risk of severely worsened lung function if an additional dose were given prior to recovery.

Based upon the clinical trial data with evidence of bronchospasm, especially in patients with underlying respiratory conditions, and the additional considerations above, DPARP has concerns for bronchospasm and the potential for respiratory decompensation, including respiratory arrest, with inhaled loxapine.

5.2. Benefits of inhaled loxapine

This document is focused on the pulmonary safety of inhaled loxapine. The pulmonary safety risks of inhaled loxapine must be weighed against the benefits obtained with a non-invasive sedative for acutely agitated patients. See the reviews by Dr. Francis Becker and Dr. Robert Levin for a discussion of the efficacy of inhaled loxapine. The overall risk-benefit determination is deferred to DPP.

5.3. Risk-related dosing considerations

Studies in patients with asthma and COPD clearly demonstrate a larger decrease in FEV1 following a second dose of inhaled loxapine, even though patients with decreases >20% after the first dose were prohibited from receiving the second dose. It is particularly concerning that in asthmatics the FEV1 did not return to baseline for at least 24 hours following a second dose of inhaled loxapine. The full duration of lung function decrease following a second dose of inhaled loxapine is not known because patients were not monitored beyond 24 hours after the second dose. In addition, while the sponsor proposed dosing as frequently as every 2 hours up to a maximum of 3 doses in a 24 hour period, the pulmonary safety trials were performed with dosing 8 hours apart in healthy volunteers and 10 hours apart in patients with asthma or COPD.

Based on these considerations, the PDAC recommended limiting administration of inhaled loxapine to a single dose in 24 hours. DPARP concurs with this recommendation. In addition, the sponsor is proposing two different doses, 5 mg and 10 mg, depending on physician judgment. Since it is unknown if the lower 5 mg dose would have a decreased frequency of bronchospasm, we recommend applying the limit of one dose in a 24 hour period regardless of which dose was given.

Additional pulmonary safety trials are unlikely to be helpful in delineating the risk of inhaled loxapine administered every 2 hours. As the sponsor correctly notes, the sedative effects of loxapine in non-agitated volunteers would likely limit the ability to perform PFTs. In addition, given the known effects of inhaled loxapine dosed 10 hours apart, dosing two hours apart would be likely to show more profound decreases in lung function with potential risks for study participants.

5.4. Risk Evaluation and Mitigation Strategy

The sponsor proposes to manage pulmonary safety risks of inhaled loxapine using a REMS consisting of a medication guide for patients, a communication plan (Dear Healthcare Professional Letter, Prescriber Brochure, Safe Use Checklist, and Education Program), and Elements to Assure Safe Use [ETASU; healthcare facility must register and assure that albuterol (MDI) is available at the site]. In addition, the sponsor proposes

a boxed warning for bronchospasm in the product label. The sponsor's proposed REMS is inadequate to assure safe use of the product for the following reasons:

- The REMS limits use to health care facilities that have an albuterol MDI readily available. Since serious outcomes may occur quickly in patients with bronchospasm, it is important to have a complete repertoire of respiratory treatment options available, including nebulizers, IV access, intubation, and mechanical ventilation.
- The REMS permits use of dosing every 2 hours up to a maximum of 3 doses in 24 hours.
- A medication guide is unlikely to be helpful as patients are in an agitated state when receiving the medication, thus are unlikely to be able to read and comprehend a medication guide.
- No practitioner training is required.

For a complete review of the sponsor's proposed REMS as well as alternative risk mitigation options, see the review by Kim Lehrfeld, Pharm.D., Division of Risk Management.

From a pulmonary standpoint, the National Heart, Lung, and Blood Institute Guidelines for the Diagnosis and Management of Asthma, provide evidence-based information to practitioners for treatment of acute bronchospasm occurring as part of an asthma exacerbation. The following guidelines may also apply to treatment of respiratory adverse events occurring after administration of inhaled loxapine:

Mild

- Early treatment is the best strategy, which requires recognition of early signs and taking prompt action
- Inhaled short-acting beta agonists (via MDI or in more severe cases nebulization)
- Removal of the environmental factor causing bronchospasm (i.e. avoiding additional doses of inhaled loxapine)

Moderate to Severe

- Oxygen
- Short acting beta-agonists with addition of ipratropium bromide in severe bronchospasm (repetitive or continuous administration, usually via nebulization)
- Systemic corticosteroids (oral or IV) in patients who do not respond promptly to bronchodilators
- Consideration for adjunct treatments such as intravenous magnesium sulfate or heliox in severe bronchospasm
- Intubation and mechanical ventilation in patients with evidence of poor response or impending respiratory failure (patients generally do not wheeze on physical examination due to poor airflow, and are drowsy and confused)

Based on these treatment guidelines and the known risk profile of inhaled loxapine, a REMS with ETASU is recommended with the following concepts:

- Screen patients for a history of underlying respiratory conditions, acute respiratory signs or symptoms, or use of medications to treat respiratory conditions. These conditions represent contraindications to inhaled loxapine administration.
- Administer inhaled loxapine only in a healthcare setting that is equipped to handle bronchospasm and the potential for respiratory decompensation. This includes the availability of nebulized albuterol, oxygen, and staff trained to treat bronchospasm and perform advanced airway management, including intubation and mechanical ventilation.
- Train relevant staff on the safe use of inhaled loxapine.
- Monitor patients frequently following administration of inhaled loxapine. Monitoring should include vital sign assessment and physical examination, including chest auscultation, every 15 minutes for at least one hour following administration.
- Limit administration of inhaled loxapine to one dose in a 24 hour period.

6. Labeling

Based on the risk of bronchospasm, DPARP recommends the following or similar language be included in a boxed warning for inhaled loxapine:

Adasuve can cause bronchospasm that can lead to respiratory distress and respiratory arrest. Administer Adasuve only in an enrolled healthcare facility that has immediate access on site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation). Patients with asthma or other pulmonary diseases, such as chronic obstructive pulmonary disease (COPD) are at increased risk of bronchospasm, and Adasuve is contraindicated in these patients. Prior to administering Adasuve, screen and examine patients. Monitor patients for signs and symptoms of bronchospasm following treatment with Adasuve.

We also recommend the following or similar language for Warnings and Precautions:

ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. Administer ADASUVE only in an enrolled healthcare facility that has immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation).

Clinical demonstrated that patients with asthma or other pulmonary diseases, such as chronic obstructive pulmonary disease (COPD) are at increased risk of bronchospasm. ADASUVE is contraindicated in patients with the following conditions:

- *A history of asthma, chronic obstructive pulmonary disease (COPD), or other lung disease associated with bronchospasm*

- *Acute respiratory signs or symptoms (e.g., wheezing)*
- *Use of medications to treat asthma or COPD*
- *A history of bronchospasm following ADASUVE treatment*

Prior to administering ADASUVE, screen patients for a history of asthma, COPD, or other pulmonary disease, and examine patients (including chest auscultation) for respiratory signs and symptoms (e.g. wheezing). Monitor patients (e.g. vital signs and chest auscultation) for signs and symptoms of bronchospasm at least every 15 minutes for a minimum of one hour following treatment with ADASUVE. ADASUVE causes sedation, which can mask the symptoms of bronchospasm.

Because clinical trials in patients with asthma or COPD demonstrated that the degree of bronchospasm was greater following a second dose of ADASUVE, limit ADASUVE use to a single dose (either 5 or 10 mg) within a 24 hour period.

Advise all patients of the risk of bronchospasm. Advise them to inform the healthcare professional if they develop any breathing problems such as wheezing, shortness of breath, or other symptoms of bronchospasm following treatment with ADASUVE.

7. Conclusions

There is a significant risk of post-inhalation bronchospasm following administration of inhaled loxapine, particularly in patients with underlying airway hyperresponsiveness caused by conditions such as asthma and COPD. The severity of obstruction is greater following a second dose and does not return to baseline for 24 hours or more following repeat dosing. Characteristics of the patient population, including a high prevalence of smoking and inability to give a reliable history, increase the risk of bronchospasm following inhaled loxapine administration.

The FDA-proposed REMS and labeling is intended to both limit administration in patients at highest risk of bronchospasm and monitor patients following use of inhaled loxapine so that developing bronchospasm can be treated early. These restrictions likely will limit, but may not completely eliminate, potentially severe adverse airway events that may occur with inhaled loxapine. This risk must be weighed against the clinical need for a rapidly acting, non-invasive treatment of acute agitation and potential benefit in this patient population. If approved, additional post-marketing surveillance including a post-marketing requirement for a clinical trial to evaluate safety in a real-world setting using the REMS and labeling would be beneficial.

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I concur

CLINICAL REVIEW

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Trade Name Staccato Loxapine for
Inhalation (ADASUVE)
Therapeutic Class Antipsychotic
Applicant Alexza Pharmaceuticals
Related IND 73248

Priority Designation Standard

Formulation Single-Use Inhaler: 5 mg, 10
mg
Dosing Regimen 5-10 mg Q 2 hrs PRN (max: 30
mg/day)
Indication Agitation
Intended Population Adults with Schizophrenia or
Bipolar Disorder

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1. Introduction

ADASUVE (loxapine) inhalation powder (*Staccato* Loxapine) is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery by inhalation of a thermally generated aerosol of loxapine. *Staccato* Loxapine represents a new dosage form for loxapine, an antipsychotic with dopamine D₂ blocking activity that has been available in the United States (US) since 1975. *Staccato* Loxapine (5-mg and 10-mg dose levels) has been developed by the sponsor for the treatment of agitation in patients with Schizophrenia or Bipolar Disorder. Since agitation in these psychiatric populations is an acute and intermittent condition, it is expected that patients will be treated with *Staccato* Loxapine on an infrequent basis.

Oral loxapine is used in the treatment of schizophrenia. Although no longer marketed, an intramuscular (IM) formulation was previously approved for the management of acutely agitated patients. The pharmacological, pharmacokinetic, toxicological, and clinical safety and efficacy profiles of oral and IM formulations of loxapine have been previously established in the context of the NDAs for these approved formulations (NDA 17-525 and NDA 18-039, respectively).

Staccato Loxapine is based on the proprietary *Staccato* delivery system developed by the sponsor. Oral inhalation through the *Staccato* Loxapine for Inhalation 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 resulting rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration.

2. Regulatory History

Alexza (the sponsor) has completed quality, nonclinical and clinical development programs to support the marketing approval of *Staccato* Loxapine (5 mg and 10 mg dosage units) in adult patients for the indication of *acute treatment of agitation associated with schizophrenia or bipolar disorder*. The completed development programs reflect feedback received at several key development meetings with the Agency (IND 73,248: *End-of-Phase 2 Meeting*, September 13, 2007; *Type C CMC Meeting*, December 3, 2008; and *Pre-NDA Meeting*, July 14, 2009).

The original IND was submitted to the FDA on September 6, 2005. On February 6, 2006, FDA issued a “May Proceed” letter in which more frequent spirometry assessments in the initial phase 1 study (Trial **004-101**: a single-dose, dose escalation study in healthy volunteers) were recommended in order to establish the pulmonary safety profile of this new formulation. The sponsor proposed spirometry assessments at screening, baseline, pre-treatment, and 2 and 6 hours after treatment. However, the Agency, in consultation with the Division of Pulmonary and Allergy Products (DPAP, renamed the Division of Pulmonary, Allergy, and Rheumatology Products [DPARP] on March 15, 2010),

recommended spirometry assessments as soon as possible after dosing (e.g., 5-10 minutes) as well as at ~30 minutes, and 1, 2, 4, and 6 hours. At the End-of-Phase 2 Meeting on September 13, 2007, it was noted that this recommendation was not followed and that “the evaluation for the potential to cause acute bronchospasm is inadequate.” During the meeting, the design of future pulmonary safety studies was discussed, and it was agreed that the pulmonary safety database “should adequately characterize the change in pulmonary function (spirometry) following administration of *Staccato* Loxapine.” It was also agreed that, because of the difficulty of obtaining this information in the planned phase 3 studies in agitated patients, the pulmonary assessments could be done in healthy adults and that patients with asthma and COPD should be included in the pulmonary safety studies.

The sponsor submitted NDA 22549 on December 11, 2009 to support the approval of *Staccato* Loxapine as a prescription drug product for the rapid treatment of agitation associated with Schizophrenia or Bipolar Disorder in adults. Filing confirmation was received in February, 2010 and a standard 10-month review time was confirmed. On October 8, 2010, the Division of Psychiatry Products (the Division) issued a Complete Response letter in which the risk of respiratory adverse reactions was identified as a key issue.

The sponsor met with the Division on December 17, 2010 (*End of Review Meeting*) to discuss the issues raised in the CR letter and how they should be resolved. Further conceptual guidance on the content of product labeling and the components of a Risk Evaluation and Mitigation Strategy (REMS) to manage the risk of bronchospasm was received at a *Type C Meeting* on April 29, 2011.

A Psychopharmacologic Advisory Committee (PDAC) Meeting is scheduled for December 12, 2011.

3. Clinical Overview

The clinical program to support the use of *Staccato* Loxapine for the treatment of agitation comprised 11 clinical trials, which are discussed in detail in this reviewer’s **Clinical Review** of the original NDA submission dated September 17, 2010.

3.1 Clinical Pharmacology

Briefly, the clinical pharmacology program included a single-dose pharmacokinetic (PK) study in healthy subjects (**004-101**), a multiple-dose PK study in non-agitated patients on chronic, stable antipsychotic regimens (**004-102**), a PK study comparing smokers to nonsmokers (**004-106**), and a clinical bioequivalence study (**004-103**) demonstrating bioequivalence of the commercial version of the inhaler (used in some of the earlier trials) compared to the clinical version (used in the efficacy trials and planned for marketing). A thorough QT/QTc study (**004-107**) was also conducted in healthy subjects and demonstrated no significant QTc prolongation effect of *Staccato* Loxapine.

3.2 Clinical Efficacy

The clinical efficacy of *Staccato* Loxapine for the treatment of agitation was demonstrated in two Phase 3 placebo-controlled clinical studies that investigated 1 to 3 doses of *Staccato* Loxapine (5 mg or 10 mg) in agitated patients with Schizophrenia (004-301) or Bipolar disorder (004-302). In both studies a second dose (at least 2 hours after first dose) and third dose (at least 4 hours after second dose) was allowed as needed for persistent or recurrent agitation over a 24 hour period. In these two pivotal studies, both the 5- and 10-mg doses met the primary efficacy endpoint (change in Positive and Negative Symptom Scale, Excited Component [PEC] score from baseline to 2 hours after Dose 1, active vs. placebo) and key secondary endpoint (Clinical Global Impression – Improvement Scale [CGI-I] score 2 hours after Dose 1, active vs. placebo). In both trials, the effect size was larger in the 10-mg group compared to the 5-mg group, providing evidence for a dose-response pattern. A phase 2 study (004-201) of similar design but utilizing only a single dose (5 mg or 10 mg) in agitated patients with Schizophrenia and Schizoaffective Disorder provided supportive evidence of efficacy.

Table 1: Efficacy and Safety Studies of *Staccato* Loxapine for Acute Agitation

Study Number	Study Design	Drugs/Dose/Duration	Number and Type of Subjects
004-201	Phase 2A, randomized, double-blind, placebo-controlled, parallel-group, single-dose study	<i>Staccato</i> Loxapine 5 mg or 10 mg or <i>Staccato</i> Placebo; single dose in 24 hours	129 patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder, clinically agitated
004-301	Phase 3, randomized, double-blind, placebo-controlled, parallel-group study	<i>Staccato</i> Loxapine 5 mg or 10 mg or <i>Staccato</i> Placebo; each patient received up to 3 doses in 24 hours, with Doses 2 and 3 administered only if needed	344 patients with Schizophrenia, clinically agitated
004-302	Phase 3, randomized, double-blind, placebo-controlled, parallel-group study	<i>Staccato</i> Loxapine 5 mg or 10 mg or <i>Staccato</i> Placebo; each patient received up to 3 doses in 24 hours, with Doses 2 and 3 administered only if needed	314 patients with Bipolar I Disorder, manic or mixed, clinically agitated

3.3 Clinical Safety

3.3.1 Safety Population

The clinical safety of *Staccato* Loxapine was investigated in an overall safety population of 1653 subjects (active drug and placebo), which included a total of 524 agitated patients with Schizophrenia or Bipolar Disorder who received *Staccato* Loxapine at doses of 5 mg or 10 mg.

Table 2: Summary of Exposure (Controlled Studies in Agitated Patient population)

Doses of Study Medication, n (%)	Placebo (N=263)	Staccato Loxapine Dose		All Staccato Loxapine (N=524)
		5 mg (N=265)	10 mg (N=259)	
1 dose	124 (47.1%)	152 (57.4%)	176 (68.0%)	328 (62.6%)
2 doses	104 (39.5%)	93 (35.1%)	67 (25.9%)	160 (30.5%)
3 doses	35 (13.3%)	20 (7.5%)	16 (6.2%)	36 (6.9%)

In addition, safety data was provided from two trials in patients with migraine headaches (**104-201** and **104-202**).

The pulmonary safety program comprised three double-blind, placebo-controlled studies that evaluated two 10 mg doses of *Staccato* Loxapine in 30 healthy subjects with normal pulmonary function (**Study 004-104**), in 52 subjects with mild to persistent asthma (**Study 004-105**), and in 53 subjects with chronic obstructive pulmonary disease (**Study 004-108**). In **Study 004-104**, the two doses were separated by 8 hours, and in **Studies 004-105** and **004-108**, the two doses were separated by 10 hours.

Table 3: Pulmonary Safety Studies: Staccato Loxapine

Study Number	Study Design	Drugs/Dose/Duration	Number and Type of Subjects
004-104	Phase 1, randomized, double-blind, placebo-controlled, 2-period crossover pulmonary safety study	<i>Staccato</i> Loxapine 10 mg or <i>Staccato</i> Placebo; in each of 2 treatment periods, subjects received 2 doses of same treatment within 24 hours (doses separated by 8 hours)	30 healthy nonsmokers
004-105	Phase 1, randomized, double-blind, placebo-controlled, parallel-group, pulmonary safety study	Each subject was to receive 2 doses of <i>Staccato</i> Loxapine 10 mg or <i>Staccato</i> Placebo in 24 hours (doses separated by 10 hours)	52 subjects with mild to moderate persistent asthma
004-108	Phase 1, randomized, double-blind, placebo-controlled, parallel-group, pulmonary safety study	Each subject was to receive 2 doses of <i>Staccato</i> Loxapine 10 mg or <i>Staccato</i> Placebo in 24 hours (doses separated by 10 hours)	53 subjects with COPD

3.3.2 General Adverse Events:

In general, the adverse events (AEs) associated with *Staccato* Loxapine were either expected from the known adverse event profile of loxapine or related to the method of loxapine administration (inhalation). In the agitated patient population, the most frequently reported AEs in patients treated with *Staccato* Loxapine were dysgeusia (All *Staccato* Loxapine ~13%) and sedation (All *Staccato* Loxapine 10.5%). Most AEs (96.3%) were mild to moderate. Dysgeusia, sedation (including sedation combined with somnolence), fatigue, and throat irritation were identified as potential adverse reactions associated with *Staccato* Loxapine (incidence rate $\geq 2\%$ and greater than placebo in either the 5-mg or 10-mg *Staccato* Loxapine groups). Dysgeusia was the only adverse event that exhibited evidence for dose-dependency. Akathisia and tremor were observed rarely,

each occurring in 2 patients (0.4%). There was one report of neck dystonia combined with oculogyration.

Table 4: *Staccato* Loxapine Adverse Events with an Incidence of at Least 2% and Greater than Placebo (Controlled Studies in Agitated Patient Population)

MedDRA Preferred Term n (%)	Placebo (N=263)	<i>Staccato</i> Loxapine 5 mg (N=265)	<i>Staccato</i> Loxapine 10 mg (N=259)
Dysgeusia	13 (4.9%)	30 (11.3%)	37 (14.3%)
Sedation/Somnolence	25 (9.5%)	32 (12.1%)	31 (12.0%)
Sedation	20(7.6%)	28 (10.6%)	27 (10.4%)
Fatigue	5 (1.9%)	6 (2.3%)	3 (1.2%)
Throat Irritation	1 (0.4%)	2 (0.8%)	7 (2.7%)

3.3.3 Pulmonary Adverse Events:

Significant pulmonary adverse events, particularly in subjects with asthma or COPD, were reported and are a major safety concern.

In subjects with asthma (Trial **004-105**), eighteen (69%) loxapine-treated subjects and 3 (12%) placebo-treated subjects had notable respiratory signs or symptoms, defined as the forced expiratory volume in the first second (FEV₁) decrease from baseline of $\geq 20\%$, an airway AE, or use of rescue (bronchodilator) medication. In this trial, ~54% of loxapine-treated subjects had airway adverse events compared to 11.5% of placebo-treated subjects. The most common airway adverse events in subjects with asthma were bronchospasm (~27%), chest discomfort (~23%), wheezing (~15%), and dyspnea (11.5%).

Table 5: Adverse Events Related to Airways (Safety Population) - Trial 004-105

Adverse Event, n (%)	<i>Staccato</i> Placebo (N=26)	<i>Staccato</i> Loxapine (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.

In subjects with COPD (Trial **004-108**), fifteen (~58%) loxapine-treated subjects had notable respiratory signs or symptoms compared to six (~22%) placebo-treated patients, and airway adverse events were reported for ~19% of loxapine-treated patients compared to ~11% of placebo-treated patients. Airway AEs that occurred in more than a single loxapine-treated subject in Trial **004-108** were dyspnea (3 subjects, 11.5%), cough (3 subjects, 11.5%), and wheezing (2 subjects, ~8%). No airway AEs occurred in more than a single placebo-treated subject in this trial.

Table 6: Adverse Events Related to Airways (Safety Population) - Trial 004-108

Adverse Event, n (%)	<i>Staccato</i> Placebo (N=27)	<i>Staccato</i> Loxapine (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%) ^a
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 FEV₁ from baseline" as an AE; there were no other airway AEs for this subject.

In the controlled studies in agitated patients population (subjects from the 2 pivotal trials, **004-301** and **004-302**, and the phase 2 proof of concept trial, **004-201**), the most frequently reported respiratory system AEs in loxapine-treated subjects versus placebo-treated subjects were throat irritation (~2% vs. 0.4%), pharyngeal hypoesthesia (0.6% vs. 0%), and wheezing (0.4% vs. 0%). The two subjects with AEs of wheezing did not require treatment. Bronchospasm was reported for one subject in the *Staccato* Loxapine 10 mg group in Trial **004-301**, resulted in early discontinuation, and required treatment with a bronchodilator. All the respiratory AEs were mild to moderate.

Table 7: Adverse Events in the Respiratory, Thoracic, and Mediastinal Disorders System Organ Class (Controlled Studies in Agitated Patients Population)

MedDRA System Organ Class Preferred Term, n (%)	Placebo (N=263)	Staccato Loxapine Dose		All Staccato Loxapine (N=524)
		5 mg (N=265)	10 mg (N=259)	
Patients with at least 1 respiratory, thoracic, and mediastinal disorders AE	3 (1.1%)	6 (2.6%)	13 (5.0%)	19 (3.6%)
Throat irritation	1 (0.4%)	2 (0.8%)	7 (2.7%)	9 (1.7%)
Pharyngeal hypoaesthesia	0 (0.0%)	1 (0.4%)	2 (0.8%)	3 (0.6%)
Wheezing	0 (0.0%)	2 (0.8%)	0 (0.0%)	2 (0.4%)
Breath sounds decreased	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)
Bronchitis	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
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%)
Hiccups	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Parosmia	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Pharyngitis	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Rhinitis allergic	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)
Upper respiratory tract infection	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Nasal congestion	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rhinorrhoea	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

In the trials of healthy volunteers, there were no incidences of wheezing or bronchospasm; however, a high incidence of cough (~7% of loxapine-treated subjects compared to ~2% of placebo-treated subjects) was noted, which may be suggestive of underlying bronchospasm.

Table 8: Adverse Events in the Respiratory, Thoracic, and Mediastinal Disorders System Organ Class (Healthy Volunteer Population)

MedDRA System Organ Class Preferred Term, n (%)	Placebo (N=90)	Staccato Loxapine Dose			All Staccato Loxapine (N=177)
		<5 mg (N=21)	5 mg (N=23)	10 mg (N=133)	
Respiratory, thoracic, and mediastinal disorders	5 (5.6%)	0 (0.0%)	1 (2.3%)	24 (18.0%)	25 (14.1%)
Cough	2 (2.2%)	0 (0.0%)	0 (0.0%)	13 (9.8%)	13 (7.3%)
Pharyngeal hypoesthesia	0 (0.0%)	0 (0.0%)	1 (4.3%)	2 (1.5%)	3 (1.7%)
Pharyngitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.3%)	3 (1.7%)
Pharyngolaryngeal pain	2 (2.2%)	0 (0.0%)	0 (0.0%)	3 (2.3%)	3 (1.7%)
Nasal congestion	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.5%)	2 (1.1%)
Rhinitis allergic	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.6%)
Sinus headache	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.6%)
Throat irritation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.6%)
Upper respiratory tract infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.6%)

Thus, although a particularly high incidence of respiratory adverse events was not found in the pivotal trials or in the Phase 1 and 2 trials, it is noteworthy that subjects with clinically significant acute or chronic pulmonary disease, such as clinically apparent asthma, chronic bronchitis, or emphysema, were excluded from these trials. In the trials of healthy volunteers (**004-101**, **004-102**, **004-103**, **004-104**, and **004-107**), subjects who reported regular tobacco use within the last year were excluded. The only exception was in Trial **004-106**, a pharmacokinetic study of healthy smokers compared to nonsmokers, but in this trial subjects were excluded for FEV₁ < 80% of predicted or FVC < 80% of predicted.

4. Agency's Complete Response Action

Having identified pulmonary toxicity as a major safety issue, the Agency expressed concern as to whether the patients included in the pivotal trials were truly representative of the intended population. This concern was primarily due to two factors: 1) the pattern of recruitment of subjects in the pivotal trials, and 2) the exclusion of smokers in the Phase 1 and 2 trials and subjects with clinically significant pulmonary disease from the pivotal trials.

In a controlled study setting, obtaining an accurate history and physical, providing instructions on use of the device, and monitoring for the development of respiratory signs and symptoms may be easier than in a real world setting such as an acute presentation to an emergency room. The Agency expressed doubt as to whether acutely agitated and, in

many cases, psychotic patients presenting in a real world setting could 1) give a reliable history of respiratory disease, 2) cooperate for effective pulmonary examination, 3) be able to understand and follow instructions on how to use the device, 4) be able to accurately communicate to healthcare personnel if they experience respiratory symptoms post-dose.

In addition, it was noted that patients who received *Staccato* Placebo also had respiratory adverse events and changes in pulmonary function, raising the question as to whether the device itself has a respiratory irritant effect.

Lastly, the Agency considered that safer, alternative medication is available for treatment of agitation in patients with schizophrenia and bipolar I disorder.

Based on the original NDA submission and on discussions with the sponsor during the first review cycle, it appeared that most patients were recruited from referrals in the community, undergoing device training and extensive pre-treatment screening (up to 2 days or more in Trial **004-301**, and up to 24 hours in Trial **004-302**). No patients were reported to have been recruited from psychiatric emergency rooms, yet psychiatric emergency rooms would likely be a common setting for use of *Staccato* Loxapine if it is approved. Although device failure rate in the pivotal trials was low, patients presenting to a psychiatric emergency room may be less cooperative and are less likely to have an established relationship with the health care provider. Under such circumstances, it is unclear if device training would be as effective as it was in the pivotal trials and if *Staccato* Loxapine could be effectively administered.

The high rate of smoking in patients with Schizophrenia and Bipolar Disease has been well-documented. In one study, Hughes et al (*American Journal of Psychiatry* 1986, **143**: 993-997) reported that the prevalence of smoking among psychiatric outpatients was significantly higher than among either local or national population-based samples (52% versus 30% and 33%) and that smoking was especially prevalent among patients with Schizophrenia (88%) or Mania (70%) and among the more severely ill patients. In another study, Goff et al (*American Journal of Psychiatry* 1992, **149**: 1189-1194) reported that 74% of a group of schizophrenic outpatients smoked. Therefore, a high rate of asthma and COPD in the intended treatment population would be expected, and it is likely that excluding subjects with clinically significant pulmonary disease from the pivotal trials and subjects who reported regular tobacco use from the Phase 1 and 2 trials resulted in a better pulmonary safety profile than would be expected in the target population.

Furthermore, in the 3 pulmonary safety studies, doses of *Staccato* Loxapine were given 8 to 10 hours apart. In addition, subjects who required rescue medication (albuterol) for pulmonary events, developed clinically significant pulmonary adverse reactions, or had evidence of significant airway obstruction based on spirometry (decrease in FEV₁ ≥20%) after Dose #1 were excluded from receiving Dose #2. Changes in pulmonary function by spirometry usually precede development of respiratory symptoms. The sponsor's recommended dosing interval for *Staccato* Loxapine is 2 hours; therefore, particularly in

the absence of frequent spirometry assessments, airway adverse events and significant decreases in FEV₁ may prove to be more frequent and more severe in clinical practice than noted in the pulmonary safety studies.

It is unlikely that schizophrenic or bipolar patients presenting with acute agitation would be able to give a reliable medical history. In a case-matched, retrospective review, Roberts et al. (*Family Practice*; 24: 34-40) demonstrated that patients with Schizophrenia were less likely than asthma controls to have smoking status noted and in general were less likely to receive some important general health checks than patients without Schizophrenia. Thus, it would be extremely difficult for practitioners to exclude patients at risk for airway adverse reactions (ie, patients with asthma or COPD), especially in an emergency room setting where the patient's medical history may not be known or readily available. In many settings (e.g., a psychiatric inpatient ward or a psychiatrist's office), early recognition and prompt treatment of an airway adverse reaction in an already agitated patient may not be feasible, and appropriate rescue medication may not be readily available.

Appropriate, safer alternatives to *Staccato* Loxapine have already been approved. Intramuscular medication (aripiprazole, ziprasidone, and olanzapine) is available for treatment of acute agitation associated with Bipolar disorder or Schizophrenia. These medications have a reasonably rapid onset and have a safety profile similar to loxapine. However, the possibility of potentially serious respiratory adverse events is greatly decreased with intramuscular administration of these medications.

Therefore, the Complete Response (CR) letter identified pulmonary toxicity as the primary clinical safety concern based on data from Phase I pulmonary safety studies. In particular, the forced expiratory volume in the first second (FEV₁) changes and respiratory signs and symptoms related to bronchospasm in subjects with asthma and chronic obstructive pulmonary disease (COPD) were identified as major safety concerns. Specifically, the CR letter stated the following:

The primary clinical safety concern is the pulmonary toxicity associated with the use of loxapine inhalation powder. Clearly, the toxicity is drug-related. However, an additional component of the toxicity appears to be related to use of the device itself, as demonstrated by the responses in the placebo group. In the 3 pulmonary safety studies, pulmonary function testing revealed clinically significant decreases in FEV₁ that were greater than 10%, 15%, and 20% for individual subjects. A decrease in FEV₁ of greater than 10% is considered clinically significant. To place these findings in perspective, one should note that the standard bronchoprovocation tests cause a decrease in FEV₁ of 10-20%. In healthy subjects, 27% of the loxapine group and 27% of the placebo group had a decrease in FEV₁ of >10%. Approximately 19% of healthy subjects treated with loxapine and 4% treated with placebo had decreases in FEV₁ >15%. In addition, 4% of healthy subjects treated with loxapine had decreases in FEV₁ >20%. The

decreases in FEV1 observed above occurred in the 8 hours after either dosing.

In subjects with asthma or COPD, the FEV1 findings were marked. In asthma subjects, 85%, 62%, and 42% had decreases in FEV1 >10%, >15%, and >20%, respectively. In COPD subjects, 80%, 56%, and 40% had decreases in FEV1 >10%, >15%, and >20%, respectively. Furthermore, a high proportion (58-69%) of asthmatic and COPD subjects had significant respiratory signs/symptoms or required rescue treatment with bronchodilator medication. Respiratory signs and symptoms included bronchospasm, dyspnea, wheezing, chest discomfort, and cough.

Pulmonary toxicity was dose-related in the safety studies. Subjects treated with a second dose of loxapine inhalation powder had greater decreases in FEV1 (compared to their first dose), which did not return to baseline at 24 hours post-dose. A significant proportion of asthmatic and COPD subjects discontinued from the study before receiving the second dose, due to a decreased FEV1 and/or the need for rescue treatment of respiratory signs and symptoms. As a result, one cannot determine the true nadir of the FEV1 following treatment with loxapine inhalation powder in the pulmonary safety studies.

Additional factors could contribute to an unacceptable risk of pulmonary toxicity in the intended population. Patients with schizophrenia and bipolar disorder have a high prevalence of tobacco smoking. Thus, many of these patients will have some degree of respiratory disease burden at baseline. As noted above, exposure to loxapine inhalation powder can result in acute obstructive exacerbations requiring rescue bronchodilator treatment in patients with baseline obstructive disease. Another concern is that acutely agitated patients with schizophrenia or bipolar disorder may be incapable of providing an accurate history of pulmonary disease during the episode. Similarly, healthcare professionals may not be able to perform an adequate respiratory examination during an acute episode of agitation. Furthermore, rescue treatment may not be readily available in some settings in which patients would be treated with loxapine inhalation powder. Moreover, sedation from loxapine inhalation powder could obscure respiratory signs and symptoms. Finally, the dosage and administration section of proposed labeling states that loxapine inhalation powder could be administered every 2 hours up to 3 times, which would allow repeat dosing prior to recovery of FEV1 or respiratory symptoms.

5. End of Review Meeting

The sponsor met with the Division on December 17, 2010 to discuss the issues raised in the CR letter and how they should be resolved. In the pre-meeting package, the sponsor disagreed with the Division's position that the data from the Phase 1 pulmonary safety

studies signal an unacceptable risk in the intended population and argued that the full evaluation of the efficacy and safety data support a positive risk benefit assessment for *Staccato* Loxapine in the proposed indication. Specifically, the sponsor provided the following arguments:

1. The Phase 2 and 3 studies affirmatively demonstrate the safety and effectiveness of *Staccato* Loxapine in the intended population. The sponsor argued that *Staccato* Loxapine was studied in a large and diverse population (787 patients in the Phase 2/3 program, 524 treated with *Staccato* Loxapine) composed of agitated patients drawn from two diagnostic groups: Schizophrenia and Bipolar I Disorder.
2. The integrated safety database from the two Phase 3 studies (N=658), as well as the clinically relevant Phase 2 study in schizophrenia or schizoaffective patients (N=129) did not show evidence of pulmonary toxicity associated with *Staccato* Loxapine or *Staccato* Placebo in the intended population, the majority of whom were smokers. Airway-related adverse events in the pooled population for the highest dose (10 mg), including wheezing, bronchospasm, and cough, were observed at a rate of less than 1 percent.
3. The Phase 1 pulmonary safety studies add to the overall understanding of the safety profile of the product but do not negate the Phase 2 and 3 findings in the intended population.
4. The sponsor acknowledged the decrease in FEV₁ in the Phase 1 pulmonary safety studies but argued that there are different underlying causes for the FEV₁ decreases in these studies. Specifically, the sponsor attributes the decreases in FEV₁ to variable testing effort due to testing fatigue and the sedative nature of *Staccato* Loxapine.
5. In the asthma challenge study (**004-105**), the sponsor noted that the FEV₁ decreases are associated with bronchospasm and that the effects were generally transient and resolvable with the use of an inhaled bronchodilator.
6. The risk of bronchospasm appeared to be significantly less in COPD patients (**004-108**) compared with asthma subjects (**004-105**) with fewer airway AEs after treatment with *Staccato* Loxapine in COPD patients and, in the FEV₁ categories, a much smaller distinction between active and placebo.

At the meeting, the sponsor acknowledged the Agency's concern regarding the ability to identify all patients who are at risk of bronchospasm but proposed that this group can be screened out with appropriate mechanisms that could be detailed in a Risk Evaluation and Mitigation Strategy (REMS) package. The sponsor provisionally outlined that the REMS would comprise a medication guide and a communication plan. The Agency agreed conceptually that a REMS would be an appropriate tool. The sponsor agreed to provide a comprehensive REMS at the time of resubmission to demonstrate how the potential risks to patients with clinically active airway disease would be mitigated, including details of who should/shouldn't get the product. The sponsor also agreed to provide an estimate of the percent of patients who would present with asthma or COPD and be ineligible for treatment. The Division Director suggested that the Sponsor consider as part of the REMS a post-approval open cohort study in a real-world setting that would provide useful information on the population presenting for treatment.

Other items discussed at the End of Review Meeting include the following:

1. The Agency suggested that the patients in the Phase 2 and 3 studies were carefully screened and may have had prior experience with the device which may have affected the efficacy and safety findings. The Agency pointed out that screening for asthma and familiarity with the device would not be the case for actual patients entering the Emergency Room. The sponsor provided clarification on the recruitment and enrollment/screening procedures. During the procedures to determine eligibility, patients did not see the device and during the baseline assessment they were shown only a shell of the device. They had no sensory experience with the actual device prior to treatment.
2. The Agency asked the sponsor to summarize in the resubmission the recruitment and enrollment procedures to demonstrate that the patients were representative of patients that healthcare providers would treat for agitation in clinical practice. The Agency commented, “We remain concerned about whether you have demonstrated efficacy in the intended population, particularly in acutely agitated patients who would present to an emergency room or an acute inpatient setting. It appears that the majority of patients were recruited and studied as outpatients. It is not clear whether the efficacy results would be fully generalizable.” From the Division’s point of view, it is important to establish that the Phase 3 population is representative of the intended population since there was a very low incidence of adverse events in this population.
3. The Agency commented that it could be difficult to get a history from some patients. The sponsor replied that based on research conducted with a small sample of psychiatric and medical ER doctors as well as clinical practice guidelines, it is typical to obtain a relevant medical and/or medication history (from patient, family or records) and to conduct a brief physical examination. The Agency noted that this is the case to be made in the resubmission ie to demonstrate patients can be screened.
4. The sponsor stated that no further studies were planned to characterize the device in terms of a placebo effect (drops in FEV₁). The Information Package had presented a thorough evaluation of all data from the Phase 1 studies; additionally, aerosol characterization had not demonstrated anything present of concern. Some asthma and COPD patients who had airways-related adverse events with *Staccato* Placebo were symptomatic at home and therefore it might be expected that they would have some symptoms during the testing period.

6. NDA Resubmission: Sponsor’s Response and Risk-Benefit Assessment

In the current submission and in response to the Agency’s concerns, the sponsor provides the following arguments which will be discussed in detail below:

1. *Staccato* Loxapine is effective in controlling agitation.
2. *Staccato* Loxapine provides rapid onset of therapeutic effect.

3. *Staccato* Loxapine is well-tolerated in the intended treatment population.
4. There is no risk of pulmonary toxicity related to the *Staccato* device itself.
5. Although patients with clinically active asthma or COPD have an increased risk of respiratory adverse events from *Staccato* Loxapine, these patients can be effectively identified in a real world setting and should not receive *Staccato* Loxapine.
6. *Staccato* Loxapine provides an acceptable, easy to use, noninvasive treatment.

6.1 Sponsor’s Argument #1: *Staccato* Loxapine is Effective in Controlling Agitation

In the two Phase 3 studies, both the 5- and 10-mg doses of *Staccato* Loxapine met the primary and key secondary efficacy endpoints. Two hours after Dose 1, there were statistically significant differences favoring each *Staccato* Loxapine group over the placebo group in the change from baseline in the PEC scores (primary efficacy endpoint), as well as statistically significant differences favoring each *Staccato* Loxapine group over the placebo group in the CGI-I scores (key secondary efficacy endpoint).

Reviewer’s Comment: We acknowledge that the efficacy of Staccato Loxapine in controlling acute agitation associated with schizophrenia and bipolar disorder when properly administered has been demonstrated in the pivotal trials. The Agency’s concerns are whether Staccato Loxapine can safely be administered to acutely agitated patients in the “real world” with minimal risk of pulmonary toxicity.

6.2 Sponsor’s Argument #2: *Staccato* Loxapine Provides Rapid Onset of Therapeutic Effect

The sponsor argues that the treatment effect on agitation signs and symptoms, as reflected in the change from baseline in the total and individual five items PEC scores, 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 *Staccato* Loxapine. Furthermore, the sponsor argues that *Staccato* Loxapine compares favorably to IM formulations (aripiprazole and olanzapine) approved for acute agitation in schizophrenic and bipolar patients.

6.2.1 Comparison to Reference Therapies:

The sponsor notes that the Phase 3 *Staccato* Loxapine studies, including patient selection criteria, were designed to closely follow the programs that supported the approval of the IM formulations of Abilify (aripiprazole) and Zyprexa (olanzapine) that are approved to treat agitation in these patient groups. As with the pivotal studies for Abilify and Zyprexa IM, enrolled patients presented with a qualifying level of agitation at baseline and were treated, managed, and observed for at least 24 hours post-treatment.

In the pivotal studies conducted for *Staccato* Loxapine, as well as those for Abilify IM and Zyprexa IM, the primary efficacy endpoint was the change in Positive and Negative

Symptom Scale, Excited Component [PEC] score at 2 hours. All 3 agents also had the same key secondary endpoint (CGI-I at 2 hours). In the case of *Staccato* Loxapine, both the 5- and 10-mg doses met the primary endpoint. As shown in the table below (electronically copied and reproduced from sponsor's submission), the mean changes in PEC score are similar for *Staccato* Loxapine compared with the other 2 drugs. The sponsor argues that this confirms the relative effectiveness of *Staccato* Loxapine at both dose levels, based on comparison to the historical data from aripiprazole IM and olanzapine IM, which used the same trial design and primary endpoint.

Table 9: Mean Change in PEC Score from Baseline to 2 Hours in *Staccato* Loxapine Phase 3 Studies and Comparator Studies

<i>Staccato</i> Loxapine Studies ^a							
Study	Population	Placebo	Loxapine (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 Aripiprazole Studies							
Study	Population	Placebo	Active Comparator	Aripiprazole (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 Olanzapine Studies							
Study	Population	Placebo	Active Comparator	Olanzapine (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

PEC=Positive and Negative Symptom Scale, Excited Component; IM=intramuscular, NT=not tested
Values are LS means.

a. ITT population with LOCF

The sponsor further notes that the approved IM drugs were shown in their pivotal trials to have variable onsets of anti-agitation effect. The table below (electronically copied and reproduced from sponsor's submission) presents the time points of the first statistically significant changes from baseline in PEC scores relative to placebo in the *Staccato* Loxapine, aripiprazole (Abilify) IM, and olanzapine (Zyprexa) IM Phase 3 studies. For aripiprazole and olanzapine, there was some variability in the onset of effect based on

both the treatment population and the dose of the drug. As shown in the table, the fastest onset of effect for the IM formulations of olanzapine and aripiprazole was 15 and 45 minutes in patients with schizophrenia and 30 and 90 minutes in patients with bipolar disorder. By contrast, *Staccato* Loxapine 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).

Table 10: Time to First Statistically Significant Change from Baseline PEC Score in *Staccato* Loxapine Phase 3 Studies and Comparator Studies

<i>Staccato</i> Loxapine Studies ^a					
Study	Population	Loxapine (Inhaled)			
		5 mg	10 mg		
004-301	Schizophrenia	10 min	10 min		
004-302	Bipolar Disorder	10 min	10 min		
IM Aripiprazole Studies					
Study	Population	Aripiprazole (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 Olanzapine Studies					
Study	Population	Olanzapine (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

PEC=Positive and Negative Symptom Scale, Excited Component; IM=intramuscular, NT=not tested
 ns=not statistically significant from placebo.

a. ITT population with LOCF

Thus, the difference in time to producing a significant reduction in agitation may be more evident in patients with bipolar disorder in whom *Staccato* Loxapine had effects in 10 minutes, compared with 30 minutes and 90 minutes for the prescribed doses of olanzapine and aripiprazole, respectively. The sponsor concludes that, given its nonparenteral route of administration, the rapid onset of significant anti-agitation effects, and the overall reduction in agitation demonstrated in the Phase 3 program, *Staccato* Loxapine seems to offer advantages over the existing therapies as an acute treatment for agitation.

Reviewer’s Comment: In the two pivotal trials (004-301 and 004-302), both the 5- and 10-mg doses met the primary efficacy endpoint (change in Positive and Negative

Symptom Scale, Excited Component [PEC] score from baseline to 2 hours after Dose 1, active vs. placebo), and the key secondary efficacy endpoint (Clinical Global Impression – Improvement Scale [CGI-I] 2 hours after Dose 1, active vs. placebo). However, FDA statistician Yeh-Fong Chen, Ph.D. noted in her review that, except at 2 hours, only the tests between Staccato Loxapine 10 mg and placebo at time points 45, 30, 20, and 10 minutes were prospectively planned to be tested in terms of controlling the overall study-wise type I error rate. Therefore, Dr. Chen concluded that, statistically speaking, the efficacy finding of Staccato Loxapine 5 mg at individual time points other than 2 hours and the description of the efficacy of Staccato Loxapine 10 mg beyond 45 minutes cannot be described in labeling. In the absence of head-to-head studies, it is not possible to make definitive conclusions concerning the onset and sustainability of anti-agitation effect of Staccato Loxapine compared to IM Abilify (aripiprazole) and IM Zyprexa (olanzapine).

6.2.2 Efficacy Information Amendment:

On October 25, 2011, the sponsor submitted an Efficacy Information Amendment (SN 28) which provided results of two post-hoc analyses conducted on the two pivotal studies (**004-301** and **004-302**):

1. Responder analyses of total Positive and Negative Symptom Scale, Excited Component (PEC) scores from 10 minutes through 2 hours after Dose 1
2. Analyses of the changes in individual PEC scale items from 10 minutes through 2 hours after Dose 1

6.2.2.1 PEC Scale Responder Analysis

The sponsor conducted post-hoc responder analyses evaluating the total PEC scores from all time points within the first 2 hours after Dose 1. A “responder” was defined as a patient with a $\geq 40\%$ decrease from baseline in the total PEC score. The sponsor notes that this was the same criterion used in responder analyses of PEC scale data from the pivotal trials of IM Abilify and IM Zyprexa.

The sponsor reports that in Studies **004-301** and **004-302**, at each assessment time from 10 minutes through 2 hours after Dose 1, the number of responders was significantly larger in the groups treated with *Staccato* Loxapine compared with *Staccato* Placebo (Study **004-301**, $p < 0.01$ at all time points; Study **004-302**, $p < 0.01$ at all time points). Furthermore, at each assessment time from 10 minutes through 2 hours, the responder rate was numerically larger in the 10-mg group compared to 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 ($p < 0.0001$) (Cochran-Mantel-Haenszel tests). 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 ($p = 0.0002$) (Cochran-Mantel-Haenszel tests).

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 ($p<0.0001$) (Cochran-Mantel-Haenszel tests). 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 ($p<0.0001$) (Cochran-Mantel-Haenszel tests).

Figure 1: PEC Scale Responders ($\geq 40\%$ Decrease from Baseline) in the First 2 Hours after Dose 1 – Study 004-301 (ITT Population with LOCF)

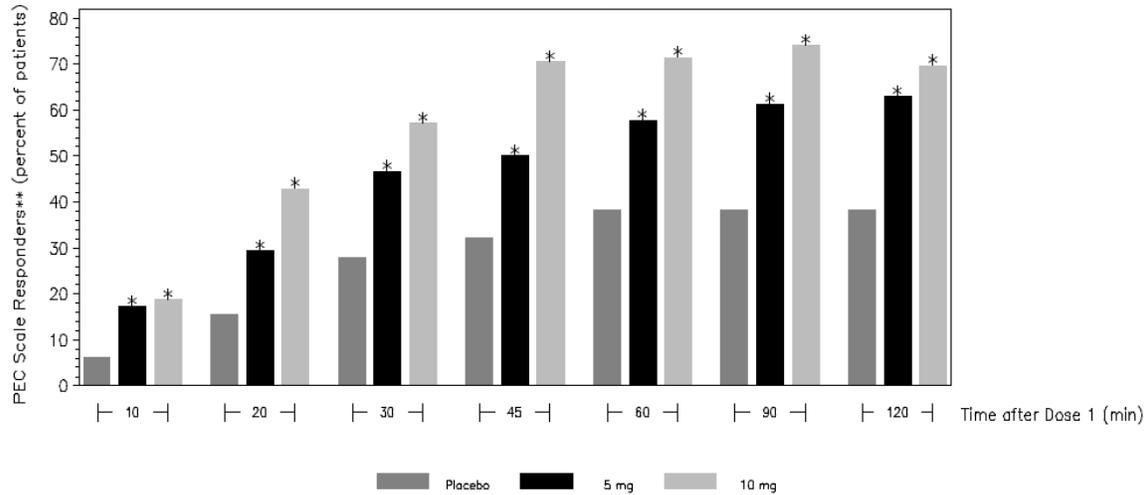
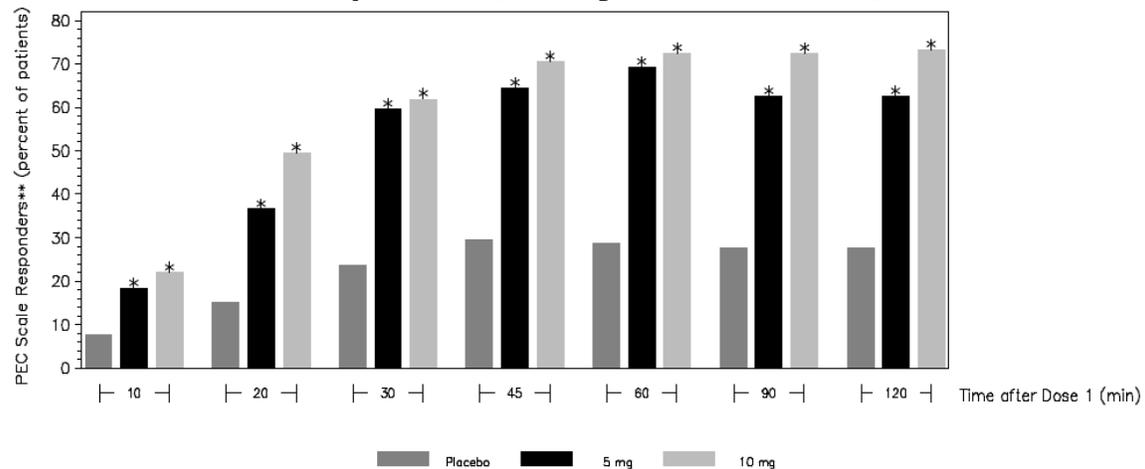


Figure 2: PEC Scale Responders ($\geq 40\%$ Decrease from Baseline) in the First 2 Hours after Dose 1 – Study 004-302 (ITT Population with LOCF)



6.2.2.2 Changes in Individual PEC Scale Items

The PEC scale comprises 5 items (poor impulse control, tension, hostility, uncooperativeness, and excitement), each of which is scored on a scale of 1 (absent) to 7 (extreme). To evaluate the effect of *Staccato* Loxapine on each of these 5 components of agitation, the sponsor conducted post-hoc analyses to assess the changes in each of the individual PEC items at each assessment time from 10 minutes to 2 hours after Dose 1.

According to the sponsor, each PEC scale item showed improvement after treatment with *Staccato* Loxapine, 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 ($p < 0.05$, 2-way nonparametric ANCOVA by ranks [within strata]). 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, $p = 0.0853$).

Figure 3: Changes in Individual PEC Scale Items in the First 2 Hours after Dose 1 in Study 004-301 (ITT Population with LOCF)

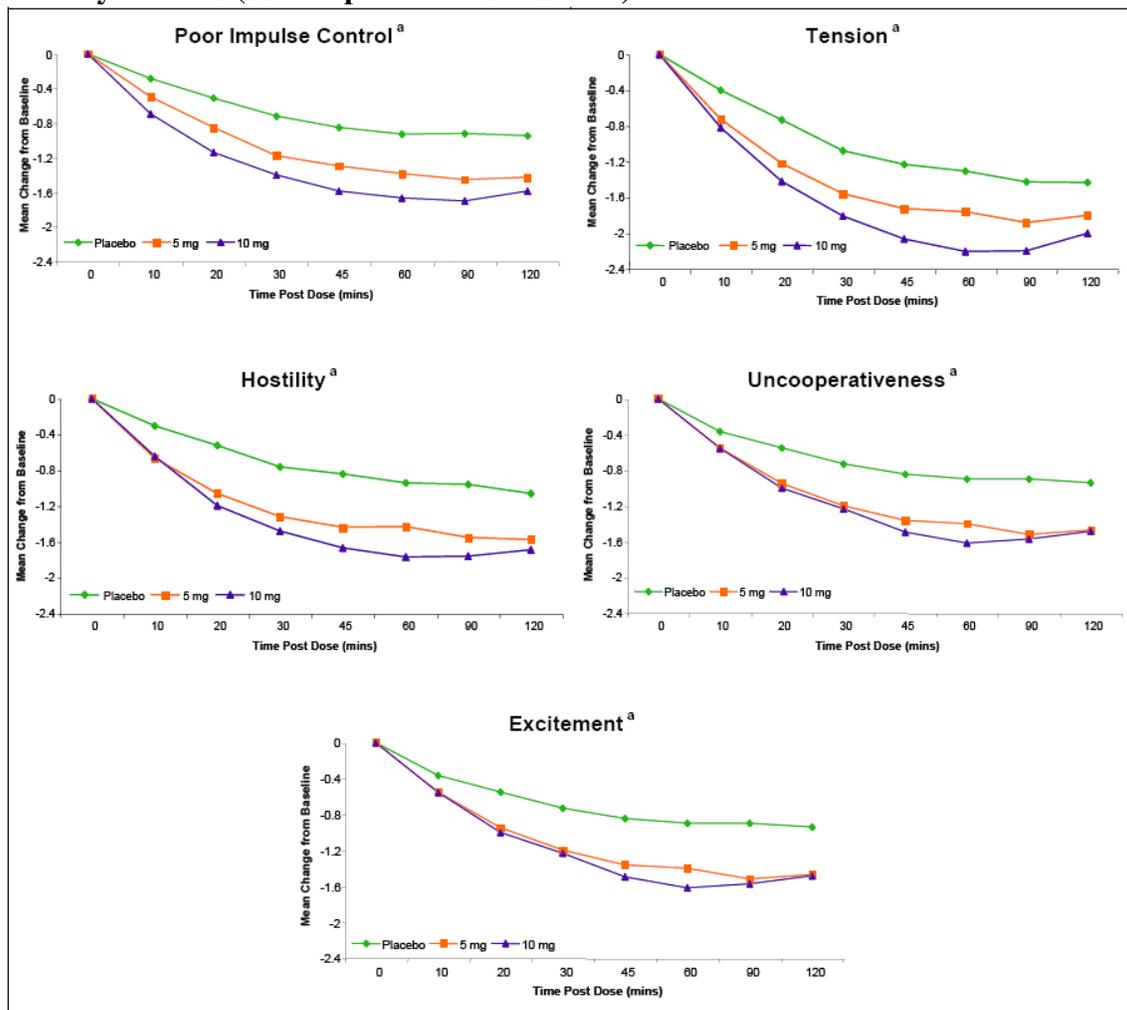
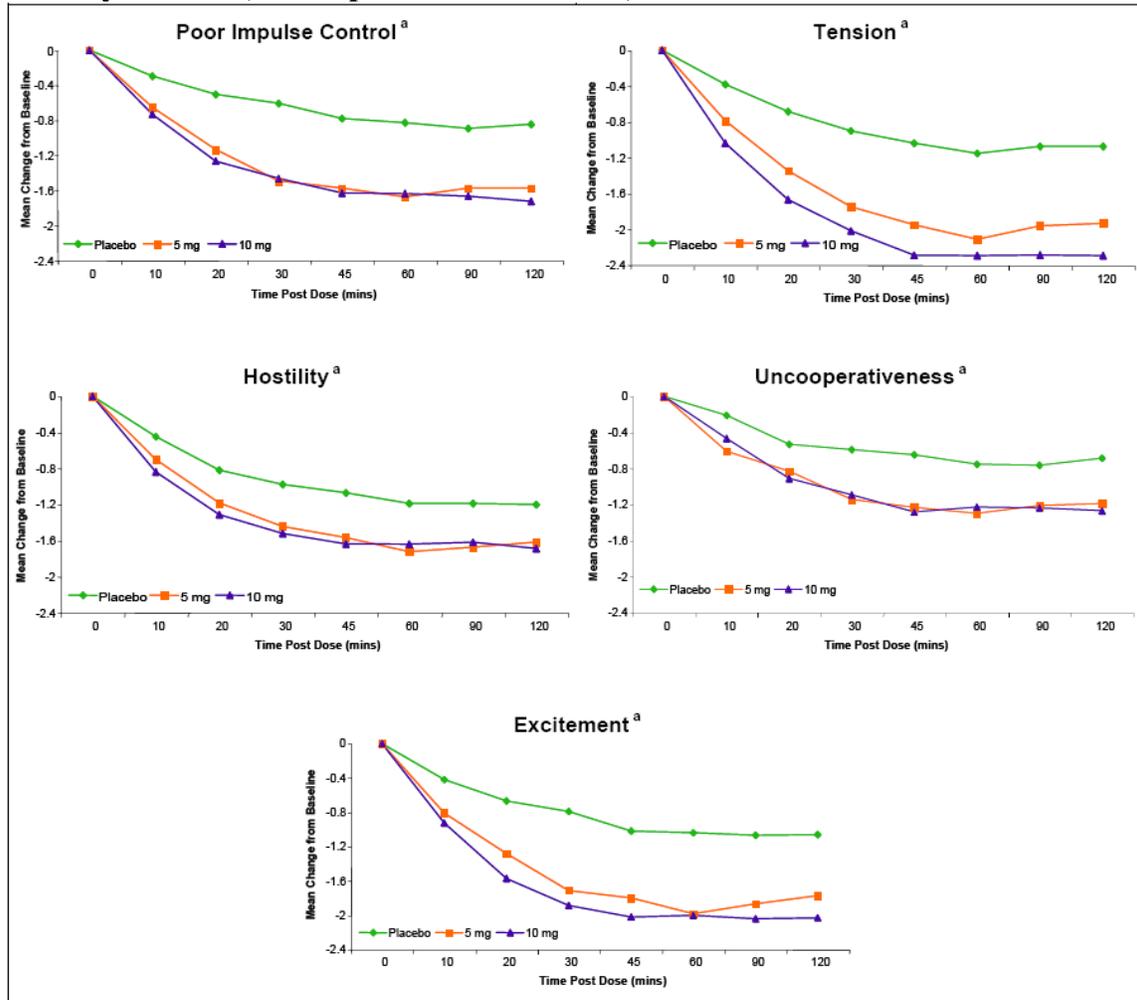


Figure 4: Changes in Individual PEC Scale Items in the First 2 Hours after Dose 1 in Study 004-302 (ITT Population with LOCF)



Reviewer Comments: Consultation with Dr. Yeh-Fong Chen (Biostatistics) regarding the above Efficacy Information Amendment has been requested and is pending at this time.

6.3 Sponsor's Argument #3: *Staccato* Loxapine is Well-Tolerated in the Intended Treatment Population

In essence, the sponsor argument that *Staccato* Loxapine is well-tolerated in the intended treatment population is based on two arguments: 1) that the patients studied in the pivotal trials were representative of the intended treatment population such that the intended treatment population has been well characterized based on the results of the pivotal and pulmonary safety trials; and 2) that *Staccato* loxapine was well-tolerated based on the results of the pivotal trials, the pulmonary safety study in healthy volunteers, the overall experience with *Staccato* Loxapine in the clinical development program, and the inhalation toxicology studies in rats and dogs.

6.3.1 Sponsor’s Argument #3, Part 1: Intended Treatment Population was Well Characterized

The sponsor provides an argument that the patients enrolled in the Phase 3 studies were representative of the intended population. The sponsor argues that the Phase 3 studies enrolled patients with either schizophrenia or bipolar I disorder who were, on average, moderately agitated at baseline, and who presented to study sites through normal channels by which psychiatric patients obtain treatment for agitation. The sponsor bases this argument on an analysis of: 1) the identification and enrollment of patients in the pivotal (phase 3) studies and 2) the characteristics of the phase 3 study population.

6.3.1.1 Identification and Enrollment of Patients

The sponsor provides an analysis of how patients were enrolled and identified in the phase 3 studies based on: 1) the sources of enrolled patients, and 2) the psychiatric screening criteria used for patients enrolled in the phase 3 studies.

6.3.1.1.1 Sources of Enrolled Patients in the Phase 3 Studies

The sponsor notes that 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 had previously participated in psychiatric trials. The Institutional Review Board site profiles completed by the investigators indicate that, of the 24 sites in Study **004-301**, 7 were located within or connected to a hospital, 9 were psychiatric institutions and/or included a medical office, and 8 were referred to as research clinics only. Of the 17 sites in Study **004-302** (which were a subset of the study **004-301** sites), 5 were located within or connected to a hospital, 5 were psychiatric institutions or included a medical office, and 7 were described as research clinics only. Therefore, the sponsor reports that two-thirds of the study sites were hospitals or clinics with an active clinical practice, and the sponsor concludes that such sites have access to patients from a wide variety of referral channels.

To determine the specific sources of the enrolled patients, the sponsor contacted all Phase 3 investigators. Responses were received from 19 sites that enrolled 89.2% of patients. As shown in the table below (electronically copied and reproduced from sponsor’s submission), most study patients (59.1%) presented directly to the site for treatment. According to the sponsor, discussions with investigators indicate that the types of psychiatric centers that were used as study sites are known to patients in the community and are viewed by many patients as attractive alternatives to general medical emergency rooms when acute treatment is needed (e.g., they typically have shorter waiting times).

Another 33.0% of the study patients were enrolled from the community following referral by a medical/mental health professional. The sponsor notes that those who refer psychiatric patients for acute care – including community physicians, ER physicians, social workers, case managers, subinvestigators who also work at other clinics, and managers of “board and care” homes – are typically aware of the studies being conducted at neighboring research sites.

A much smaller number of patients were enrolled from inpatient wards or emergency rooms (ERs). The sponsor believes that the small number of inpatient ward and emergency room referrals reflect the limited referral channels from ERs to other clinical sites (because the ER treats the agitation), as well as the difficulty of obtaining informed consent from the most severely agitated patients.

Table 11: Sources of Patient Enrollment (Studies 004-301 and 004-302)

Study	Presented Directly to the Study Site	Referred by a Medical/Mental Health Professional (not via an ER)	Inpatient (i.e., already hospitalized)	Presented Via an ER or a Designated Psychiatric ER
004-301 ^a	181 (58.0%)	98 (31.4%)	25 (8.0%)	8 (2.6%)
004-302 ^b	166 (60.4%)	96 (34.9%)	7 (2.5%)	6 (2.2%)
Total (004-301 ^a + 004-302 ^b)	347 (59.1%)	194 (33.0%)	32 (5.5%)	14 (2.4%)

Source: Data on file

Percentages are based on the number of patients for whom information was obtained.

^a Information was received from 19 of the 24 investigators.

^b Information was received from 15 of the 17 investigators.

All patients either presented or were referred 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 small numbers were enrolled from inpatient wards or emergency rooms.

6.3.1.1.2 Psychiatric Screening Criteria for Patients Enrolled in Phase 3 Studies

The sponsor states that only patients who met the study inclusion criteria and who were not ineligible based on exclusion criteria were enrolled. The inclusion criteria for Studies **004-301** and **004-302** were similar to the inclusion criteria used in the Abilify IM and Zyprexa IM pivotal studies, as shown in the tables below:

Table 12: Summary of Enrollment Criteria for Phase 3 Studies of Agitation in Schizophrenia

	<i>Staccato</i> Loxapine ^a	Zyprexa ^b	Zyprexa ^b	Abilify ^c	Abilify ^c
Study ID	004-301	MC-HGHB	MC-HGHV	CN138012	CN138050
Study N	344	311	270	448	357
Patients	<ul style="list-style-type: none"> Adults ≥18 Schizophrenia by DSM-IV Inpatient during study 	<ul style="list-style-type: none"> Adults ≥18 Schizophrenia, schizophreniform disorder, or schizoaffective disorder by DSM-IV Inpatient during study 	<ul style="list-style-type: none"> Adults ≥18 Schizophrenia, schizophreniform disorder, or schizoaffective disorder by DSM-IV Inpatient during study 	<ul style="list-style-type: none"> Adults ≥18 Schizophrenia or schizoaffective disorder by DSM-IV Inpatient during study 	<ul style="list-style-type: none"> Adults ≥18 Schizophrenia, schizophreniform disorder, or schizoaffective disorder by DSM-IV Inpatient during study
Baseline PEC	≥14; at least 1 item ≥4	≥14; at least 1 item ≥4	≥14; at least 1 item ≥4	≥15 (and ≤32); at least 2 items ≥4	≥15 (and ≤32); at least 2 items ≥4
Study arms	<ul style="list-style-type: none"> placebo <i>Staccato</i> Loxapine 5 mg <i>Staccato</i> Loxapine 10 mg 	<ul style="list-style-type: none"> placebo Zyprexa 10 mg haloperidol 7.5 mg 	<ul style="list-style-type: none"> placebo Zyprexa 2.5 mg, 5 mg, 7.5 mg or 10 mg haloperidol 7.5 mg 	<ul style="list-style-type: none"> placebo Abilify 10 mg haloperidol 6.5 mg 	<ul style="list-style-type: none"> placebo Abilify 1 mg, 5 mg, 10 mg, or 15 mg haloperidol 7.5 mg

^a m5.3.5.1, CSR 004-301, Sections 5.3, 5.4.1, and 6.1

^b Olanzapine, Statistical Review, NDA 21-253, 23 March, 2001

^c Aripiprazole, Medical Review, NDA 21-866, 30 November 2005

Table 13: Summary of Enrollment Criteria for Phase 3 Studies of Agitation in Bipolar Disorder

	<i>Staccato</i> Loxapine ^a	Zyprexa ^b	Abilify ^c
Study ID	004-302	MC-HGHW	CN138013
Study N	314	201	301
Patients	<ul style="list-style-type: none"> Adults ≥18 Bipolar disorder by DSM-IV and M.I.N.I. 5.0.0 Inpatient during study 	<ul style="list-style-type: none"> Adults ≥18 Bipolar disorder by DSM-IV and SCID Inpatient during study 	<ul style="list-style-type: none"> Adults ≥18 Bipolar disorder by DSM-IV Inpatient during study
Baseline PEC	≥14; at least 1 item ≥4	≥14; at least 1 item ≥4	≥15 (and ≤32); at least 2 items ≥4
Study arms	<ul style="list-style-type: none"> placebo <i>Staccato</i> Loxapine 5 mg <i>Staccato</i> Loxapine 10 mg 	<ul style="list-style-type: none"> placebo Zyprexa 10 mg lorazepam 2 mg 	<ul style="list-style-type: none"> placebo Abilify 10 mg or 15 mg lorazepam 2 mg

^a m5.3.5.1, CSR 004-302, Sections 5.3, 5.4.1, and 6.1

^b Olanzapine, Statistical Review, NDA 21-253, 23 March, 2001

^c Aripiprazole, Medical Review, NDA 21-866, 30 November 2005

6.3.1.2 Characteristics of the Phase 3 Study Population

The sponsor’s analysis of the phase 3 study population is based on: 1) the severity of agitation at baseline; 2) the number of inpatient bed days required by the phase 3 study patients; 3) the psychiatric history of the phase 3 study patients; and 4) the smoking and pulmonary history of the phase 3 study patients.

6.3.1.2.1 Severity of Agitation at Baseline

The sponsor notes that all patients in both pivotal studies (**004-301** and **004-302**) were clinically agitated at baseline. The sponsor argues that, consistent with the pivotal IM Zyprexa studies, one of the main study inclusion criteria in the *Staccato* Loxapine Phase 3 studies was a baseline PEC total score of ≥14, with at least 1 item score ≥4 (≥ *moderate*). Baseline PEC scores in the *Staccato* Loxapine studies ranged from 14 to 28 in the **004-301** study and 14 to 31 in the **004-302** study, with median scores of approximately 17. The sponsor points out that the baseline PEC scores are similar to those reported in the pivotal trials for IM Zyprexa and Abilify, as shown in the tables below (electronically copied and reproduced from sponsor’s submission). Furthermore, more than 80% of patients in the *Staccato* Loxapine Phase 3 studies had at least 2 PEC item scores ≥4 (*moderate*) at baseline. Approximately 30% of patients had at least 1 PEC item rated as moderate/severe (a rating of 5), and more that 3% in each trial had a PEC symptom that was rated as severe (a rating of 6):

Table 14: Baseline Agitation as Assessed by PEC Scale Item Scores in the Phase 3 Studies Patients in the Phase 3 Studies (Studies 004-301 and 004-302)

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

Source: m5.3.5.1, CSR 004-301, Appendix 12.2, Listing 2.1.2; m5.3.5.1, CSR 004-302, Appendix 12.2, Listing 2.1.2

Analysis population: Intent to Treat with Last Observation Carried Forward

^a A patient can be counted in multiple rows.

^b Total number of enrolled patients: 004-301=344, 004-302=314

In both pivotal studies (**004-301** and **004-302**), the Clinical Global Impression – Severity (CGI-S) score was used to establish the baseline level of agitation, prior to treatment. The mean baseline CGI-S score in Study **004-301** was 4.0, and the mean baseline score in Study **004-302** was 4.1. While the majority of the patients in Studies **004-301** (73.5%) and **004-302** (75.5%) had baseline CGI-S scores of 4 (*moderately agitated*), another 13.7% and 15.3% in Studies **004-301** and **004-302**, respectively, had baseline scores of 5 (*markedly agitated*) or 6 (*severely agitated*).

Baseline Agitation-Calmness Evaluation Scale (ACES) scores also indicated that the majority of patients enrolled in Studies **004-301** and **004-302** were considered moderately agitated at baseline. While the majority of the patients in Studies **004-301** (72.6%) and **004-302** (82.5%) had a baseline ACES score of 2 (*moderately agitated*), another 3.2% and 5.1% in Studies **004-301** and **004-302**, respectively, had baseline scores of 1 (*markedly agitated*). The mean baseline ACES score in Study **004-301** was 2.2, and the mean baseline ACES score in Study **004-302** was 2.1.

Thus, the sponsor concludes that the mean baseline scores for the PEC, CGI-S, and ACES scales in Studies **004-301** and **004-302** all establish that the patients enrolled in these studies were, on average, moderately agitated at baseline, as shown in the table below (electronically copied and reproduced from sponsor’s submission):

Table 15: Mean Baseline Agitation Scores (Studies 004-301 and 004-302)

Product	Population	Pivotal Trial Study ID(s)	Mean Baseline PEC Score	Mean Baseline CGI-S Score (4=moderate)	Mean Baseline ACES Score (2=moderate)
<i>Staccato</i> Loxapine	Schizophrenia	004-301	17.6	4.0	2.2
<i>Staccato</i> Loxapine	Bipolar Disorder	004-302	17.5	4.1	2.1

In addition, Study **004-301** allowed a screening period of up to 2 weeks, but most subjects were dosed within 2 days of screening (82.6%) and only 3.5% of patients (12 of 344) were dosed beyond 7 days of screening. Based on that finding, the screening period for Study **004-302** was narrowed to 24 hours.

6.3.1.2.2 Inpatient Bed Days

All Phase 3 patients required inpatient psychiatric treatment. Per protocol, they were required to stay in the clinic from the time of baseline assessments until at least 24 hours after the first dose of study drug and until at least 12 hours after the last dose of study drug. Additional time at the study site was allowed per protocol if, in the clinical judgment of the investigator, the patient needed more time for psychiatric stabilization.

The total duration of the inpatient stay was not captured in the study case report form. However, the sponsor reports that bed-day reimbursements are known for 329 (95.6%) of the patients in Study **004-301** and 306 (97.4%) of those in Study **004-302**, as shown in the table below (electronically copied and reproduced from sponsor’s submission):

Table 16: Bed Day Reimbursement (Studies 004-301 and 004-302)

Study	Bed Days ^a (No., % of Patients)					
	1 day	2 days	3 days	4 days	5 days	6 days
004-301	45 (14.7%)	182 (55.3%)	95 (28.9%)	3 (0.9%)	2 (0.6%)	2 (0.6%)
004-302	57 (18.6%)	161 (52.6%)	79 (25.8%)	5 (1.6 %)	1 (0.3%)	3 (1.0%)

Source: Data on file

^a Bed-day calculation includes the 24 hours after the first dose (and when applicable, 12 hours after the last dose). Percentages are based on the number of patients for whom data were available.

The range of inpatient bed days for which reimbursement was requested was 1 to 6 days in both studies, with the majority of patients being inpatients for 2 to 3 days. The additional time in the unit reflected the need for additional psychiatric stabilization, beyond study discharge.

Thus, the sponsor argues that the number of inpatient bed days is another indicator of the severity of psychiatric illness in study patients.

6.3.1.2.3 Psychiatric History

The sponsor argues that the patients in Studies **004-301** and **004-302** had significant and longstanding disease. In Study **004-301**, the mean time since diagnosis of schizophrenia was 17.8 years (range, 0-49). In Study **004-302**, the mean time since diagnosis of bipolar disorder was 12.2 years (range, 0-45). As shown in the table below (electronically copied and reproduced from sponsor’s submission), almost all of the patients in both studies had a history of at least 1 previous psychiatric hospitalization, with a majority of patients having had 2 or more psychiatric hospitalizations:

Table 17: Previous Psychiatric hospitalizations (Studies 004-301 and 004-302)

Psychiatric Hospitalizations	Study 004-301 (N=344)	Study 004-302 (N=314)
Patients with a History of Previous Hospitalization	324 (94.2%)	269 (85.7%)
No. of Previous Hospitalizations:		
0	20 (5.8%)	45 (14.3%)
1	30 (8.7%)	51 (16.2%)
2-5	102 (29.7%)	117 (37.3%)
6-10	98 (28.5%)	59 (18.8%)
>10	94 (27.3%)	42 (13.4%)

6.3.1.2.4 Smoking and Pulmonary History

A total of 787 patients, the majority of whom were smokers (78.9%), were enrolled and received either *Staccato* Placebo or *Staccato* Loxapine in the Phase 2 and Phase 3 studies, as shown in the Table below (electronically copied and reproduced from sponsor's pre-meeting package submission):

Table 18: Clinical Studies in Agitated Patients

Study No./Phase	Psychiatric Condition	No. of Patients	No. of Doses	Current Smokers
004-301 / Phase 3	Schizophrenia	344	1-3 doses, as required	281/344 (81.7%)
004-302 / Phase 3	Bipolar I disorder	314	1-3 doses, as required	234/314 (74.5%)
004-201 / Phase 2	Schizophrenia or schizoaffective disorder	129	Single-dose	106/129 (82.2%)

The sponsor further notes that ~22% had ≥ 20 pack-years of cigarette use. According to the sponsor, none of the patients with a ≥ 20 pack-year history of cigarette use had an airway adverse event. Thus, the sponsor concludes that smoking per se (even heavy smoking) did not appear to confer a significant risk of an airway adverse event.

With respect to pre-existing pulmonary conditions, patients were excluded as follows:

Studies 301 / 302:

- *Clinically significant acute or chronic pulmonary disease (eg, clinically apparent asthma, chronic bronchitis, emphysema)*

Study 201:

- *A history of acute or chronic pulmonary disease that precluded administration of Staccato Loxapine (asthma, bronchitis, emphysema)*

The sponsor reports that 11 patients were excluded from these studies at enrollment due to clinically active airway disease (10 patients with asthma and one patient was excluded with emphysema) based on these exclusion criteria. Thus, the sponsor argues that patients enrolled in these studies were representative of the patients most likely to be treated in the clinical setting.

The sponsor further argues that, since the majority of the patients were smokers, it is reasonable to expect that some of these patients would have had a degree of respiratory impairment at baseline. Therefore, the sponsor conducted a review of the medical histories for enrolled patients across the 3 efficacy studies and found that 103 of 787 patients had a history of respiratory illness or disease, including asthma and/or COPD. Of these 103 patients, 52 subjects (7%) had a history of asthma or COPD. Of the asthma and COPD subjects, 17 received *Staccato* Placebo and 35 received at least one dose of *Staccato* Loxapine. The sponsor notes that none of the 52 patients with a medical history of asthma or COPD had an airway adverse event and none required intervention with a bronchodilator following dosing with *Staccato* Loxapine.

Reviewer Comments: The sponsor has submitted a listing of the subjects in the three efficacy studies with pulmonary medical history. A careful review of this listing reveals that there were actually only 90 patients (not 103) who had a total of 103 conditions listed as respiratory illness or disease. The conditions listed as history of respiratory illness or disease include positive Tb test, pneumonia, URI, cough, bronchitis (not active at present), bronchitis (no current symptoms), episode shortness of breath while running, smoking, smoker's cough, unknown lung infection, collapsed lung, sleep apnea, and point tenderness in right anterior lower chest. On my review of the listing, 50 subjects (not 52) were listed as having asthma or COPD (three subjects were listed as having both asthma and COPD, so two of the three may have been counted twice). Of the 50 asthma and COPD subjects, 6 had childhood asthma, 1 was reported to have mild asthma (no current symptoms), 1 had asthma not clinically significant or clinically apparent, 1 had asthma not clinically apparent, 1 had history of asthma (not clinically apparent), 1 had asthma 1971, 1 had asthma (8/2006), 1 had asthma (1993), 1 had asthma – UNK-1978 – UNK 1992, and 1 had asthma – no symptoms in many years. Of the remaining patients with asthma or COPD, 6 had asthma (or history of asthma) which was described as resolved. The remaining 29 subjects had asthma or COPD described as

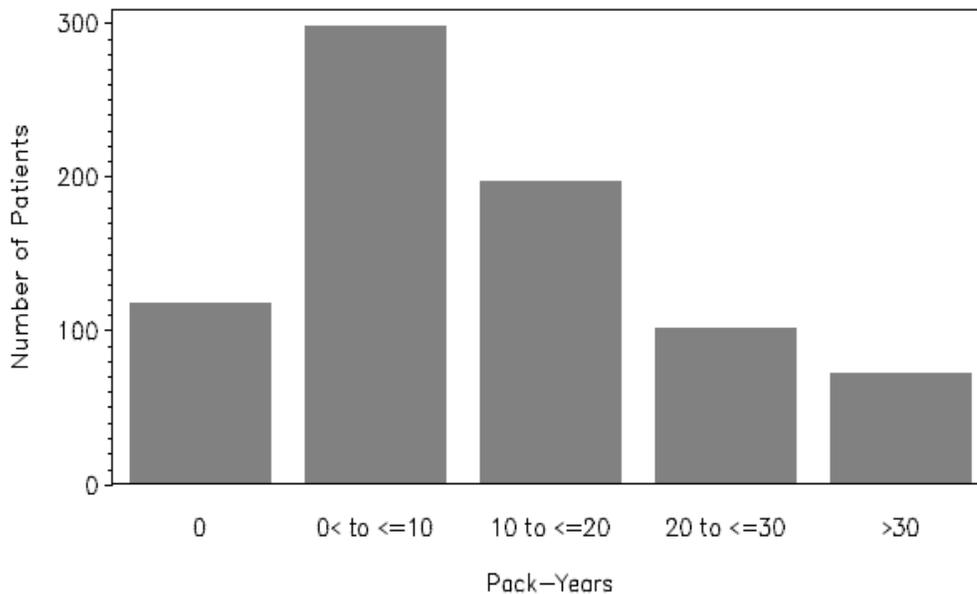
stable. Eleven of these 29 patients received placebo, leaving 18 subjects with stable asthma or COPD who received Staccato Loxapine.

It is not clear how the diagnosis of asthma or COPD was made in these patients. A remote history of “asthma” in childhood or in association with an acute respiratory illness is not sufficient for a true diagnosis. For COPD, diagnosis is made by spirometry evaluation demonstrating obstructive airway disease that is not fully reversible by bronchodilators.

Therefore, this reviewer does not consider the sponsor’s argument as conclusive proof that subjects with a true diagnosis of asthma or COPD may be safely administered ADASUVE. The listing also raises questions about whether a history of asthma or COPD can be accurately diagnosed in the intended patient population in an acute setting.

In addition, although the sponsor claims that a high percentage of subjects in the pivotal studies smoke (and are therefore representative of the intended treatment population, most of whom smoke), only 22.1% of the controlled studies in agitated patients population had ≥ 20 pack-years of cigarette abuse. As shown in the figure below (electronically copied and reproduced from sponsor’s submission), many had a less than 10 pack-year history, which, for the purposes of clinical trials in asthma and COPD, is generally classified with nonsmokers.

Figure 5: Smoking History in Pack-Years (Controlled Studies in Agitated Patients Population)



Thus, it is still not clear that the intended treatment population was adequately characterized in the pivotal trials. Patients with clinically significant acute or chronic pulmonary disease were excluded from the trials. In addition, the controlled conditions of the clinical trials allowed for careful screening of patients for underlying pulmonary disease and careful instructions for use of the inhaler. In a clinical setting in which an

acutely agitated patient presents to an emergency room and where medical history may not be known, careful screening and instructions to patients prior to administration of Staccato Loxapine may not be possible.

6.3.2 Sponsor's Argument #3, Part 2: Staccato Loxapine was Well Tolerated

The sponsor argues that *Staccato* loxapine was well-tolerated in the patients studied in the pivotal trials and that pulmonary toxicity is not associated with the use of loxapine inhalation powder in healthy subjects, based on the following 3 lines of evidence:

1. Analysis of all safety data following administration of *Staccato* Loxapine in Study **004-104**, including a blinded independent assessment of the spirometry tracings, does not demonstrate treatment-related bronchospasm, and suggests that the categorical decreases in FEV₁ are most likely attributable to variations in testing effort. The sponsor uses the following observations to support this conclusion:
 - The sponsor reports that a detailed case review of each subject with a $\geq 10\%$ decrease in FEV₁ from baseline shows, in each case, one or more features that were inconsistent with bronchospasm and/or provided an alternate explanation. Independent expert review of the spirometry tests finds no evidence for new treatment-related obstructive defects on spirometry tracings in these individuals with decreases in FEV₁ $\geq 10\%$. Additionally, no respiratory adverse events or significant changes in respiratory rate or O₂ saturation were observed.
 - There is a high degree of variability observed across the time points in the FEV₁ data both within and between individual subjects. For each subject, the variability seems to be greater when treated with loxapine as compared to placebo. Further, the time course of decreases in FEV₁ $\geq 10\%$ in subjects following *Staccato* Loxapine is consistent with the time course of sedation (measured by Visual Analog Scale). Also corresponding to the time course of sedation is an increase from baseline in mean FEV₁/FVC, a signal of reduced testing effort.
2. Review of the large safety database across the development program demonstrates a very low incidence of airway-related adverse events that could be related to the use of *Staccato* Loxapine.
3. In inhalation toxicology studies in rats and dogs, there were no drug-related findings in respiratory issues.

The data and evaluation used by the sponsor in support of each of the above arguments are summarized in the following sections:

6.3.2.1 Risk of Pulmonary Toxicity in Healthy Subjects (Study 004-104)

The sponsor suggests that the possibility of variable test efforts in the *Staccato* Loxapine pulmonary safety studies may have been exacerbated by prolonged and intensive testing after both Dose 1 and Dose 2, and by the need for 16 post-baseline tests in each of two

treatment periods (crossover study). The sponsor points out that American Thoracic Society/European Respiratory Society (ATS/ERS) guideline require a minimum of 3 acceptable blows into the spirometry machine, from which the highest FEV₁ and FVC are selected. In accordance with these guidelines, subjects in Study **004-104** performed an average of 4 efforts per test. The average number of exhalations performed by subjects from baseline to 8 hours was 32, and the average number following Dose 2 was 36, for an average of approximately 68 forced exhalations for each treatment period. In addition, the sponsor suggests that the possibility of suboptimal test efforts was a particular concern regarding subjects on the day they received loxapine, a known sedating medication.

To investigate this further and in response to the Agency's concerns, the sponsor initiated an external blinded review of the spirometry results from Study **004-104** which was conducted by an independent pulmonologist expert (James Donohue, MD, FCCP, Division Chief, Pulmonary Diseases and Critical Care Medicine, University of North Carolina).

In this placebo-controlled crossover study, healthy subjects were randomized to receive two 10-mg doses of *Staccato* Loxapine in 1 study period and 2 doses of *Staccato* Placebo in the other study period. Doses were administered at Hours 0 and 8 of each 32-hour study period, and in each study period spirometry testing was conducted immediately before the first dose and at 0.25, 0.5, 1, 2, 4, 6, 8, 8.25, 8.5, 9, 10, 12, 14, 16, 24, and 32 hours after the first dose.

The sponsor argues that the changes from same-period baseline FEV₁ were very small after either loxapine or placebo treatment, and there was no difference between treatments. The largest change after loxapine was -0.104 L (-0.178, -0.031) at 0.25 hours after Dose 2, and the largest change after placebo was -0.103 L (-0.181, -0.024) at 0.5 hours after Dose 2 [LSmean (90% LSmean CI)]. The largest treatment difference (loxapine - placebo) was 0.0917 L (-0.028, 0.212) at 2 hours after Dose 2 [LSmean (90% LSmean CI)].

In the 8 hours after each dose, the same percentage of subjects had a $\geq 10\%$ FEV₁ decrease from same-period baseline after loxapine treatment and placebo treatment (26.9%). Decreases of $\geq 15\%$ occurred in more subjects after loxapine treatment than after placebo treatment (loxapine 19.2%, with 1 of them having a $\geq 20\%$ decrease; placebo, 3.8%, none with a $\geq 20\%$ decrease). No subject had a maximum decrease of $\geq 25\%$ after either treatment.

The sponsor also argues that there was no identifiable relationship between the time of the first FEV₁ decrease $\geq 10\%$ and the time of placebo treatment, a finding that supports the argument that such FEV₁ decreases after placebo treatment are not due to the development of a new obstructive defect.

In addition, the sponsor argues that there were no AEs that suggested an effect on airways. After treatment with *Staccato* Loxapine, there were no SAEs, severe AEs, or

AEs leading to discontinuation, and the only AE reported for more than 2 subjects was mild or moderate dysgeusia.

6.3.2.1.1 Case Review of Subjects with a Decrease in FEV₁ ≥ 10%

For each of the 7 subjects with a decrease in FEV₁ ≥ 10% following *Staccato* Loxapine administration, the spirometry data at the time of the maximum FEV₁ decrease are summarized in the table below (electronically copied and reproduced from sponsor's submission) along with other relevant clinical parameters (respiratory rate, O₂ saturation, and airway adverse events), and key findings which the sponsor argues suggest that the cause was not bronchospasm. The table includes the outcome of the blinded review of all spirometry tracings for each case conducted by the independent pulmonologist.

As shown in the table, the pulmonologist noted several cases in which FEV₁ and FVC decreased in proportion (with preserved or increased FEV₁/FVC ratios), consistent with decreased efforts, and no specific evidence for treatment-related obstruction. One subject had variable flattening of the late expiratory flow loops, but this abnormality was present at baseline. Findings were similar for placebo.

Table 19: Subjects with Maximum FEV₁ Decrease of ≥10% following *Staccato* Loxapine (Study 004-104; Spirometry Population)

Subject No.:	01-008	01-014	01-016	01-017	01-022	01-023	01-029
Max FEV ₁ decrease	17%	15%	21%	10%	18%	10%	19%
Time after Dose 1 to max FEV ₁ decrease	10 h	16 h	8.25 h	0.25 h	16 h	12 h	8.5 h
Time of next FEV ₁ within 10% of baseline	12 h ^a	24 h ^a	8.5 h ^a	0.5 h ^a	32 h	14 h ^a	9 h ^a
FEV ₁ /FVC at time of max FEV ₁ decrease ^b	0.84	0.79	0.81	0.86	0.72	0.85	0.89
FEV ₁ /FVC at same-period baseline	0.84	0.85	0.78	0.82	0.81	0.87	0.82
Max FEV ₁ decrease was during notable sedation	Yes	Yes	No	Yes	No	No	Yes
Corresponding RR or O ₂ saturation change	No	No	No	No	No	No	No
Corresponding airway AE	No	No	No	No	No	No	No
Key Findings:	-Large FEV ₁ fluctuations during treatment period suggest highly variable testing effort -Maximum decrease in FEV ₁ was associated with preserved FEV ₁ /FVC -Max FEV ₁ decrease occurred at a time of notable sedation	-The only ≥10% decrease in FEV ₁ occurred at 8 h after Dose 2 -Max FEV ₁ decrease occurred at a time of notable sedation -Flow-volume loops at 16 h show evidence of incomplete expiratory effort	-Max decrease in FEV ₁ was associated with increase in FEV ₁ /FVC ratio compared to baseline -Quick recovery to within 10% of baseline FEV ₁ within 15 min -Evidence of incomplete effort on spirometry tracing	-The only ≥10% decrease was associated with an increased FEV ₁ /FVC ratio vs. baseline -No recurrence of FEV ₁ decrease after Dose 2 -FEV ₁ highly variable from time 0.25 to 4 h, ranging from ↓10% to ↑12.5%	-The only ≥10% decrease occurred at 8 h after Dose 2 -A change of the same magnitude was observed on placebo day, but at a different time (1 h after Dose 1) -Flow-volume loops showed variable contours within individual tests (can't be treatment effect)	-The only ≥10% decrease occurred at 4 h after Dose 2	-Max FEV ₁ decrease was associated with an increase in FEV ₁ /FVC and occurred at a time of notable sedation -Quick recovery to within 10% of baseline FEV ₁ within 30 min
New obstructive defect based on blinded expert of review of spirometry tracings (See Appendix 3)	No	No	No	No	Abnormal expiratory tracings and ↓FEV ₁ /FVC—were present at baseline	No	No

FEV₁=forced expiratory volume in 1 second; FVC=forced vital capacity; max=maximum; RR=respiratory rate; O₂ saturation=oxygen saturation by pulse oximetry

a. This was the next spirometry test after the maximum FEV₁ decrease.

b. Stable or increased FEV₁/FVC ratio suggests suboptimal testing effort as the source of the decrease in FEV₁ (see Section 2.3)

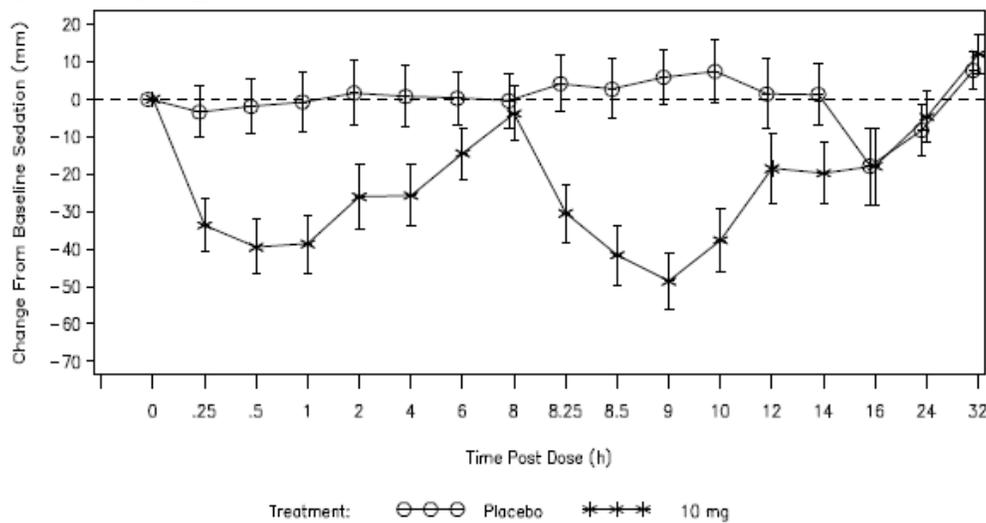
Thus, the sponsor argues that, for the 7 cases in which there was at least one decrease in $FEV_1 \geq 10\%$ after *Staccato* Loxapine, there was (1) no specific evidence for development of a new obstructive defect, based on the contour of the spirometry flow loop, (2) no AEs that suggested an effect on airways, and (3) no clinically significant changes in respiratory rate (or O_2 saturation) at the time of $\Delta FEV_1 \geq 10\%$. Furthermore, the sponsor argues that each subject had one or more features that either were inconsistent with drug-induced bronchospasm or provided an alternate explanation. The sponsor cited the following as examples of such findings: the maximum decrease in FEV_1 occurred long after dosing; the maximum decrease in FEV_1 occurred at a time of notable sedation; the time to recovery of FEV_1 was short; the spirometry tracing showed specific evidence of incomplete effort, an increase in the FEV_1/FVC ratio compared with baseline suggested incomplete effort; and/or there was evidence of high test to test variability.

6.3.2.1.2 Sedative Effects, High Variability in FEV_1 Data and Time to decreases in $FEV_1 \geq 10\%$

For the active treatment, the sponsor argues that the sedative effects of loxapine are a likely source of variability. Since spirometry testing is effort dependent, the sponsor believes that sedation associated with *Staccato* Loxapine treatment is highly likely to affect spirometry assessments. The sponsor points out that in the Phase 1 dose escalation study (Study **004-101**), a single administration of 10 mg was reported to be the maximum tolerated dose because of the high incidence of dizziness and somnolence. The sponsor also reports that, during the course of the pulmonary safety study in healthy subjects (**004-104**), the investigator made several comments to the medical monitor regarding the challenges of performing optimal spirometry tests in sleepy subjects.

As reported in the Clinical Study Report, clinically significant sedation as assessed by the Visual Analog Scale (VAS) was apparent after each dose of *Staccato* Loxapine, as shown in the figure below (electronically copied and reproduced from sponsor's submission):

Figure 6: Sedation Change from Same-Period Baseline, by Treatment (Study 004-104, Spirometry Population)



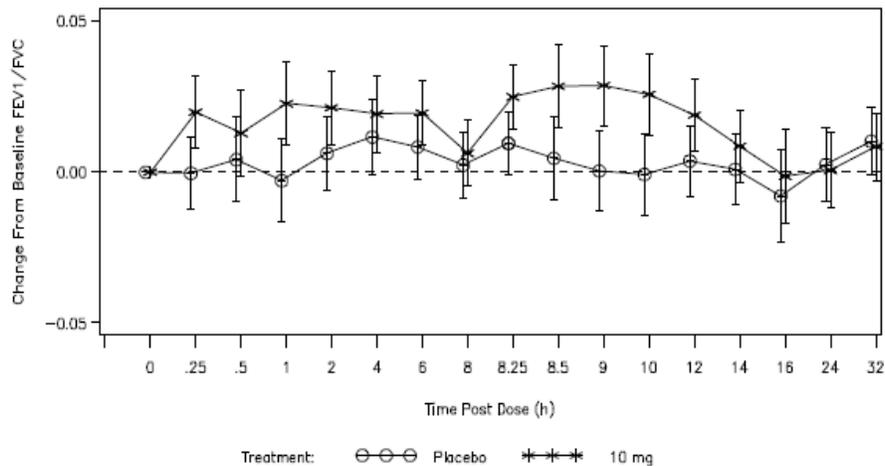
LSMean, 90% LSMean CI

Program Name:f-3-19.sas Date:19AUG2009: 7:35:41 Source Data:Table 3.25

LSmean and 90% LSmean CI: a negative excursion indicates a sedative effect

The sponsor concludes that the possibility of a sedative effect of loxapine on performance of spirometry tests is supported by the group data for the FEV₁/FVC ratio. LSmean FEV₁/FVC increased from same-period baseline at 15 of the 16 assessment times after loxapine treatment, as well as at 12 of the 16 assessment times after placebo treatment, as seen in the figure below (electronically copied and reproduced from sponsor's submission). These increases, suggestive of reduced testing effort, were larger after loxapine treatment than after placebo treatment, particularly after Dose 2. The sponsor argues that, by comparing the two figures, it is apparent that the time course of the FEV₁/FVC findings matched the time course of sedation.

Figure 7: FEV₁/FVC Change from Same-Period Baseline, by Treatment (Study 004-104, Spirometry Population)



LSMean, 90% LSMean CI
 Program Name:f-3-63.sas Date:19AUG2009: 7:36:44 Source Data:Table 3.18
 LSmean and 90% LSmean CI

The sponsor also notes that, for individual FEV₁ changes following administration of *Staccato* Loxapine, there is a high degree of variability observed across the time points in the FEV₁ data, both within and between individual subjects. For each subject, the range of FEV₁ values over the 16 spirometry assessments (difference between an individual's most negative and most positive FEV₁ percent change from baseline value on each day) was on average 37% greater on loxapine day than that on placebo day (average negative and positive percentage FEV₁ change across all subjects). The positive and negative changes from baseline FEV₁ were larger with *Staccato* Loxapine than *Staccato* Placebo (ie, a maximum positive change of +6.3% for loxapine compared with +4.9% for placebo; a maximum negative change of -8.6% for loxapine compared with -7.1% for placebo). Thus loxapine produced greater variability in FEV₁, rather than simply a larger decrease in FEV₁.

6.3.2.1.3 Overall Experience with *Staccato* Loxapine in the Clinical Development Program: Sponsor's Analysis of the Safety Database

The sponsor argues that, as shown in the table below, a review of the safety database established during the clinical development program for *Staccato* Loxapine reveals very few airway-related adverse events have been reported in healthy subjects in Phase 1 studies and in patients in the Phase 2 and 3 studies who were treated with *Staccato* Loxapine. The most frequent airway-related adverse event was cough which occurred at an incidence of 19/1095 ie 1.7%. Cough was mild in 18/19 cases and moderate in one case; no treatment was required in any of the cases. Specifically, in agitated patients with schizophrenia and bipolar disorder, airway-related adverse events were reported in only 4 subjects (0.8%).

Table 20: Airway-Related Adverse Events in *Staccato* Loxapine Safety Database (Electronically copied and reproduced from sponsor’s submission)

ISS Analysis Population	Study Number	Total <i>Staccato</i> Loxapine Subjects (N=1,095)	Airway-Related Adverse Events*
CSAP: Controlled Studies in Agitated Patient Population	004-201, 004-301, 004-302	524	Wheezing: 2 (0.4%) Bronchospasm: 1 (0.2%) Cough: 1 (0.2%)
HV: Healthy Volunteer Population	004-101, 004-103, 004-104, 004-106, 004-107	177	Cough: 13 (7.3%)
Subjects on stable antipsychotic regimens	004-102	24	Cough: 3 (12.5%)
Patients with migraine headache (in-clinic)	104-201	129	Cough: 1 (0.8%)
Patients with migraine headache (out-patient)	104-202	241	Cough: 1 (0.4%)

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

Reviewer’s Comment: It is noteworthy that over 7% of the healthy volunteer population and 12.5% of the subjects on stable antipsychotic regimens developed cough. Although the cough was generally classified as mild, cough can be a manifestation of reactive airway disease (i.e., bronchospasm). No further information on the characterization of cough in these subjects is available.

6.3.2.2 Airway-Related Adverse Reactions in Agitated Patients (Pivotal Trials)

The sponsor argues that there were few adverse events in the Phase 2 and 3 studies that suggested an effect on airways. In a total of 524 patients who received 756 doses of ADASUVE in these studies, 4 events related to bronchospasm were reported (all of which were reported in Study **004-301**), as shown in the table below (electronically copied and reproduced from sponsor’s pre-meeting package submission). No airway adverse events were reported for patients who received *Staccato* Placebo.

Table 21: Airway Adverse Events in Agitated Patients

Airway Adverse Event* Preferred Term, n (%)	Placebo (N=263)	<i>Staccato</i> Loxapine Dose		All <i>Staccato</i> Loxapine (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

Of the 4 events, 3 were considered possibly or probably related to treatment and one was considered unrelated. The sponsor notes that none of the previously noted 52 subjects (see *Reviewer Comments*: page 32-33) with asthma and COPD recorded in the medical

history had a respiratory adverse event and none required intervention with a bronchodilator following dosing with either *Staccato* Placebo or *Staccato* Loxapine.

6.3.2.2.1 Description of individual events in pivotal trials

Patient 19-405 (10 mg, female, 59 years) experienced moderate bronchospasm that started 5 minutes after administration of Dose 1, resolved with use of an inhaled bronchodilator, and was judged to be probably treatment related. This event led to withdrawal of the patient from the study.

Patient 04-290 (5 mg, male, 32 years) had mild wheezing that was judged to be probably treatment related. The patient received a single dose of *Staccato* Loxapine on May 7 at 18:12. The wheezing started the next day, May 8 (onset time not specified), and resolved without intervention on May 10.

Patient 24-350 (5 mg, female, 42 years) had mild wheezing that was judged to be unrelated to treatment. The patient received doses of *Staccato* Loxapine on April 22 at 13:45 and 21:40. The wheezing started the next day, April 23, at 13:45; it resolved without intervention on April 24 at 10:00.

Patient 06-417 (10 mg, male, 42 years) experienced mild cough after Dose 1 was administered and resolved without intervention 2 minutes later. It was judged to be possibly treatment related. The patient later received a second dose of *Staccato* Loxapine (15.4 hours after Dose 1), and no recurrence of the cough was reported.

The sponsor argues that, of the treatment-related events in these 4 patients, one event was temporally unrelated to administration and resolved without intervention, one event was a non-serious cough, and one event resolved after the use of an inhaled bronchodilator. Therefore, the sponsor calculates that the rate of occurrence of airway adverse events judged to be related to *Staccato* Loxapine in the intended population was 3/756 (0.4%) exposures. The sponsor further points out that there was no evidence for additional risk of an airway-related adverse event following a second or third dose of *Staccato* Loxapine because, of the above events, only 1 occurred after Dose 2 of *Staccato* Loxapine, and it was 16 hours after the last dose and scored as unrelated.

Thus, the sponsor concludes that, “The assessment of the adverse event profile of the intended treatment population, the majority of whom were smokers, demonstrates a low risk for airway-related adverse events associated with either *Staccato* Loxapine or *Staccato* Placebo. Patients reporting a history of asthma, COPD, or other pulmonary conditions did not have any respiratory adverse events associated with treatment.

Reviewer Comments: As noted in above reviewer comments, it is not clear that patients in the pivotal trials truly represented the intended treatment population since patients with clinically significant acute or chronic pulmonary disease were excluded from the trials. Despite this exclusion, after treatment with Staccato Loxapine, two patients (0.4%) developed wheezing, one patient (0.4%) developed cough, and one patient (0.4%)

developed bronchospasm requiring albuterol treatment and discontinuation from the trial. Furthermore, as noted above (see Reviewer Comments: pages 32-34), those subjects included in the study with history of asthma or COPD may have been inaccurately assessed, and the controlled conditions of the clinical trials allowed for careful screening of patients for underlying pulmonary disease and careful monitoring post-dose.

Since the mechanism by which Staccato Loxapine may cause respiratory adverse reactions is unknown, it is not possible to conclude that a respiratory adverse reaction is not related to Staccato Loxapine based on time of occurrence post-dose. Furthermore, the fact that only 1 respiratory adverse reaction occurred after Dose 2 of Staccato Loxapine is not reassuring. The patient who developed treatment-induced bronchospasm (Patient 19-405) was withdrawn from the study, and 1 patient who developed wheezing (Patient 04-290) was very much improved in agitation scores after Dose 1 and so did not require Dose 2. Thus, it is unknown whether these two patients would have suffered a more severe reaction if they had received a second dose.

6.3.2.3 Animal Inhalation Toxicology Studies

In order to support the safety of inhalation delivery of loxapine, inhalation toxicology studies were performed in the rat and dog with repeated daily exposure to loxapine aerosol for 14 and 28 days, respectively. In the rat, effects on respiratory tissues were limited to minimal squamous metaplasia of the larynx; this change was considered a nonspecific effect due to particle impaction and its incidence was greatly reduced by the end of the 14-day recovery period. Beagle dogs with repeated inhalation exposure to loxapine showed no macroscopic or microscopic effects on the respiratory tissues.

The sponsor concludes that the doses administered to rats and dogs were considered to have adequately assessed the potential for local toxicity in humans.

6.3.2.4 Sponsor's Conclusion

Based on the above data, the sponsor believes that the results support the conclusion that the categorical decreases in FEV₁ in healthy subjects administered *Staccato* Loxapine in Study **004-104** are attributable to variations in testing effort, associated with intensive testing regimen and the administration of a sedating drug, rather than an adverse effect on airways. The sponsor concludes that there is a very low risk of pulmonary toxicity associated with the use of loxapine inhalation powder.

*Reviewer Comments: Despite the sponsor's arguments, the Division remains concerned that the true severity and extent of pulmonary toxicity in the intended treatment population is unknown. The fact remains that, in Study **004-104**, more healthy subjects who received *Staccato* Loxapine had drops in FEV₁ of at least 15% after Dose 1 or Dose 2 compared to those who received Placebo, as shown in the table below:*

Table 22: Maximum FEV₁ Decrease from Same-Period Baseline in the 8 Hours after Dosing – Study 004-104

	Maximum FEV ₁ decrease in the 8 hours after each dose ^{a,b}	Staccato Placebo (N=26)	Staccato Loxapine (N=26)
After either dose	≥10%	7	7
	≥15%	1	5
	≥20%	0	1
After Dose 1	≥10%	4	5
	≥15%	1	2 ^c
	≥20%	0	0
After Dose 2	≥10%	5	6
	≥15%	0	5
	≥20%	0	1

Table presents the number of subjects.

- This analysis was based on the 8 hours after each dose (ie, Hours 0.25 to 16) and excludes Hours 24 and 32. However, these two 8-hour windows included all subjects with an FEV₁ decrease of ≥15%.
- FEV₁ categories are cumulative (eg, a subject with a maximum decrease of 21% would be included in the ≥10%, ≥15%, and ≥20% categories)
- Subject 01-008 had a maximum decrease of 14.5% after Dose 1 of loxapine, which was rounded to 15% and resulted in his inclusion in this category. (His maximum decrease after Dose 2 of loxapine was 17%.)

Furthermore, one subject in this study (Subject 01-011) withdrew consent after a single dose of Staccato Loxapine. This subject was randomized to receive two doses of loxapine in Period 1 and two doses of placebo in Period 2. The subject actually received Dose 1 of Staccato Placebo in error and withdrew consent after receiving a single dose of Staccato Loxapine as Dose 2. After the single dose of loxapine, the subject had a 24% decrease in FEV₁, so it is unknown if a further decrease in FEV₁ would have occurred if the subject had received two doses of Staccato Loxapine. In addition, another subject (Subject 01-003) who received two doses of placebo in Period 1 was discontinued from the study before receiving Staccato Loxapine in Period 2 because he no longer met the inclusion criteria (i.e., the subject's FEV₁ was <85% of predicted). Thus, it is unknown whether this patient would have had further decreases in FEV₁ after dosing with Staccato Loxapine and calls into question whether in an acute clinical setting in the absence of frequent spirometry assessments patients at increased risk of pulmonary toxicity can be readily identified.

The fact that patients were sedated to the point that spirometry efforts may have been effected is concerning. This implies that the full extent of pulmonary toxicity was not conclusively identified in this study. In a clinical setting, sedation may suppress respirations, and identifying respiratory signs and symptoms in sedated schizophrenic

and bipolar patients may prove difficult. It is conceivable that the small number of reported airway adverse events in subjects treated with Staccato Loxapine in this study could be due in part to the failure of sedated subjects to recognize and report respiratory symptoms.

In the studies in healthy volunteers, subjects were excluded if they reported any tobacco use in the past year, calling into question whether the low incidence of respiratory adverse reactions would also be expected in patients with schizophrenia or bipolar disorder, most of whom smoke. Yet, ~7% of the healthy volunteer population in the phase 1 and 2 studies, and 12.5% of subjects on stable antipsychotic regimens (Study 004-102) developed cough after receiving Staccato Loxapine, a symptom which can be due to underlying bronchospasm.

Thus, the true extent and severity of respiratory compromise in the healthy volunteer population and how this relates to the intended population may not be fully appreciated.

6.4 Sponsor's Argument #4: There is No Risk of Pulmonary Toxicity Related to Use of the Device Itself

The sponsor proposes three lines of evidence to demonstrate that there is no risk of pulmonary toxicity related to the device itself:

1. Analysis of all the safety data following administration of *Staccato* Placebo in Study 004-104, including a blinded independent assessment of the spirometry tracings, does not demonstrate pulmonary toxicity, and suggests that the categorical decreases in FEV₁ are most likely attributable to variations in testing effort.
2. Review of the large placebo safety database from the Phase 2 and Phase 3 studies of patients with agitation provides no evidence of airway-related adverse events that could be related to the use of the device.
3. The placebo device is the same device as the active device without any drug. There are no binders or excipients in the placebo device. The physical analysis of the output (or airstream) from the device demonstrates that it does not contain substances from the device at any level of significance that would raise a concern for pulmonary toxicity.

6.4.1 Evaluation of Spirometry and Safety Assessments in Healthy Subjects Treated with Staccato Placebo (Study 004-104)

The sponsor argues that the decreases in FEV₁ after treatment with *Staccato* Placebo are not sufficient to discriminate between obstruction and reduced effort. The sponsor bases this conclusion on the following observations:

- As is the case with *Staccato* Loxapine treatment, a detailed case review of placebo data from each subject with a $\geq 10\%$ decrease in FEV₁ from baseline shows, in each case, one or more features that were inconsistent with bronchospasm and/or

provided an alternate explanation. Independent expert review of the spirometry tests finds no evidence for new treatment-related obstructive defects on spirometry tracings in these individuals with decreases in FEV₁ ≥ 10%. Additionally, no respiratory adverse events or significant changes in respiratory rate or O₂ saturation were observed.

- Although spirometry testing was performed in accordance with ATS criteria, there was a high degree of variability observed across time points in the FEV₁ data both within and between individual subjects following placebo treatment, and no consistent pattern can be identified in the time of occurrence of decreases in FEV₁ ≥ 10% relative to the administration of either of the 2 doses.

6.4.1.1 Case Review of Subjects with a Decrease in FEV₁ ≥ 10%

The sponsor argues that, for each of the 7 spirometry-population subjects with a decrease in FEV₁ ≥ 10% following *Staccato* Placebo administration, the spirometry data at the time of maximum FEV₁ decrease along with other relevant clinical parameters (respiratory rate, O₂ saturation, and airway adverse events), suggest that the cause was not bronchospasm. The sponsor summarizes this data in the table below, which also includes the outcome of the blinded review of spirometry tracings conducted by the independent pulmonologist.

Table 23: Subjects with Maximum FEV₁ Decrease of ≥10% following *Staccato* Placebo (Study 004-104; Spirometry Population)

Subject No.:	01-002	01-010	01-015	01-016	01-017	01-022	01-024
Max FEV ₁ decrease	11%	12%	14%	12%	10%	18%	10%
Time after Dose 1 to max FEV ₁ decrease	12 h	0.5 h	32 h	8.5 h	10 h	1 h	0.25 h
Time of next FEV ₁ within 10% of baseline	14 h ^a	1 h ^a	No later test	9 h ^a	12 h ^a	4 h	0.5 h ^a
FEV ₁ /FVC at the time of max FEV ₁ decrease ^b	0.77	0.89	0.87	0.76	0.83	0.67	0.87
FEV ₁ /FVC at same-period baseline	0.71	0.86	0.83	0.77	0.86	0.73	0.92
Corresponding RR or O ₂ saturation change	No	No	No	No	No	No	No
Corresponding wheezing, dyspnea, cough	No	No	No	No	No	No	No
Key findings:	-The only ≥10% decrease occurred at 12 h (4 h after Dose 2) and was associated with an increase in FEV ₁ /FVC ratio compared to baseline	-The only ≥10% decrease occurred at 0.5 h and was associated with increase in FEV ₁ /FVC ratio compared to baseline. There was no corresponding FEV ₁ change seen after Dose 2	-Max decrease in FEV ₁ was at 32 h after Dose 1 (24 h after Dose 2), and was associated with increase in FEV ₁ /FVC compared to baseline.	-The only ≥10% decrease occurred at 8.5 h (0.5 h after Dose 2); FEV ₁ returned to within 10% of baseline by 0.5 h later without intervention.	-There was a 9.5% decrease at 10 h (2 h after Dose 2); included in 10% category only because of rounding	-FEV ₁ was highly variable throughout testing protocol, ranging from ↓17.9% to ↑10.3% -Flow-volume loops show variable contours within individual tests (can't be treatment effect)	-There was a 9.5% decrease at 0.25 h after Dose 1; included in 10% category only because of rounding -Note that the FEV ₁ after Dose 2 remained within 0.9% of baseline in the 30 min after that dose
New obstructive defect based on blinded expert review of spirometry tracings (See Appendix 3)	No	No	No	No	No	Abnormal expiratory tracings and ↓FEV ₁ /FVC – were present at baseline	No

FEV₁=forced expiratory volume in 1 second; FVC=forced vital capacity; max=maximum; RR=respiratory rate; O₂ saturation=oxygen saturation by pulse oximetry

^aThis was the next spirometry test after the maximum FEV₁ decrease.

^bA stable or increased FEV₁/FVC ratio suggests suboptimal testing effort as the source of the decrease in FEV₁ (see Section 2.3)

As shown in the table, the pulmonologist noted several cases in which the FEV₁ and FVC decreased in proportion (with preserved or increased FEV₁/FVC ratios) consistent with decreased efforts and no specific evidence for treatment-related obstruction. One subject had variable flattening of the late expiratory loops, but this was present at baseline.

The sponsor notes that, in all 7 cases in which there was at least one decrease in FEV₁ ≥ 10% after *Staccato* Placebo, there was (1) no specific evidence for development of a new obstructive defect, based on the contour of the spirometry flow-volume loop, (2) no AEs that suggested an effect on airways, and (3) no clinically significant changes in O₂ saturation or respiratory rate at the time of ΔFEV₁ ≥ 10%. Furthermore, the sponsor argues that each subject had one or more features that either were inconsistent with treatment-induced bronchospasm or provided an alternate explanation. Examples of such findings are as follows: the maximum decrease in FEV₁ occurred long after dosing; the time to recovery of FEV₁ was short; the spirometry tracing showed specific evidence of incomplete effort, an increase in the FEV₁/FVC ratio compared with baseline suggested incomplete effort; and/or there was evidence of high test to test variability.

In addition, the sponsor notes that, in this crossover study, 4 of the 7 subjects with ≥10% decreases in FEV₁ after placebo did not have any such changes after loxapine. The sponsor reasons that any true airway effects of placebo administration should have been replicated on the other treatment day.

6.4.1.2 High Variability in FEV₁ data and Time to Decreases in FEV₁ ≥ 10%

The sponsor argues that, following administration of *Staccato* Placebo, there is a wide range of variability in FEV₁ data across time points both within and between individual subjects. The sponsor can identify no consistent pattern in the time of occurrence of decreases in FEV₁ ≥ 10% relative to either the first or second inhalation through the *Staccato* Placebo device. As shown in the table below (electronically copied and reproduced from sponsor's submission), for the 7 subjects in the Spirometry Population who had one or more occurrences of a decrease of FEV₁ ≥ 10% after *Staccato* Placebo, the time of first occurrence ranged between 0.25 hrs after Dose 1 to 4 hrs after Dose 2. The time of maximum FEV₁ decrease also occurred at variable times with no evidence of a correlation to administration of the doses.

Table 24: Time to First and Maximum Decrease $\geq 10\%$ in Healthy Subjects Administered *Staccato* Placebo (Study 004-104; Spirometry Population)

Subject No.	First \downarrow FEV ₁ $\geq 10\%$		Maximum \downarrow FEV ₁ $\geq 10\%$	
	Time (hours)	% Change from Baseline	Time (hours)	% Change from Baseline
01-002	4 h after Dose 2	- 10.5	4 h after Dose 2	- 10.5
01-010	0.5 h after Dose 1	- 12.2	0.5 h after Dose 1	- 12.2
01-015	4 h after Dose 1	- 9.9	24 h after Dose 2	- 14.1
01-016	0.5 h after Dose 2	- 11.5	0.5 h after Dose 2	- 11.5
01-017	2 h after Dose 2	- 9.5	2 h after Dose 2	- 9.5
01-022	1 h after Dose 1	- 17.9	1 h after Dose 1	- 17.9
01-024	0.25 h after Dose 1	- 9.5	0.25 h after Dose 1	- 9.5

Note: one additional subject in the Spirometry Population, Subject 01-019, also had a decrease in FEV₁ $\geq 10\%$ 4 hours after the 2nd placebo dose. This patient was excluded from the categorical analysis of FEV₁ decreases since the patient interrupted treatment and did not receive the 2nd dose of loxapine.

6.4.2 Sponsor's Review of the Placebo Safety Database: Phase 2 and Phase 3 Studies

6.4.2.1 Low Incidence of Airway-Related Adverse Events following Placebo Administration

The sponsor notes that, as shown in the table below (electronically copied and reproduced from sponsor's submission), very few airway-related adverse events have been reported in placebo-treated healthy subjects and patients (without clinically significant airways disease) that could be related to the use of the device. In fact, the only airway-related adverse events reported in subjects who received one or more doses of *Staccato* Placebo are a few cases of cough, reported by 4/525 subjects (0.8%).

Table 25: Airway-Related Adverse Events in Placebo Safety Database

ISS Analysis Population	Study Number	Total Placebo Subjects (N=525)	Airway-Related Adverse Events* in Placebo Subjects
CSAP: Controlled Studies in Agitated Patient Population	004-201, 004-301, 004-302	263	None reported
HV: Healthy Volunteer Population	004-101, 004-103, 004-104, 004-106, 004-107	90	Cough: 2 (2.2%)
Subjects on stable antipsychotic regimens	004-102	8	None reported
Patients with migraine headache (in-clinic)	104-201	39	Cough: 1 (2.6%)
Patients with migraine headache (out-patient)	104-202	125	Cough: 1 (0.8%)

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

6.4.2.2 Low Incidence of FEV₁ Decreases in Asthma Subjects

Since it is well known that subjects with asthma are more sensitive than normal subjects to a variety of irritants and other triggers to bronchospasm, the sponsor theorizes that if the *Staccato* Placebo device was associated with a toxic or irritant effect, a higher incidence of FEV₁ decreases would be expected in asthma subjects. As shown in the table below (electronically copied and reproduced from sponsor's submission), the incidence of decreases in FEV₁ \geq 10% in asthma subjects (**Study 004-105**) after *Staccato* Placebo was lower than in the healthy subject population. The sponsor believes this finding to be consistent with the much greater experience of asthma patients in the performance of spirometry tests and inconsistent with an irritant effect of the placebo device.

Table 26: Incidence of Maximum FEV₁ Decreases (10%, 15%, or 20%) in Healthy Subjects (Study 004-104 and Asthma Subjects (Study 004-105) administered *Staccato* Placebo

	Maximum FEV ₁ Decrease from Baseline ^a	<i>Staccato</i> Placebo Treatment	
		Healthy Subjects ^b (Study 004-104) (N=26)	Asthma Patients ^c (Study 004-105) (N=26)
After either dose (ie, at any time)	\geq 10%	7 (27%)	3 (12%)
	\geq 15%	1 (4%)	1 (4%)
	\geq 20%	0 (0%)	1 (4%)

a. FEV₁ categories are cumulative (eg, a subject with a maximum decrease of 21% would be included in the \geq 10%, \geq 15%, and \geq 20% categories)

b. Analysis based on the 8 hours after each dose (ie, Hours 0.25-16) and excludes Hours 24 and 32

c. Dose 1 analysis based on Hours 0.25-10; Dose 2 analysis based on Hours 10.25-24; excludes Hour 34

6.4.3 Characterization of Device Output – Possible Emission of an Airway Irritant

The sponsor has conducted studies to fully characterize the composition of the output (airstream) from the device. The sponsor argues that, based on comparisons to published standards or industry practice, the data from those studies demonstrate that the output from the device does not contain substances from the device at any level of significance that would raise a concern for pulmonary toxicity. Furthermore, the sponsor notes that the testing demonstrates that potential contaminants from the thermite reaction are not detected in the aerosol, confirming that the heat package stays intact and that the reaction is contained within the heat package. Lastly, the sponsor points out that these studies reported in the NDA were based on testing of the aerosol from loxapine-coated devices. The sponsor states that, for the placebo device, which is a functional device without drug coating that does not generate an aerosol, there is nothing additional that could get into the warm air from the device that could be implicated in pulmonary toxicity.

6.4.4 Conclusion on Risk of Pulmonary Toxicity Related to Use of the *Staccato* Device

Thus, the sponsor concludes that there is no clear evidence of an adverse effect on pulmonary function following administration of *Staccato* Placebo and that the categorical

decreases in FEV₁ in healthy subjects administered *Staccato* Placebo are most likely attributable to variations in testing effort.

*Reviewer's Comments: It should be noted that drops in FEV₁ are usually the first evidence of respiratory insufficiency, generally occurring prior to the development of respiratory adverse events or significant changes in respiratory rate or O₂ saturation. Therefore, the absence of respiratory adverse events or significant changes in respiratory rate or O₂ saturation is not conclusive proof that there is no risk of pulmonary toxicity from the placebo device. However, the sponsor notes that a few cases of cough were noted in subjects who received *Staccato* Placebo, and cough may be indicative of underlying bronchospasm. Furthermore, the variations in testing effort makes accurate interpretation of spirometry results difficult and may explain why 4 of the 7 subjects with $\geq 10\%$ decreases in FEV₁ after placebo in Study 004-104 did not have any such changes after loxapine. Although the sponsor notes that no aerosol is generated from the placebo device, 11.5% of asthma subjects who received *Staccato* Placebo in Study 004-105 and 18 of 27 (~67%) COPD subjects who received *Staccato* Placebo in Study 004-108 had FEV₁ decrease $\geq 10\%$. Perhaps the heat generated from the inhaler played a role in the decreases in FEV₁.*

6.5 Sponsor's Argument #5: Patients with Increased Risk of Respiratory Adverse Reactions from Treatment with *Staccato* Loxapine can be effectively identified

The sponsor's argument that patients with increased risk of respiratory adverse reactions from treatment with *Staccato* Loxapine can be effectively identified is based on the sponsor's assessment of pulmonary safety in the phase 1 safety studies of subjects with asthma and COPD.

6.5.1 Airway Adverse Reactions: Phase 1 Asthma and COPD Studies

Airway adverse events and categorical decreases in FEV₁ were documented after treatment with *Staccato* Loxapine 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. Details are as follows:

6.5.1.1 Asthma:

In asthma subjects, decreases from baseline FEV₁ of $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$ occurred much more frequently in *Staccato* loxapine subjects (84.6%, 61.5%, and 42.3%, respectively) than placebo subjects (11.5%, 3.8%, and 3.8%, respectively). The maximum change from baseline FEV₁ occurred within the first 1 hour after dosing (either Dose 1 or Dose 2) in 16 of 22 *Staccato* loxapine subjects with a $\geq 10\%$ decrease in FEV₁.

In asthma subjects, bronchospasm (which includes reports of wheezing, shortness of breath, and cough) occurred in 14 (53.8%) subjects after *Staccato* loxapine and in 3

(11.5%) subjects after placebo, as shown in the table below (electronically copied and reproduced from sponsor's submission):

Table 27: Study 004-105 (Asthma) – Airway Adverse Events

Adverse Event, n (%)	<i>Staccato</i> placebo (N=26)	<i>Staccato</i> loxapine (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.

In 12 of the 14 *Staccato* loxapine 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).

Albuterol was used by a total of 14 (53.8%) asthma subjects after *Staccato* loxapine treatment (13 with bronchospasm, 1 asymptomatic) compared with 3 subjects (11.5%) after placebo. In *Staccato* loxapine subjects who received albuterol for bronchospasm, 9 of 13 (69.2%) had their FEV₁ return to within 10% of baseline documented in the subsequent 1 hour time period; the remainder had recovery to within 10% of baseline documented at later, scheduled spirometry evaluation time points.

6.5.1.2 COPD:

In COPD subjects, decreases from baseline FEV₁ of $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$ were more common in *Staccato* loxapine subjects (80.0%, 56.0%, and 40.0%, respectively) than placebo subjects (66.7, 33.3%, and 11.1%, respectively). The maximum change from baseline FEV₁ occurred within the first 1 hour after dosing (either Dose 1 or Dose 2) in 12 of 21 *Staccato* loxapine subjects with a $\geq 10\%$ decrease in FEV₁.

In COPD subjects, bronchospasm (which includes reports of wheezing, shortness of breath, and cough) occurred in 5 (19.2%) subjects after *Staccato* loxapine and in 3 (11.1%) subjects after placebo, as shown in the table below (electronically copied and reproduced from sponsor's submission):

Table 28: Study 004-108 (COPD) – Airway Adverse Events

Adverse Event, n (%)	<i>Staccato</i> placebo (N=27)	<i>Staccato</i> loxapine (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%) ^a
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 FEV1 from baseline” as an AE; there were no other airway AEs for this subject.

In 4 of the 5 *Staccato* loxapine 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.

Albuterol was used by a total of 6 (23.1%) COPD subjects (7 total uses) after *Staccato* loxapine treatment compared with 4 subjects (14.8%) after placebo. In 4 of the 7 (57.1%) uses of albuterol by *Staccato* loxapine -treated subjects, a return of FEV₁ 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.

6.5.2 Characterization of Bronchospasm

Based on the above data, the sponsor concludes that, in subjects with clinically active airway disease, the nature of airway adverse events (ie, bronchospasm) was consistent with a short-lived and fully reversible effect characterized as follows:

- Bronchospasm is typically mild or moderate in severity, and occurs shortly after dosing (in most cases within 25 minutes).
- Bronchospasm is not accompanied by clinically significant changes in respiratory rate or O₂ saturation, or by other clinical sequelae, for example, the need for systemic steroids or emergency room visits.
- When treatment is required, the bronchospasm resolves quickly and easily with an inhaled bronchodilator without sequelae.

6.5.3 Population at Risk

As noted above, the sponsor believes that the risk of bronchospasm was very low in the agitated patient population in the Phase 2 and 3 studies in which the sponsor claims that ~7% (52/787) of patients had a history of asthma and COPD and a further proportion of patients likely had some degree of respiratory impairment due to their smoking history.

However, the sponsor argues that, in contrast, by challenging subjects in potentially high risk groups (eg, asthma or COPD subjects) under test conditions that would make them particularly susceptible to irritant effects of an aerosol (eg, repeat spirometry, not allowing their short-acting bronchodilator during the study, etc), the clinical program has identified a subset of patients who are susceptible to bronchospasm following treatment with *Staccato* loxapine. The sponsor believes that the at-risk group has been identified as patients with clinically active asthma or COPD including those who have acute respiratory signs/symptoms (eg, wheezing) or who are taking medications to treat their respiratory condition.

6.5.4 Risk of Pulmonary Toxicity in Asthma and COPD Patients

The sponsor argues that both Study **004-105** (asthma) and Study **004-108** (COPD) enrolled subjects with substantial and clinically obvious airways disease, in whom the withholding of quick-relief bronchodilators for up to 40 hours (per protocol in order to avoid obscuring FEV₁ response to study drug) would be expected to strongly predispose to irritant effects of a non-bronchodilator aerosol. According to the sponsor:

- By the National Heart, Lung, and Blood Institute criteria for asthma surveillance, a third of asthma subjects were in the “not well controlled “ category, as indicated by an abnormal (<80% predicted) FEV₁ at screening. Approximately ¾ used an inhaled steroid as a controller medication. Although controller medications were allowed to continue during the study, subjects were not allowed to use quick-relief bronchodilators within the 6 hours before baseline spirometry testing. These short-acting bronchodilators were also not allowed until the end of the 34 hour testing period unless medically necessary as rescue treatment.
- In the COPD study, the sponsor claims that most of the enrolled patients had a moderate or severe COPD, with FEV₁ values approaching 1 L in many cases. Although about half of the subjects were using quick-relief agents at home (including ipratropium), such medications were prohibited throughout the 34-hour assessment period with the exception of albuterol if required for rescue.

Table 29: Asthma and COPD Disease Severity at Screening (Studies 004-105 and 004-108; electronically copied and reproduced from sponsor’s submission)

Study 004-105: Indicator of Disease Severity	(N=52)
Screening pre-bronchodilator FEV ₁ (% of predicted): Median (range)	85.5% (60.0% - 117.0%)
Asthma classification at screening, n (%):	
Well controlled (FEV ₁ ≥80% of predicted)	34 (65.4%)
Not well controlled (FEV ₁ <80% of predicted)	18 (34.6%)
Using inhaled steroid, n (%)	40 (76.9%)
Study 004-108: Indicator of Disease Severity	(N=53)
Screening post-bronchodilator FEV ₁ (% of predicted): Median (range)	55.0% (40.0% - 96.0%)
COPD severity at screening, 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%)
Using inhaled steroid, n (%)	17 (32.1%)

The sponsor believes that the circumstances of these studies (testing regimen, withholding of short-acting bronchodilators) increased the probability of observing FEV₁ decreases – whether due to irritant effects of non-bronchodilator aerosol, the sedation effects of loxapine, or to variability of the underlying disease.

The sponsor further believes that the outcome of these studies provides important information to mitigate this risk. Based on the observed FEV₁ decreases and the reported respiratory signs and symptoms observed in these studies, the sponsor acknowledges that an acute, transient airway response to *Staccato* Loxapine may be anticipated in some patients with clinically active airways disease who are undergoing active treatment for their condition. Specifically, the sponsor believes that the anticipated airways response has been characterized as follows:

- All airway-related adverse events were mild or moderate (no SAEs), and none was accompanied by clinically significant changes in respiratory rate or O₂ saturation. No airway adverse event or FEV₁ decrease led to withdrawal from the study, prevented a subject from completing the spirometry testing regimen, or delayed discharge at the end of the evaluation period.
- Airway-related adverse events resolved easily with an inhaled bronchodilator (a single treatment via metered-dose inhaler in most cases). FEV₁ decreases showed a prompt response to inhaled bronchodilator treatment.
- The risk of an airway response to *Staccato* Loxapine is less in COPD than asthma subjects based on the smaller group mean decreases in FEV₁, fewer airway AEs, and need for rescue medication in COPD versus asthma subjects.

6.5.5 Characteristics of Airway-Related Adverse Events in Asthma and COPD Subjects

According to the sponsor, the clinical course of the airway adverse events was notable for the following:

- All airway AEs were mild or moderate and resolved; none was severe or serious or resulted in withdrawal from the study. (The 4 severe AEs in the **004-105** study were actually sedation, 3 in loxapine-treated subjects and one in a placebo-treated subject).
- None of the events was associated with clinically significant changes in respiratory rate or O₂ saturation.
- None of the airway AEs resulted in a course of steroids, administration of oxygen, or referral to an emergency room.
- Nearly all subjects were able to continue the 34-hour testing regimen and were discharged from the study center at the scheduled time; none of these events delayed discharge. There were two exceptions (one subject in Study **004-105** who discontinued early due to a death in the family and one subject in Study **004-108** who withdrew consent early but had no AEs).

Thus, the sponsor notes that none of the airway-related adverse events were serious or severe. The events were self-limiting or, as described below, promptly reversible with albuterol treatment.

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

In Studies **004-105** and **004-108**, notable respiratory signs or symptoms were defined as an FEV₁ decrease from baseline of $\geq 20\%$, an airway adverse event or use of rescue medication.

The sponsor notes the following:

Eighteen (69.2%) of the loxapine-treated asthmatic subjects and 15 (57.7%) of the loxapine-treated COPD subjects 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 Study **004-105**, 14 of the loxapine-treated subjects were treated with albuterol, 13 of them for airway-related adverse events. Three of the 18 subjects with notable respiratory sign and/or symptoms had a $\geq 20\%$ decrease in FEV₁ but were not treated with albuterol. Of the 14 loxapine-treated asthma subjects who received rescue medication, 11 received only 1 treatment from a metered-dose inhaler, which is a standard prn treatment for such patients at home. The others received albuterol via nebulizer +/- MDI.

In Study **004-108**, only 6 loxapine-treated subjects were treated with albuterol – 3 of them for airway-related adverse events and 2 for a decrease in FEV₁. Almost two-thirds

of subjects (9 of 15) 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 metered-dose inhaler. The other subject received albuterol via a nebulizer.

In the loxapine-treated subjects who received albuterol in both studies, there was a prompt FEV₁ response to rescue medication. In Study **004-105**, as shown in the table below (electronically copied and reproduced from sponsor's submission), 10 of 14 subjects who received albuterol had an FEV₁ within 10% of baseline documented in the subsequent one hour. The other four had recovery to within 10% of baseline documented at later scheduled spirometry time points. Of the latter four, 2 (subjects 04-006 and 04-104) had airway AEs that began 6-12 hours after dosing (and were therefore scored as unrelated to treatment), and 2 (subjects 02-034 and 03-110) had steady improvements with each follow-up test, and no evidence of respiratory distress (all respiratory rates were ≤ 20 and O₂ saturations $\geq 93\%$).

Table 30: Study 004-105 (Asthma) – Time from Rescue to Return of FEV₁ to within 10% of Baseline

Patient No.	Albuterol Rescue (indication)	Last FEV ₁ Before Rescue (change from baseline)	Post-rescue FEV ₁ ^a (change from baseline)
01-004	MDI (increase in asthma)	-21.7% at 3 min pre-rescue	-8.0% at 12 min post-rescue
01-025	MDI (increased asthma symptoms)	-22.9% at 5 min pre-rescue	-7.4% at 30 min post-rescue
01-102	MDI (increased asthma)	-10.3% at 1 min pre-rescue	-18.5% at 14 min post-rescue -7.5% at 28 min post-rescue
02-011	MDI (bronchospasm)	-21.7% at 4 min pre-rescue	+1.4% at 9 min post-rescue
02-034	MDI MDI Nebulizer (for 1 AE of bronchospasm)	-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
02-106	MDI (asthma)	-36.8% at 5 min pre-rescue	-13.0% at 11 min post-rescue +0.5% at 40 min post-rescue
02-116	MDI (asthma)	-25.0% at 3 min pre-rescue	+3.2% at 11 min post-rescue
02-117	MDI (chest tightness)	-3.0% at 20 min pre-rescue	+0.4% at 32 min post-rescue
03-008	Nebulizer (wheezing FEV ₁ reduced 23%)	-19.3% at 7 min pre-rescue	+3.0% at 19 min post-rescue
03-010	MDI (cough)	+9.1% at 14 min pre-rescue	+8.1% at 7 min post-rescue
03-110	Nebulizer (wheezing shortness of breath)	-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
03-112	Nebulizer (wheezing)	-31.8% at 3 min pre-rescue	+2.3% at 23 min post-rescue
	MDI (tight chest shortness of breath)	-8.7% at 9 min pre-rescue	+16.1% at 6 min post-rescue
04-006	MDI (chest tightness)	-18.0% at 3 min pre-rescue	-6.3% at 7 h 57 min post-rescue
04-104	MDI (bronchoconstriction)	-12.4% at 7 min pre-rescue	-9.4% at 1 h 53 min post-rescue ^b

AE=adverse event; MDI=metered-dose inhaler; indication=indication for rescue as specified in Listing 1.16

- Data obtained after FEV₁ returned to within 10% of baseline are not in this table; all FEV₁ data are reported in Listing 3.17.
- Unscheduled spirometry test(s) should have preceded this test and were not done (ie, if FEV₁ 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 FEV₁ returned to within 10% of baseline)

In Study **004-108**, as shown in the table below, in 4 of the 7 instances (in 6 loxapine-treated subjects) in which albuterol was administered, subjects had an FEV₁ within 10% of baseline documented in the subsequent 1 hour. In the three remaining instances recovery to within 10% of baseline or higher was documented at later scheduled spirometry time points. In the latter three instances, subjects had airway AEs (02-027 and 02-114) or received albuterol (02-023) several hours after dosing (3, 24 and 6h, respectively). The adverse events were scored as unrelated to treatment.

Table 31: Study 004-108 (COPD) - Time from Rescue to Return of FEV₁ to within 10% of Baseline

Patient No.	Albuterol Rescue (indication)	Last FEV ₁ Before Rescue (change from baseline)	Post-rescue FEV ₁ ^a (change from baseline)
02-023	MDI (shortness of breath due to COPD)	-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
02-027	MDI (shortness of breath due to COPD)	-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
02-114	MDI (increased wheezing)	pre-rescue test was the baseline test	-10.0% at 2 min post-rescue +0.9% at 18 min post-rescue
	MDI (increased shortness of breath)	-12.7% at 8 min pre-rescue	+22.7 at 9 h 40 min post-rescue ^b
03-010	MDI (FEV ₁ drop)	-46.1% at 4 min pre-rescue	-25.0% at 13 min post-rescue -2.6% at 43 min post-rescue
03-112	Nebulizer (decreased FEV ₁)	-28.5% at 5 min pre-rescue	-0.9% at 51 min post-rescue ^c
05-033	MDI (COPD - 20% drop from baseline)	-28.7% at 4 min pre-rescue	+2.1% at 35 min post-rescue

AE=adverse event; MDI=metered-dose inhaler; indication=indication for rescue as specified in Listing 1.16

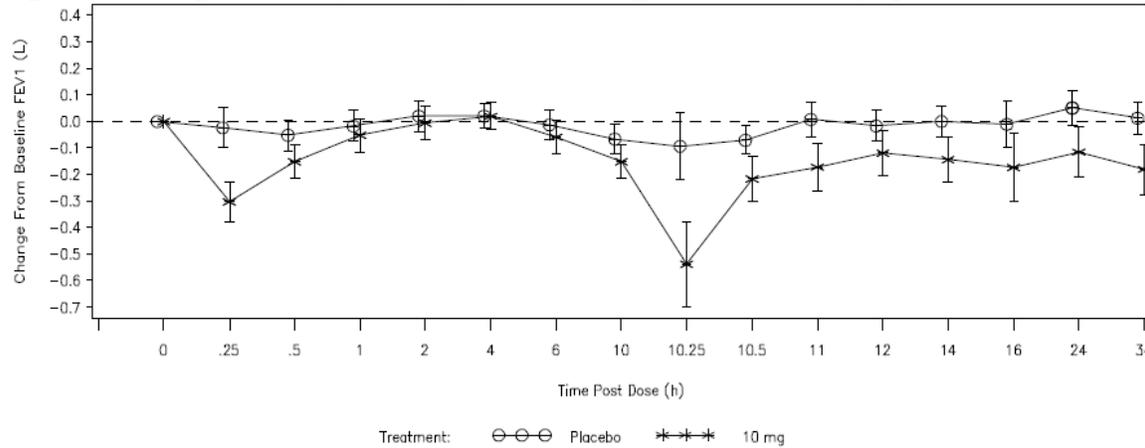
- Data obtained after FEV₁ returned to within 10% of baseline are not in this table; all FEV₁ data are reported in Listing 3.17.
- Unscheduled spirometry test(s) should have preceded this test and were not done (ie, if FEV₁ decreased from baseline by ≥20% or there was AE of wheezing, dyspnea, or bronchospasm, repeat spirometry and chest auscultation were to be performed every 30 minutes—for a maximum of 2 hours—until FEV₁ returned to within 10% of baseline)
- This unscheduled spirometry test was 21 minutes late.

The sponsor concludes that these data are consistent with a short-lived and fully reversible irritant effect that responds to albuterol without sequelae.

6.5.7 Risk of Airway Response in Subjects with Asthma versus COPD

The sponsor argues that the risk of an airway response to *Staccato* Loxapine is less in COPD subjects than in asthma subjects based on the smaller group mean decreases in FEV₁, fewer airway AEs, and the need for rescue medication. In the asthma population, as shown in the figure below (electronically copied and reproduced from sponsor's submission), there were notable decreases in FEV₁ after *Staccato* Loxapine, especially at the 0.25- and 10.25-hour time points (ie, 15 minutes after Dose 1 and Dose 2, respectively). The largest changes from baseline FEV₁ in the *Staccato* Loxapine group were -0.303 L (-0.378, -0.228) [LSmean (90% LSmean CI)] at 0.25 hours and -0.537 L (-0.696, -0.378) at 10.25 hours (ie, 0.25 hours after Dose 2). These decreases were transient and the means returned quickly toward baseline.

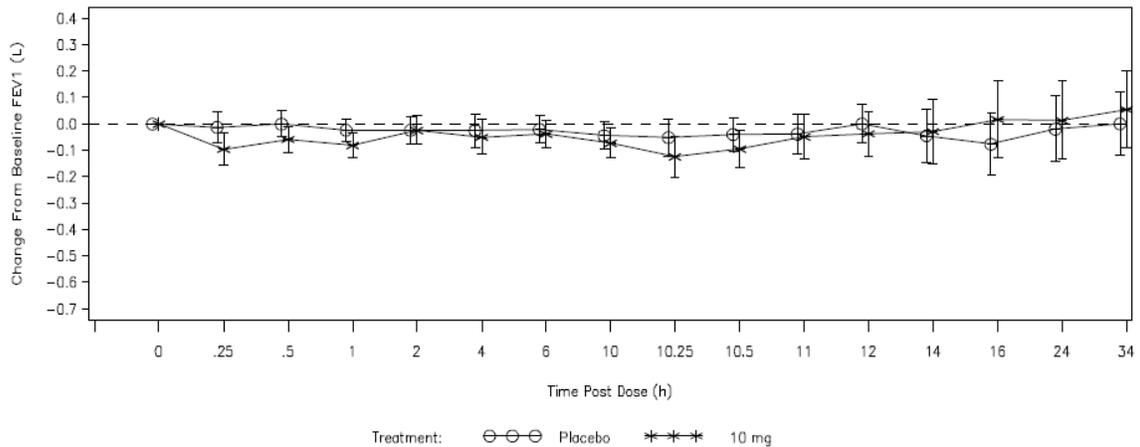
Figure 8: Study 004-105 (Asthma), FEV₁ Change from Baseline, by Treatment



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. Active:	26	26	22	22	22	21	20	20	17	12	12	12	12	12	11	10

As shown in the figure below (electronically copied and reproduced from sponsor’s submission), corresponding decreases were much less apparent with the COPD population. There were very small decreases from baseline in the LSmean FEV₁ at most assessment times after placebo or loxapine treatment, with a slightly larger decrease after loxapine treatment. 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) [LSmean (90% LSmean CI)], which occurred at a late-night assessment, 16 hours after Dose 1 (ie, 6 hours after Dose 2). The largest change from baseline FEV₁ following loxapine 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 9: Study 004-108 (COPD), FEV₁ Change from Baseline, by Treatment



When the placebo response for each study population is taken into account, there were fewer COPD subjects who fell into the FEV₁ decrease categories compared with asthma subjects. Finally, there were fewer reports of airway AEs, notable respiratory signs and symptoms or need for rescue medication in COPD subjects when compared with asthma subjects. These differences are highlighted in the table below (electronically copied and reproduced from sponsor's submission):

Table 32: Different Pulmonary Safety Profile in Asthma versus COPD Subjects

		Study 004-105 (Asthma)		Study 004-108 (COPD)	
		<i>Staccato</i> Placebo	<i>Staccato</i> Loxapine	<i>Staccato</i> Placebo	<i>Staccato</i> Loxapine
(Spirometry Population)		(N = 26) ^a	(N = 26) ^a	(N = 27) ^a	(N = 25) ^a
Maximum % FEV ₁ decrease after either dose (ie, at any time):	≥10%	3 (11.5%) ^a	22 (84.6%) ^a	18 (66.7%) ^f	20 (80.0%) ^f
	≥15%	1 (3.8%) ^a	16 (65.4%) ^a	9 (33.3%) ^f	14 (56.0%) ^f
	≥20%	1 (3.8%) ^a	11 (46.2%) ^a	3 (11.1%) ^f	10 (40.0%) ^f
Maximum mean FEV ₁ change from baseline		-0.093 L ^b (@ 0.25 hr post Dose 2)	-0.537 L ^b (@ 0.25 hr post Dose 2)	-0.077 L ^g (@ 6 hr post Dose 2)	-0.125 L ^g (@ 0.25 hr post Dose 2)
(Safety Population)		(N = 26) ^e	(N = 26) ^e	(N = 27) ^j	(N = 26) ^j
Subjects with Airway AEs		3 (11.5%) ^c	14 (53.8%) ^c	3 (11.1%) ^h	5 (19.2%) ^h
Notable Respiratory Signs and Symptoms (SS)		3 (11.5%) ^d	18 (69.2%) ^d	6 (22.2%) ⁱ	15 (57.7%) ⁱ
SS requiring albuterol		3/3 (100%) ^d	14/18 (78%) ^d	4/6 (66%) ⁱ	6/15 (40%) ⁱ
SS resolving spontaneously		0 ^d	4/18 (22%) ^d	2/6 (33%) ⁱ	9/15 (60%) ⁱ
Subjects receiving rescue medication at any time		3 (11.5%) ^a	14 (53.8%) ^e	4 (14.8%) ^j	6 (23.1%) ^j

Thus, the sponsor concludes that the risk of an airway response to *Staccato* Loxapine is less in COPD subjects than asthma subjects.

6.5.8 Dose-Related Airway AEs and Changes in FEV₁

The protocol in Studies **004-105** and **004-108** prohibited administration of Dose 2 if a subject's FEV₁ decreased by ≥20% from baseline after any dose of study medication, if there was an AE of wheezing, dyspnea, or bronchospasm, or if rescue albuterol was administered. There were greater mean decreases in FEV₁ after Dose 2 vs. Dose 1 in the asthma study. However, the sponsor notes that, in 24/26 asthma subjects after *Staccato* Loxapine, FEV₁ was within 10% of baseline at 24 h (and was within 10% at 34 h in the other 2). Furthermore, mean decreases in FEV₁ in the COPD study were very small and similar after Dose 2 compared with Dose 1. The sponsor argues that the intensive nature of the spirometry testing (15 spirometry sessions in pulmonary compromised subjects)

and the approximately 7 hr half-life of loxapine are confounding factors in interpretation of the Dose 2 effects.

6.5.9 Prevalence of Asthma and COPD in Patients with Psychiatric Illness

The sponsor conducted an assessment to determine the extent of the “at-risk” or “sub-group” patient population with schizophrenia or bipolar disorder that is not appropriate for treatment with *Staccato* loxapine. Since the sponsor has concluded that the treatment of active airways disease is an important predictor of bronchospasm in these patients, 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 data that covers 3 billion transactions per year 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 was obtained from a one-year period (Nov 2009 – Oct 2010) and was limited to patients 18 years or older. The concomitance of respiratory symptoms 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, and leukotriene antagonists).

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 one respiratory medication in the 12-month period evaluated.

Thus, the sponsor concludes that the SDI database search indicates that ~5% of schizophrenia and bipolar disorder patients are actively treating asthma or COPD and therefore would not be appropriate patients for treatment with *Staccato* Loxapine.

The sponsor also reviewed the medical literature (PubMed) over the past 10 years to determine the degree to which psychiatric patients have asthma or COPD but concluded that, due to variations in study designs and populations, it was not possible to determine a reliable estimate of prevalence based on the literature review.

Reviewer’s Comment: As I have previously noted, the high rate of smoking in patients with schizophrenia and bipolar disease has been well-documented. In one study, Hughes et al (American Journal of Psychiatry 1986, 143: 993-997) reported that the prevalence of smoking among psychiatric outpatients was significantly higher than among either local or national population-based samples (52% versus 30% and 33%) and that smoking was especially prevalent among patients with schizophrenia (88%) or mania (70%) and among the more severely ill patients. In another study, Goff et al (American

Journal of Psychiatry 1992, **149**: 1189-1194) reported that 74% of a group of schizophrenic outpatients smoked.

Considering this extremely high rate of smoking in patients with schizophrenia and bipolar disorder, a high rate of asthma and COPD would be expected. In a case-matched, retrospective review, Roberts et al. (Family Practice; 24: 34-40) demonstrated that patients with schizophrenia were less likely than asthma controls to have smoking status noted and in general were less likely to receive some important general health checks than patients without schizophrenia. In general, patients with schizophrenia and bipolar disorder are less likely to have regular follow-ups with a primary health care provider. Thus, it is possible that a proportion of patients with schizophrenia or bipolar disorder may have undiagnosed pulmonary disease (asthma or COPD). As a result, the incidence of asthma and COPD in patients with schizophrenia or bipolar disorder may be higher than the sponsor's estimation from the SDI database.

6.5.10 Sponsor's Conclusions on Risk of Pulmonary Toxicity in Asthma and COPD Subjects

Thus, the sponsor concludes that the responses in asthma and COPD subjects represent a functional worst-case scenario in these populations. The sponsor believes that in clinical practice, patients with airway compromise equal to or greater than that of the **004-105** and **004-108** study participants would be both clinically apparent and very unlikely to be treated with a non-respiratory aerosol therapy. Furthermore, the sponsor concludes that any patient in the intended population who had a clinically apparent adverse reaction to a first dose would not be given a second dose.

Reviewer's Comments: It is noteworthy that, although most subjects in the asthma and COPD studies developed bronchospasm within 25 minutes after dosing and/or had their biggest decrease in FEV₁ within 1 hour after dosing, some subjects had bronchospasm and/or their maximum decrease in FEV₁ much later. Six of 22 and 9 of 21 Staccato loxapine-treated patients with a $\geq 10\%$ decrease in FEV₁ in the asthma and COPD studies, respectively, had their maximum decrease in FEV₁ more than 1 hour post-dose. Two of 14 and 1 of 5 Staccato loxapine-treated patients in the asthma and COPD studies, respectively, developed bronchospasm later than 25 minutes after dosing. Since the mechanism by which Staccato Loxapine causes bronchospasm is not known, it cannot be known if these later reactions are not related to treatment as the sponsor claims.

It is not surprising that subjects with COPD had smaller group mean decreases in FEV₁, fewer airway AEs, and less need for rescue medication compared to subjects with asthma. By definition, subjects with COPD, unlike subjects with asthma, have chronic and less reversible airway disease. However, it is important to realize that small decreases in FEV₁ in patients with COPD, who already have respiratory compromise, may result in significant increases in morbidity.

The fact that short-acting bronchodilators were withheld during the asthma and COPD studies does not change the implications of the study results. Short-acting

bronchodilators in patients with asthma and COPD are indicated for acute treatment on a PRN basis, and good control of respiratory symptoms in these patients is based on use of long-acting medication. One cannot conclude that acutely agitated schizophrenic and bipolar patients with asthma and COPD presenting in a clinical setting will have happened to take a short-acting bronchodilator shortly before presentation and therefore would be at less risk of pulmonary adverse reactions.

As noted in previous reviewer comments, it does not appear that the sponsor's claim that 52 subjects in the pivotal trials had true asthma or COPD is accurate and, although the sponsor claims that a high percentage of subjects in the pivotal studies smoke (and are therefore representative of the intended treatment population, most of whom smoke), only 22.1% of the controlled studies in agitated patients population had ≥ 20 pack-years of cigarette abuse.

As previously noted, a decrease in FEV₁ is an early sign of respiratory compromise. The patient may not develop signs and symptoms (e.g., wheezing, decreases in O₂ saturation, increased respiratory rate) until much later. In the controlled setting of the clinical trials where otherwise healthy patients are carefully monitored and frequent spirometry assessments are done, early diagnosis and treatment of respiratory adverse reactions is possible. In a clinical setting, where patients with schizophrenia or bipolar disorder are presenting with acute agitation and in many cases are psychotic, uncooperative, and severely disorganized and where frequent spirometry assessments are not possible, it may be much less likely that signs and symptoms of pulmonary toxicity are identified in a timely fashion, increasing the possibility of less favorable outcomes compared to the outcomes in the clinical trials. The sedation effect of Staccato Loxapine may further compromise the patient's ability to report respiratory symptoms, and a casual observation may convince the healthcare provider that the patient is resting quietly when in fact the patient is developing respiratory distress. In addition, dosing of Staccato Loxapine in the pulmonary safety studies was 8-10 hours apart compared to the every 2 hour dosing proposed for labeling, and patients were ineligible for further dosing of Staccato Loxapine if FEV₁ decreased by $\geq 20\%$ from baseline after any dose of study medication, if there was an AE of wheezing, dyspnea, or bronchospasm, or if rescue albuterol was administered. Thus, the true severity of pulmonary toxicity of Staccato Loxapine is unknown, and it is likely that some acutely agitated patients receiving every 2 hour dosing will develop severe respiratory distress.

6.6 Sponsor's Argument #6: Staccato Loxapine Provides an Acceptable, Easy to Use, Noninvasive Treatment

The sponsor believes that 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. The sponsor notes that, even with a high degree of agitation, no patient in the pivotal studies refused or was unable to use the product.

6.6.1 Instructions to Patients for Using the Device:

The sponsor states that all patients in the Phase 3 studies were naïve to the working device at the time of initial dosing. They did not train with a working device, nor did they read any instructions for use. The sponsor reports that the protocol-specified “inhalation training” of patients, which was explained at the investigator meetings, consisted of simple verbal instructions to the patient:

- At screening, the protocols instructed, “*Initiate training for the use of the device and evaluate the patient’s ability to use the device properly.*” The study staff was told to simply ask the patient to perform an exhalation, followed by a slow, deep inhalation and breath-hold. This was done without any device.
- At baseline, the protocols again asked that patients demonstrate the inhalation maneuver required for dosing: “*The baseline period (beginning with repeat device training) should begin within 1 h prior to Study Drug Administration.*” At the investigator meeting, the study staff was instructed to again ask the patients to perform an exhalation, followed by a slow, deep inhalation and a breath-hold. At this time, a plastic model of the device (ie, an empty shell that contained no working parts or internal components) was available and could be used.

A *Staccato* Loxapine or *Staccato* Placebo device was not used in the screening or baseline instructions. Therefore, patients had no prior exposure to any of the sensory experiences associated with the device actuation, including sounds, lights, or temperature.

Reviewer’s Comment: Staccato loxapine may provide a preferred treatment option for many patients because it is noninvasive. Regarding ease of use, the sponsor reports an extremely low incidence of device failure in the pivotal studies (0.2% in Study 004-301 and 0.9% in Study 004-302). The sponsor also reports that no patients in either study failed screening because of an inability or unwillingness to use the Staccato system.

However, it is apparent that patients in the pivotal trials underwent fairly extensive training in use of the device. At baseline, a plastic model of the device was available, and patients apparently had up to 1 hour for repeat device training prior to study drug administration. Acutely agitated schizophrenic or bipolar patients presenting to an emergency room or other acute care center where prior screening is not practical and where the goal is to treat the agitation as soon as possible may not respond as well to device training.

7. Sponsor’s Proposed REMS and Element to Assure Safe Use (ETASU)

The sponsor argues that the discrepancy between the need for a patient-considerate and fast-acting anti-agitation treatment and currently available treatment options represents a substantial unmet medical need in patients with behavioral emergencies.

The sponsor believes that the safety and efficacy findings from the clinical program for *Staccato* loxapine, along with the potential benefits for both patients and healthcare providers, support a positive risk benefit assessment for this product in the proposed indication with the proposed REMS. For the patients at risk of bronchospasm, the sponsor argues that the nature and severity of this risk make it amenable to be mitigated by a REMS. The sponsor further argues that the demonstration of a statistically and clinically significant decrease in agitation (as determined by PEC scores) 10 minutes after dosing along with an easily administered and non-invasive formulation, distinguishes ADASUVE from other agents approved for the treatment of agitation and represents an important new therapeutic option for the management of agitation. According to the sponsor, the Phase 2 and 3 studies demonstrated an acceptable safety profile in agitated patients with schizophrenia or bipolar disorder. The sponsor concludes that the observation of bronchospasm in subjects with clinically active asthma and COPD should be balanced against this favorable safety profile in the broader intended population particularly in light of the REMS designed to ensure appropriate patient selection and management of bronchospasm if it occurs.

As described in the following section, the sponsor proposes that the risk of bronchospasm from ADASUVE treatment in susceptible patients in the intended population can be addressed via labeling and a REMS that 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.

7.1 Management of the Risks of ADASUVE

Based on the results of the pulmonary safety program described above, the sponsor concludes that there is a risk of a transient, irritant airway response (ie, bronchospasm) in some patients with schizophrenia or bipolar disorder who have clinically active airways disease, and who are treated with *Staccato* Loxapine for their agitation. Bronchospasm occurs shortly after dosing (typically within 25 minutes) and responds to a standard bronchodilator without sequelae. Therefore, the sponsor proposes that this risk can be mitigated by the product labeling and the proposed REMS. Through the labeling and the REMS, Alexza will communicate the risk of bronchospasm and educate healthcare professionals to (i) identify and select only appropriate patients for treatment, (ii) observe patients for respiratory signs and symptoms for one hour after each treatment, and (iii) have a short-acting beta-agonist bronchodilator (eg, albuterol) readily accessible to manage bronchospasm, if it occurs. In addition, the sponsor is proposing that healthcare facilities be enrolled in a distribution program whereby product is only made available in facilities that ensure there is a short-acting beta-agonist bronchodilator readily accessible in the treatment settings.

7.2 Prescribing Information

A **Boxed Warning** will be included in the full prescribing information that will highlight for prescribers the following information:

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.

The full prescribing information will also include the following Contraindication:

4. CONTRAINDICATIONS

Do not use in patients with acute respiratory signs/symptoms (eg, wheezing) or who are taking medications to treat asthma or COPD.

Additionally, the full prescribing information will include the following information related to bronchospasm in the Warnings and Precautions sections:

5. WARNINGS AND PRECAUTIONS

5.1 Bronchospasm

*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)**].*

The full prescribing information will also include a Medication Guide that will be affixed to the product pouch.

7.3 REMS Rationale

The ADASUVE REMS reflects the sponsor's belief that based on the data collected in the clinical program, the sponsor has identified the patients who may be susceptible to bronchospasm, the nature of this event, and how it can be managed effectively. Specifically, the sponsor argues that the clinical program has shown:

- Patients with asthma and COPD - particularly those using inhalers and/or who are symptomatic - are at risk of bronchospasm following treatment with ADASUVE.
- Based on the completed lung safety studies, bronchospasm is typically mild or moderate in severity and is not accompanied by clinically significant changes in respiratory rate or O₂ saturation, or by other clinical sequelae. None of the airway

AEs resulted in a course of steroids, administration of oxygen, or referral to an emergency room.

- The bronchospasm in asthma and COPD subjects occurs relatively quickly after dosing (typically within 25 minutes) and resolves quickly and easily with an inhaled bronchodilator.

The sponsor also notes that it is intended that ADASUVE be used to treat patients with acute agitation in healthcare settings and under the supervision of a healthcare provider. The sponsor further concludes that it is likely that the majority of patients with agitation will present to an emergency care facility for initial treatment, with the majority of these patients being subsequently admitted to an inpatient unit. The sponsor believes that the proposed REMS is feasible within the current administrative and medical practices in these settings and therefore should not put an undo burden on healthcare systems and providers.

The sponsor proposes that the Prescribing Information be accompanied by a Medication Guide that informs patients and their caregivers about the about the risks and proper use of ADASUVE, and how to manage bronchospasm should it occur.

In addition to the Prescribing Information and Medication Guide, the sponsor proposes a multi-prong communication plan for healthcare providers. This communication plan consists of a number of communication approaches which individually reinforce the messages in the Prescribing Information and the Medication Guide. The sponsor also proposes to include an Element to Assure Safe Use in the ADASUVE REMS to ensure that ADASUVE is only available in healthcare facilities where there is a short-acting beta-agonist bronchodilator readily accessible to manage bronchospasm if it occurs.

The key communication messages of the ADASUVE REMS that inform healthcare professionals how to mitigate the risk of bronchospasm are:

1. identifying and selecting only appropriate patients for treatment,
2. observing patients for respiratory signs and symptoms for one hour after treatment, and
3. having a short-acting beta-agonist (eg, albuterol) readily accessible to manage bronchospasm if it occurs.

7.3.1 Excluding Patients with Clinically Active Airways Disease

The sponsor notes that 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. The sponsor argues that in many cases in the emergency room setting, the patient will already have a medical record or established medical history so that existence of any significant airways disease will be known. Additionally, the sponsor argues that patients who present to the emergency room with agitation are frequently accompanied by family members.

Thus, the sponsor believes that this component of the REMS – identifying and selecting appropriate patients for treatment with ADASUVE – is appropriately and responsibly accomplished through the medical clearance process. Moreover, if the patient has already been admitted to the hospital and needs treatment for agitation, the healthcare provider has access to medical records where this information might be obtained. The sponsor concludes that the REMS component of identifying the appropriate patients for ADASUVE treatment seems highly achievable given that it is consistent with current medical practice. The sponsor believes that the feasibility of excluding patients with a respiratory contraindication was demonstrated in the Phase 2 and 3 trials, which successfully excluded patients with active airways disease and experienced a very low rate of adverse events (3/756 [0.4%] exposures).

7.3.2 Post Treatment Observation for Respiratory Symptoms

The sponsor believes that the REMS anticipated the possibility that even with a screening program some patients with active airways disease will receive ADASUVE. However, the sponsor believes that that this will likely represent a small number of patients because, in addition to the anticipated effectiveness of the screening process, only about 5% of patients with schizophrenia or bipolar disorder receive medication for respiratory conditions (based on sponsor’s review of SDI database: see *Prevalence of Asthma and COPD in Patients with Psychiatric Illness* and *Reviewer Comments* above). The sponsor concludes that, assuming that this population represents the majority of patients at risk for bronchospasm, the screen failures will be a fraction of this 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, the sponsor reports that a high percentage of the asthma and COPD subjects who experienced bronchospasm did so within 25 minutes after administration. Therefore, the sponsor reasons that a dedicated one-hour observation period following each treatment appears suitable for detection of an airway adverse event, if it were to occur. The sponsor states that consultation with 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, the sponsor believes that this component of the REMS is also readily accomplished because it is consistent with established medical practices.

7.3.3 Availability of a Short Acting Beta-Agonist Bronchodilator in the Healthcare Setting

The final REMS message addresses the issue of having a short-acting beta-agonist bronchodilator (eg, albuterol) available in the event of a bronchospasm following treatment with ADASUVE. As discussed above, the sponsor notes that the clinical data have shown that albuterol was effective when it was administered to patients with bronchospasm in the clinical program; 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 to have it accessible if bronchospasm occurs.

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. The sponsor reports that 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, the sponsor believes that it appears reasonable that ready access to a short-acting beta-agonist bronchodilator as a component of the REMS is achievable.

While the sponsor considers it likely that treatment settings already have drugs like albuterol available, the sponsor considers ready access to a short-acting beta-agonist bronchodilator a key component of the risk mitigation strategy for ADASUVE. 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.

7.4 REMS Goals

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 one 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.

As discussed above, the sponsor believes that the clinical program for ADASUVE has identified the subset of patients who are susceptible to bronchospasm following treatment with ADASUVE. Specifically, the sponsor states that 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, should not receive ADASUVE. Thus, in an effort to mitigate the risks of ADASUVE, the sponsor has designed the REMS with the goal of excluding those patients identified as most likely to be susceptible to bronchospasm following ADASUVE treatment.

In addition, since the majority of cases of bronchospasm seen in the clinical program began within 25 minutes of treatment, the sponsor believes an appropriately conservative, but not unduly burdensome, goal is to have healthcare professionals observe patients for respiratory signs and symptoms for one hour after treatment.

Finally, 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.

7.5 Supporting Information and Proposed REMS Elements

7.5.1 Additional Supporting Elements

7.5.1.1 Medication Guide

The sponsor proposes the use of a Medication Guide as part of the REMS. The Medication Guide will be dispensed with each single use unit of ADASUVE and will provide instructions for successful use of ADASUVE. The Medication Guide will also explain the risks of ADASUVE to patients and caregivers.

7.5.1.2 Communication Plan

The communication plan will comprise the materials listed below:

1. Dear Healthcare Professional Letter

A Dear Healthcare Professional Letter will inform healthcare professionals of the risk of bronchospasm in patients with active airways disease, such as asthma or COPD, and provide guidance on identifying patients who should not be treated with ADASUVE and for whom an alternative therapy should be considered. Additionally, the letter will instruct healthcare professionals to have a short-acting beta-agonist bronchodilator readily accessible to manage bronchospasm if it occurs and to observe patients for bronchospasm for one hour after treatment. The letter will be accompanied by the Full Prescribing Information and Medication Guide.

2. Prescriber Brochure

The Prescriber Brochure will provide additional information related to appropriate patient selection, the importance of having a short-acting beta-agonist bronchodilator readily accessible when ADASUVE is administered and observing patients for one hour after

treatment. The brochure will also provide guidance to prescribers on how to communicate both the risk of and the signs and symptoms of bronchospasm to patients.

3. ADASUVE Safe Use Checklist

The checklist will provide the healthcare professional with steps to follow to ensure safe use before, during and after treatment with ADASUVE. The checklist will serve to remind healthcare professionals about obtaining patient medical and medication histories, appropriate patient selection, having a short-acting beta-agonist bronchodilator readily accessible, observing patients for one hour after treatment, and managing bronchospasm should it occur. The checklist will be included in the Prescriber Brochure and will also be made available as a stand alone tool.

4. ADASUVE Educational Program

The ADASUVE Educational Program will describe:

- How ADASUVE works and its proper administration
- Appropriate patient selection for ADASUVE, including clinical risk factors for bronchospasm
- Important safety information, including the importance of having a short-acting, beta-agonist bronchodilator readily accessible to manage bronchospasm if it occurs
- Appropriate observation of patients following ADASUVE treatment

Through the Communication Plan, healthcare professionals will be mailed a Dear Healthcare Professional letter, a Prescriber Brochure, and a Safe Use checklist. The audience for this communication plan will include physicians who are likely to prescribe ADASUVE (eg, emergency care physicians and psychiatrists) and other healthcare professionals who are likely to dispense or administer ADASUVE (eg, pharmacists, emergency and psychiatric nurses, nurse practitioners and physician assistants) in the enrolled healthcare facilities. They will be able to access these documents online and via telephone. Healthcare professionals will be offered an Education Program delivered in-person in their healthcare facility and they will see a reminder of the key risk mitigation messages each time they pick up the single dose unit to administer the product.

7.5.2 Elements to Assure Safe Use

To ensure that ADASUVE is available only in enrolled healthcare facilities where there is ready access to a short-acting beta-agonist bronchodilator, the sponsor proposes the following Elements to Assure Safe Use.

Before ADASUVE may be dispensed and administered in a healthcare facility, an authorized healthcare facility representative must complete and sign the Healthcare Facility Enrollment form. In signing the form, the representative attests to the following:

1. They have received and read the Healthcare Facility Enrollment Information Letter.
2. A short-acting beta-agonist bronchodilator (eg, albuterol) is readily accessible in the treatment settings within their healthcare facility.

To comply with the element an authorized representative of the healthcare facility must only attest that a short-acting beta-agonist bronchodilator is accessible in the healthcare facility. The attestation must be done at the healthcare facility level rather than before each patient is treated.

7.5.3 Implementation System

The Implementation System will include the following:

1. Maintain a validated and secured database of all enrolled healthcare facilities including the completed enrollment forms that will be available to wholesalers to ensure distribution of ADASUVE only to enrolled facilities.
2. Ensure that wholesalers/distributors distribute ADASUVE only to enrolled healthcare facilities. Wholesalers/distributors will complete a Wholesaler/Distributor Enrollment Form to acknowledge that staff will distribute ADASUVE only to enrolled healthcare facilities that are active in the distribution database.
3. Monitor and review enrollment and product distribution data to assess compliance with the requirements that ADASUVE will only be distributed to the enrolled facilities.
4. Based on the evaluation of the implementation of the Element to Assure Safe Use provided for above, take reasonable steps to improve implementation to meet the goals of the REMS.

7.5.4 Timetable for Submission of Assessment of REMS

In order to ensure that the REMS is achieving the goals, the sponsor proposes to submit REMS assessments to the FDA at 12, 24, 36, 60, and 84 months after the REMS is initially approved according to the schedule below:

Table 33: Sponsor’s Timetable for submission of REMS Assessments

Assessment Number	Estimated Reporting Interval	Estimated Date of Submission to the FDA
1	12 months	<i>To be determined based on REMS approval date</i>
2	24 months	
3	36 months	
4	60 months	
5	84 months	

7.5.5 REMS Assessment Plan

7.5.5.1 Healthcare Professional Assessments

Periodic surveys of Healthcare Professional’s knowledge and understanding of product risks will be conducted among a sample of prescribing Healthcare Professionals in order to evaluate the effectiveness of the Medication Guide and Communication Plan in communicating key risk messages. During each assessment period, a representative sample (~ 200) of Healthcare Professionals who have prescribed ADASUVE will be surveyed. Data obtained from the surveys will be analyzed to determine the percent of Healthcare Professionals who correctly identified key risk messages.

7.5.5.2 Patient Assessments

Periodic surveys will be conducted in a representative sample of patients to obtain information about the effectiveness of the Medication Guide in communicating the risk associated with the use of ADASUVE and to monitor compliance with Medication Guide distribution requirements. Given the patient’s agitated state at the time of treatment, the assessment will be conducted in conjunction with a post-treatment review of the medication guide after the patient has been stabilized and is no longer in an agitated state. Each survey will include 200 patients who have received treatment with ADASUVE since approval.

Periodic reports will be prepared to assess:

- Patients’ understanding of the risk associated with the use of ADASUVE
- Distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- Failures to adhere to distribution and dispensing requirements and corrective actions taken to address noncompliance

8. Proposed Post-Marketing Study

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 of *Staccato* Loxapine. Therefore, the current submission includes a synopsis of a proposed postmarketing study titled, “A Post-Marketing Observational Study to Evaluate the Safety and Effectiveness of *Staccato* Loxapine in Agitated Patients with Schizophrenia or Bipolar Disorder Treated in Real World Emergency Settings.”

Primary Objectives

The primary objectives of the proposed study are:

- 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 *Staccato* Loxapine in an emergency setting
- To compare the frequency of AEs and SAEs for *Staccato* Loxapine vs. IM antipsychotic and/or benzodiazepine medications used in the acute treatment of agitated patients

Secondary Objectives

The secondary objectives of the proposed study are:

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

Subjects

The study population will consist of a nonrandomized cohort of ~1400 adult male and female patients with a diagnosis of schizophrenia or bipolar disorder who require treatment for agitation (voluntarily or involuntarily) by the investigator.

Study Design

The proposed study 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. It is anticipated that the enrollment period will be 18-24 months and that the duration of patient participation will be up to 24 hours.

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.

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.

In addition to baseline data, effectiveness data will be collected at 1 hour post-treatment and safety data will be collected up to 24 hours post-treatment or until discharge/transfer from the emergency department (whichever is earlier). If informed consent is obtained

after 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.

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 *Staccato* Loxapine according to the approved Prescribing Information and the approved product REMS (eg, those who have respiratory signs/symptoms or who are currently being treated for asthma or COPD will not receive *Staccato* Loxapine)

Data Elements

Data on the following elements will be collected in the study:

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 *Staccato* Loxapine compared with patients treated with other anti-agitation medications
- Mean change in PANSS-EC score from baseline to 1 hour post-treatment (or at discharge if earlier than 1 hour)
- Usability of *Staccato* Loxapine including the number (and percent) and characteristics of patients who refused or were unable to use *Staccato* Loxapine when it was offered

- Physician treatment choices for treating agitation in an emergency room setting
- Doses of all anti-agitation medications administered (medication, dose, route of administration, timing) up to 24 hours from the 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 *Staccato* Loxapine treatment

Other Data of Interest

- The demographics of patients treated with *Staccato* Loxapine 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)

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 *Staccato* Loxapine. In the Phase 3 program, with respiratory exclusion criteria similar to those prescribed in the Prescribing Information, the observed rate of respiratory AEs in persons receiving *Staccato* Loxapine was 0.8%. The sponsor reasons that, 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, the sponsor estimates 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 $\sim <1\%$ in persons receiving comparator IM products. Given a sample size of 600 patients receiving *Staccato* Loxapine, the estimated precision for the observed respiratory AE rate in persons receiving *Staccato* Loxapine will be $\pm 1.2\%$. For comparison purposes, the sponsor will aim to enroll approximately 800 patients receiving other IM products and/or benzodiazepines; thus, the total estimated study population will be 1400.

Reviewer Comments: The sponsor has provided only a brief synopsis of the proposed post-marketing study. If ADASUVE is approved for marketing, it will be necessary for a fully developed protocol to be submitted by the sponsor for review and approval by the Agency prior to study initiation.

The submitted protocol synopsis was reviewed in consultation by Cary Parker, MPH, Division of Epidemiology, Office of Surveillance and Epidemiology (DEPI/OSE). DEPI's general comments on the study synopsis are as follows:

In general, the study objectives are reasonable. A rationale for the study setting and the criteria to be employed in the selection of study sites should be detailed in the study protocol. The study population should reflect the population receiving this product in the real world setting as closely as possible. Inclusion and exclusion criteria should be detailed in the study protocol. In particular, inclusion and exclusion criteria that rely on patients' availability of medical history or ability to report medical history reliably should be addressed. For example, this study proposes to include patients with a diagnosis of schizophrenia or bipolar disorder who require treatment for agitation in psychiatric emergency settings in the U.S. Patients diagnosed with dementia, as well as those with acute respiratory signs/symptoms or those currently treated for asthma or COPD, will be excluded from the study. However, some of these patients may enter the medical or psychiatric emergency settings without a formal diagnosis, have undiagnosed disease, may be unable to provide a reliable medical history or may not have medical history readily available. The sponsor should provide details regarding how medical diagnosis or medical history will be determined for all patients and how inability to determine diagnosis or medical history in some patients may impact the interpretability of study findings. Moreover, information regarding the generalizability of patients actually included in the study to the population of patients receiving *Staccato* Loxapine in real world settings should be discussed.

The study design and analyses should minimize potential for surveillance bias, due to differential assessment and follow-up between study groups, and bias due to lack of comparability between study groups. This study proposes that patients with a diagnosis of schizophrenia or bipolar disorder treated for agitation with IM anti-psychotic and/or benzodiazepine medications as the comparator group. It can be argued that patients who are given *Staccato* Loxapine may be significantly different from the patients who receive the other IM drugs. Theoretically, results may be biased in favor of *Staccato* Loxapine patients if this medication is more likely to be given to healthier patients (i.e. patients who are able to and compliant with the use of the inhalation device and who do not have a history of asthma or COPD). The sponsor should address the comparability of the study comparison groups as well as how any differences between study groups will be handled, including specifying important confounders and how these would be handled in the analyses. Additionally, the sponsor should discuss whether differential follow-up (e.g. if patients on a particular study group are more likely to be discharged home prior to 24 hours post medication administration) will impact interpretability of study findings and provide strategies to minimize/eliminate these discrepancies.

Additionally, standard, case definitions of all AEs and SAEs should be provided in the study protocol, including operational definitions for the respiratory outcomes of interest. Importantly, the protocol should describe the method of outcome assessment across study groups, including frequency of assessment/s and the required

expertise/training of medical team performing the assessment/s of the outcomes of interest (e.g. auscultation of lung sounds may require trained medical professionals).

Detailed sample size calculations for each outcome should be provided for each outcome. In addition, information regarding the reliability of the assumptions concerning background rates of respiratory AEs should be provided (e.g. reference from literature or information from pilot studies).

9. Sponsor's Proposed Labeling

The sponsor's proposed labeling is referenced to Loxapine (loxapine succinate capsules), revised on September 10, 2010 (Watson Pharmaceuticals, Inc.) The sponsor's proposed labeling differs from the labeling for the listed drug in three areas:

1. Since Staccato Loxapine for Inhalation (*Staccato* Loxapine) represents a new dosage form (aerosol) and route of administration (inhalation) for loxapine, information relevant to this product is included in the *Staccato* Loxapine Prescribing Information.
2. The Loxapine Capsules Prescribing Information is not available in the Physician's Labeling Rule (PLR) format. The draft Prescribing Information for *Staccato* Loxapine follows the PLR format and therefore incorporates additional sections and different sequence sections.
3. Since treatment of agitation in schizophrenia and bipolar disorder (the indication proposed for *Staccato* Loxapine) is an acute indication, it is anticipated that patients will receive treatment on an infrequent basis. In contrast, loxapine capsules are approved for chronic treatment of schizophrenia. Therefore, certain safety information related to the long-term treatment of antipsychotics was considered not applicable and not included in the sponsor's draft labeling.

In addition, the sponsor has provided the following rationale for dosing recommendations which the sponsor includes in the **Dosing and Administration** section:

9.1 Summary of Dosing Recommendations

As discussed in detail in the original NDA submission, across multiple endpoints in the Phase 2 (Study **004-201**) and Phase 3 (Studies **004-301** and **004-302**) of *Staccato* Loxapine, the magnitude of the treatment effect was larger in the 10-mg group than in the 5-mg group. These endpoints include the PEC change scores, the CGI-I scores, the overall use of the study and rescue medication, and the time to use of Dose 2 of study medication. While the 5-mg dose demonstrated clinical effectiveness in the Phase 3 studies based on the primary and key secondary endpoint analysis, the sponsor concludes that the wider assessment of efficacy across the 3 clinical efficacy studies, including both the magnitude of the treatment effect and the duration of the effect (as determined by the need for additional doses and rescue medication) supports the administration of 10 mg as the optimal dose to ensure maximum therapeutic benefit in agitated patients.

The sponsor reports that the use of up to 2 additional doses of *Staccato* Loxapine within a 24-hour period in the Phase 3 studies was based on the results of an earlier multidose pharmacokinetic study (Study **004-102**) that examined the pharmacokinetics, safety, and tolerability of 3 doses of *Staccato* Loxapine dosed every 4 hours in subjects on chronic, stable antipsychotic regimens. The pharmacokinetic profile of loxapine was characterized by rapid absorption and distribution, followed by a terminal half-life of about 7 hours. Across the 3 treatment regimens, there was minimal plasma accumulation, and concentrations decreased quickly after the peak concentrations. The difference in loxapine concentration between the 2-hour and 4-hour time points (after Dose 1) was 6 to 8% of C_{max} . Based on these concentration-time data, this study concluded that a second dose of *Staccato* Loxapine could be administered after 2 hours with minimal impact on loxapine exposure or safety vs. 4 hours.

In the Phase 3 studies the specific instructions regarding administration of additional doses were as follows: If agitation did not subside sufficiently after Dose 1 or it recurred, Dose 2 could be given >2 hours after Dose 1; if necessary, Dose 3 could be given \geq 4 hours after Dose 2.

As shown in the table below (electronically copied and reproduced from sponsor's submission), approximately one-half of the 5-mg patients and one-third of the 10-mg patients received a second dose of study drug. Of those who received Dose 2, a significant proportion did so shortly after it was first allowed (at \geq 2 hours after Dose 1): 49.6% (56/113) of the 5-mg patients and 41.0% (34/83) of the 10-mg patients received Dose 2 by 2.5 hours (ie, within the first half hour in which it was allowed).

Table 34: Time to Administration of *Staccato* Loxapine Dose 2 (Studies 004-301 and 004-302); Controlled Studies in Agitated Patients Population)

	<i>Staccato</i> Loxapine 5 mg			<i>Staccato</i> Loxapine 10 mg		
	Study 004-301 (N=116)	Study 004-302 (N=104)	Studies 004-301 + 004-302 (N=220)	Study 004-301 (N=113)	Study 004-302 (N=105)	Studies 004-301 + 004-302 (N=218)
No. (%) of patients who received Dose 2	52 (44.8%)	61 (58.7%)	113 (51.4%)	43 (38.1%)	40 (38.1%)	83 (38.1%)
No. who received Dose 2 by 3 hours ^{a,b} :						
by ≤2.25 hours	13	19	32	7	12	19
by ≤2.50 hours	24	32	56	18	16	34
by ≤2.75 hours	30	36	66	21	22	43
by ≤3 hours	35	38	73	23	23	46
No. who received Dose 2 later than 3 hours ^a	17	23	40	20	17	37
Median Time to Dose 2 ^a (h)	2.58	2.50	2.55	2.92	2.75	2.75

Source: [m5.3.5.1, 004-301 CSR, Section 12.1.9.3, Supplemental Output 5, and Section 12.2, Listing 1.17](#); [m5.3.5.1, 004-302 CSR, Section 12.1.9.3, Supplemental Output 5, and Section 12.2, Listing 1.16](#)

^a Time is relative to administration of the first dose of *Staccato* Loxapine. No patient received Dose 2 before 2 hours.

^b Patient counts in the time categories are cumulative (ie, a patient in the ≤3-hour category is also counted in the ≤2.25-, ≤2.5-, and ≤2.75-hour categories).

The sponsor reports that those patients in the Phase 3 studies who received Dose 2 of *Staccato* Loxapine in the first full hour in which it was allowed (ie, 2 to 3 hours after Dose 1) had no airway AEs and no evidence of an increased risk of AEs compared to the entire Phase 3 study group, as shown in the table below (electronically copied and reproduced from sponsor's submission). Sedation and dysgeusia were actually less frequent in these subjects after they received Dose 2 compared with all Phase 3 loxapine-treated patients. In addition, in the Phase 3 studies, there was no evidence of an increased incidence of the most frequently reported AEs (with the exception of dysgeusia) or of the emergence of any new AEs as a result of administration of additional doses of study medication.

Table 35: AEs after Dose 2 in Patients Who Received Dose 2 in the First Hour It Was Allowed (Studies 004-301 and 004-302; Controlled Studies in Agitated Patients Population)

<i>Staccato</i> Loxapine Dose, AEs After Dose 2 in Patients Who Received Dose 2 in the First Hour It Was Allowed (ie, 2-3 Hours After Dose 1) ^b (Preferred Term)	No. (%) of <i>Staccato</i> Loxapine Patients with AE ^a		No. (%) of <i>Staccato</i> Loxapine Patients with the Identified AEs in at Any Time
	Patients Who Received Dose 2 at 2.0 to ≤2.5 Hours After Dose 1 ^b	Patients Who Received Dose 2 at 2.0 to ≤3.0 Hours After Dose 1 ^b	
5-mg Dose: n	n=56	n=73	n=220
Dysgeusia	5 (8.9%)	6 (8.2%)	28 (12.7%)
Sedation/somnolence (combined)	4 (7.1%)	4 (5.5%)	25 (11.4%)
Diarrhea	2 (3.6%)	2 (2.7%)	2 (0.9%)
Akathisia	1 (1.8%)	1 (1.4%)	1 (0.5%)
Constipation	1 (1.8%)	1 (1.4%)	1 (0.5%)
Skin rash ^b (combined)	1 (1.8%)	1 (1.4%)	2 (0.9%)
Stomach discomfort	1 (1.8%)	1 (1.4%)	4 (1.8%)
Dyspepsia	0 (0.0%)	1 (1.4%)	2 (0.9%)
Headache	0 (0.0%)	1 (1.4%)	7 (3.2%)
10-mg Dose: n	n=34	n=46	n=218
Dysgeusia	2 (5.9%)	2 (4.4%)	30 (13.8%)
Hiccups	1 (2.9%)	1 (2.2%)	1 (0.5%)
Hypoaesthesia oral	1 (2.9%)	1 (2.2%)	5 (2.3%)
Pharyngeal hypoaesthesia	1 (2.9%)	1 (2.2%)	2 (0.9%)
Sedation/somnolence (combined)	1 (2.9%)	2 (4.3%)	21 (9.6%)
Hypertension	0 (0.0%)	1 (2.2%)	2 (0.9%)
Throat Irritation	0 (0.0%)	1 (2.2%)	4 (1.8%)

Source: m5.3.5.1, 004-301 CSR, Section 12.2, Listings 1.17, 3.1; m5.3.5.1, 004-302 CSR, Section 12.2, Listings 1.16, 3.1

^a Limited to patients who received *Staccato* Loxapine Dose 2 from 2.0 to 3.0 hours after Dose 1, and limited to the AEs in those patients that started at or after the time Dose 2 was administered

^b Time is relative to the administration of Dose 1. No patient received Dose 2 sooner than Hour 2.

^c Combined incidence of all preferred terms involving rash

Therefore, the sponsor concludes that the efficacy and safety data from the clinical efficacy studies of *Staccato* Loxapine support the administration of 1 to 3 doses of study medication (up to a total of 30 mg/day) during a 24-hour period. Administration of a repeat dose after 2 hours is supported by the finding that those who required Dose 2 commonly needed it shortly after the 2-hour time point, and that it was well tolerated in that circumstance.

9.2 Elements of Proposed Labeling

Elements of proposed labeling (**Boxed Warning, Contraindications, and Warnings and Precautions**) that relate to the sponsor's proposed REMS have been discussed above (see **Sponsor's Proposed REMS and Elements to Assure Safe Use; Prescribing Information**). Other important elements of the proposed labeling are summarized below:

1 Indications and Usage

The proposed labeling for **Indications and Usage** includes the following:

ADASUVE is indicated for the rapid treatment of agitation associated with Schizophrenia or Bipolar Disorder in adults.

“Psychomotor agitation” is defined in DSM-IV as “excessive motor activity associated with a feeling of inner tension.” Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care (e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior), leading clinicians to the use of rapidly absorbed antipsychotic medications to achieve immediate control of the agitation.

2 Dosing and Administration

The sponsor's proposed labeling for **Dosing and Administration** is as follows:

Adults: The efficacy of ADASUVE in controlling agitation in patients with Schizophrenia or Bipolar Disorder was demonstrated at doses of 5 mg and 10 mg [*see CLINICAL STUDIES*]. The recommended dose of ADASUVE is 10 mg. A lower dose of 5 mg may be considered when clinical factors warrant.

If agitation persists following the initial dose, cumulative doses up to a total of 30 mg/day may be given. The safety of total daily doses greater than 30 mg or administrations given more frequently than every 2 hours has not been evaluated in clinical trials [*see CLINICAL STUDIES*].

ADASUVE is administered by oral inhalation. ADASUVE is a single use product that delivers an aerosol of loxapine in a single inhalation [*see PATIENT COUNSELING INFORMATION*].

Pediatric Patients: ADASUVE has not been evaluated in pediatric patients

3 Dosage Forms and Strengths

The proposed labeling for **Dosage Forms and Strengths** is as follows:

ADASUVE is a single-use, disposable product containing either 5 mg or 10 mg of loxapine base.

5 Warnings and Precautions

5.1 Bronchospasm

In addition to the information described above in this review (see **Sponsor's Proposed REMS and Elements to Assure Safe Use; Prescribing Information** above), the sponsor includes the following:

ADASUVE has not been investigated in patients with other forms of lung disease.

5.3 Tardive Dyskinesia

The sponsor has included the information describing tardive dyskinesia from the reference listed drug labeling and has added the following to this section:

Tardive dyskinesia has not been reported in short-term (24-hour), placebo-controlled trials in which agitated patients were administered ADASUVE.

5.4 Neuroleptic Malignant Syndrome

The sponsor has included the information describing neuroleptic malignant syndrome (NMS) from the reference listed drug labeling and has added the following to this section:

NMS has not been reported in short-term (24-hour), placebo-controlled trials in which agitated patients were administered ADASUVE

5.5 Hypotension

The proposed labeling states:

ADASUVE may be associated with hypotension, orthostatic hypotension, syncope or presyncope.

This is followed by a description of the incidence of hypotension in the clinical trials. Language derived from the reference listed drug includes information regarding vasopressor therapy in the presence of severe loxapine-induced hypotension, as well as the statement that ADASUVE should be used with caution in patients with known cardiovascular disease.

5.6 Seizures / Convulsions

In addition to language from the reference listed drug about using loxapine with extreme caution in patients with a history of convulsive disorders, the labeling states:

In short-term (24 hour) placebo-controlled trials of ADASUVE, there were no reports of seizures or convulsions.

5.7 Potential for Cognitive and Motor Impairment

In addition to cautions regarding operating hazardous machinery, the labeling states:

ADASUVE, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. For example, in short-term, placebo-controlled trials, sedation and/or somnolence were reported as follows: ADASUVE 5 mg 12.1%, ADASUVE 10 mg 12.0%, and placebo 9.5%. No patients discontinued treatment due to sedation or somnolence.

5.8 Use in Patients with Concomitant Illness

In addition to language from reference listed drug regarding possible anticholinergic action, the labeling states:

Clinical experience with ADASUVE in patients with concomitant systemic illnesses is limited. ADASUVE has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies.

6 Adverse Reactions

6.1 Clinical Studies Experience

This section includes an extensive description of adverse reactions observed in the clinical program including those leading to discontinuation, commonly observed adverse reactions, less common adverse reactions, dose-related adverse reactions, and airway adverse events in the pivotal trials, and the three pulmonary safety studies. This is followed by appropriate sections on extrapyramidal symptoms, dystonia, and cardiovascular effects.

Based on the differences in FDA and sponsor interpretation of study results as described above in this review, the following statements in this section may be called in to question:

Statement #1:

The effect of ADASUVE (2 doses of 10 mg administered 8 hours apart) on pulmonary function was evaluated in 30 healthy subjects. There was no evidence for a systematic adverse effect on pulmonary function, and no reports of bronchospasm or any other respiratory events.

Reviewer's comment: As noted above, the Division has serious concerns that the decreases in FEV₁ after administration of Staccato Loxapine in the referenced study (004-104) were clinically significant.

Statement #2:

Subjects with asthma or chronic obstructive pulmonary disease (COPD): Two placebo-controlled trials investigated the pulmonary safety of ADASUVE in subjects with mild to moderate persistent asthma (N=52) and in subjects with mainly moderate-to-severe COPD (N=53).

*Reviewer's Comment: Although it is true that patients in the COPD study (004-108) were mainly those with moderate-to-severe COPD, approximately 11% of patients in the study who would be classified as having mild COPD based on baseline FEV₁ (see **Table 29**). Therefore, the patients in this study should be more accurately described as "subjects with mild-to-severe COPD."*

Statement #3:

In asthma subjects, bronchospasm (which includes reports of wheezing, shortness of breath, and cough) occurred in 14 (53.8%) subjects after ADASUVE and in 3 (11.5%) subjects after placebo. In 12 of the 14 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 (1 subject) or treated with an inhaled bronchodilator (albuterol).

Reviewer's Comment: Although this is a true statement, it is in a sense misleading, because it does not take into account that adverse events could have been much more severe requiring more extensive rescue if dosing had been given two hours apart and subjects with significant adverse respiratory reactions after the first dose (FEV₁ decrease \geq 20%, required albuterol rescue etc) had not been excluded from receiving the second dose. The same argument may be applied to similar statements regarding COPD subjects (see Statement #5 below).

Statement #4:

In ADASUVE subjects who received albuterol for bronchospasm, 9 of 13 (69.2%) had their FEV₁ return to within 10% of baseline documented in the subsequent hour; the remainder had recovery to within 10% of baseline documented at later, scheduled spirometry time points.

Reviewer's Comment: Again, this is a true statement but may be misleading because it does not take into account that some subjects had significant decreases in FEV₁ after Dose 2 that never returned to baseline during the entire 24-hour post-dosing observation period.

Statement #5:

In COPD subjects, bronchospasm (which includes reports of wheezing, shortness of breath, and cough) occurred in 5 (19.2%) subjects after ADASUVE and in 3 (11.1%) subjects after placebo. 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

Reviewer's Comment: Please see Reviewer's Comment for Statement #3.

6.2 Vital Signs and Laboratory Abnormalities

This section includes information that no important differences between ADASUVE and placebo groups in the clinical program were noted in vital sign changes, laboratory changes, or ECG changes. It includes the statement that "A thorough QT/QTc study was negative."

6.3 Postmarketing Experience

This section is based on the reference listed drug and is prefaced by the statement:

There is no previous experience with inhaled loxapine.

7 Drug Interactions

This section presents appropriate information based on in vitro studies conducted by the sponsor combined with information from labeling of the reference listed drug.

8 Use in Specific Populations

This section states:

In general, no dose adjustment for ADASUVE is required on the basis of a patient's age, gender, race, smoking, hepatic status, or renal function.

This is followed by **8.1 Pregnancy**, and **8.3 Nursing Mothers**, which are taken primarily from the reference listed drug labeling.

In **8.4 Pediatric Use**, the labeling states:

The safety and effectiveness of ADASUVE in pediatric patients have not been established.

Under **8.5 Geriatric Use** the labeling states:

No dose adjustment is recommended for elderly patients.

And:

Placebo-controlled studies of ADASUVE in patients with agitation associated with Schizophrenia or Bipolar Disorder did not include subjects over 65 years of age.

9 Drug Abuse and Dependence

In **9.3 Dependence**, the labeling states:

ADASUVE is intended for acute administration and has not been studied in humans for its potential for abuse, tolerance, or physical dependence.

10 Overdosage

In addition to information on Management of Overdosage derived from reference listed drug labeling, this section states:

ADASUVE is a product that contains and delivers a single dose

And

Human Experience: No cases of overdosage of ADASUVE were reported in clinical studies.

11 Description

This section contains a description of the active ingredient Loxapine (derived from the reference listed drug), as well as an appropriate description of ADASUVE as:

...a single-use, drug-device combination product

12 Clinical Pharmacology

This section contains appropriate information on Mechanism of Action, Pharmacodynamics, Pharmacokinetics, and Special Populations (Pharmacokinetics in Smokers and Demographic Effects), referencing specific PK studies from the clinical program and data from the reference listed drug as appropriate.

13 Nonclinical Toxicology

This section appropriately discusses Carcinogenesis, Mutagenesis, Impairment of Fertility, and Animal Toxicology and/or Pharmacology with appropriate labeling from reference listed drug and the sponsor's pre-clinical inhalation studies.

14 Clinical Studies

This section contains appropriate descriptions of the two pivotal studies. The following statement is made:

Decreased agitation was evident in patients with Schizophrenia and Bipolar Disorder at the first assessment time, 10 minutes after Dose 1, and at all subsequent assessments during the 24 hour evaluation period, for both the 5 and 10 mg doses.

*Reviewer's Comment: See section above entitled, "Sponsor's Argument: **Staccato Loxapine provides rapid onset of therapeutic effect**"*

16 How Supplied/Storage and Handling

This section contains appropriate information regarding the Staccato Loxapine for Inhalation Product.

17 Patient Counseling Information

This section appropriately advises physicians to discuss information with patients concerning risk of bronchospasm, interference with cognitive and motor performance, neuroleptic malignant syndrome, and hypotension, with references to **Boxed Warning** and *Warnings and Precautions* sections. The Medication Guide is also referenced.

10. Conclusions

ADASUVE (*Staccato* Loxapine) is effective in controlling agitation associated with schizophrenia or bipolar disorder, as demonstrated in the pivotal studies (**004-301** and **004-302**). It provides a noninvasive method of treatment, which may be preferred by some patients. In addition, it may provide a rapid onset of therapeutic effect, although it is not possible to compare its time of onset with other products approved for this indication (IM aripiprazole, IM olanzapine, and IM ziprasidone) since no head-to-head studies have been done.

However, despite the sponsor's arguments, the Division remains concerned that the full extent and severity of pulmonary toxicity in the intended treatment population is unknown. In the pivotal trials (**004-301** and **004-302**), patients with clinically significant acute or chronic pulmonary disease were excluded, and in the pulmonary safety studies in healthy volunteers (**004-104**) and subjects with asthma (**004-105**), smokers were excluded. Furthermore, dosing interval in the pulmonary safety studies (**004-104**, **004-105**, and **004-108**) was 8-10 hours (as opposed to the sponsor's proposed 2 hour dosing interval in labeling), and subjects who experienced significant respiratory adverse events, received albuterol rescue, or had a decrease in FEV₁ $\geq 20\%$ after the first dose were ineligible to receive the second dose. Since decreases in FEV₁ usually precede respiratory signs or symptoms, it is reasonable to conclude that some patients receiving dosing at 2 hour intervals in a clinical setting where frequent spirometry assessments are impractical (and who have unrecognized decreases in FEV₁ after the first dose) would have more severe respiratory decompensation than observed in the pulmonary safety studies.

As previously noted, there is a very high rate of smoking in patients with schizophrenia and bipolar disorder. Therefore, a high rate of asthma and COPD would be expected. However, acutely agitated schizophrenic or bipolar patients presenting to an emergency room or other facility may be uncooperative, psychotic, and severely disorganized. In some cases, they may need physical restraint. Such patients may be unable to give a reliable medical history and, in an emergency setting, medical records may not be readily available. In addition, these patients may be unable or unwilling to follow directions for use of ADASUVE. Furthermore, healthcare providers may have difficulty performing an adequate physical examination on an acutely agitated, disorganized patient. Therefore, even if the at-risk population can be fully characterized, a proportion of high risk patients will not be identified and will receive ADASUVE.

It may be difficult to monitor patients for early signs and symptoms of bronchospasm post-dose. Psychotic and agitated patients who develop respiratory symptoms may not be

able to notify healthcare personnel in a timely manner, and respiratory distress may be confused with acute agitation to the casual observer. In addition, the sedating effect of *Staccato* Loxapine may also mask respiratory signs and symptoms while causing further respiratory suppression.

Therefore, it is likely that, even with adequate screening for pulmonary risk factors, some patients will require respiratory support post-dose, and some patients will be at risk for respiratory failure and death after administration of *Staccato* Loxapine. It is crucial that appropriate rescue medication be readily available when *Staccato* Loxapine is administered, including short-acting beta-agonists and oxygen. The necessary equipment to provide full respiratory support (e.g., intubation, ventilator) should also be readily available, and staff must be adequately trained in airway management.

If a final determination is made that the benefits of ADASUVE are sufficient to risk bronchospasm and respiratory decompensation, a REMS with ETASU is necessary. However, the sponsor's proposal will not sufficiently mitigate the serious patient outcomes that could result from post-administration bronchospasm associated with ADASUVE. At a minimum, attestations need to be strengthened to enhance screening, monitoring, and treatment requirements. Final recommendations from the Division of Risk Management (DRISK) are pending at this time, and additional options may be considered after the planned Advisory Committee meeting.

In addition, final recommendations regarding the proposed postmarketing study cannot be made until a fully developed protocol is submitted.

In the sponsor's proposed labeling, the proposed indication, "the rapid treatment of agitation associated with Schizophrenia or Bipolar Disorder in adults," should be changed to, "the acute treatment of agitation associated with Schizophrenia or Bipolar Disorder in adults" in order to align with the Division's preferred language used in the IM Abilify label. Other recommendations on language in **Dosing and Administration**, **Boxed Warning**, **Contraindications**, **Warnings and Precautions**, and **Clinical Studies Experience** will depend in large part on the determination of appropriate REMS with ETASU.

Important questions to consider at the Advisory Committee meeting may include the following:

1. Could clinicians reliably identify and exclude from treatment those patients who are at high risk for developing pulmonary toxicity?
2. In what clinical settings could clinicians administer ADASUVE safely and effectively? (e.g., E.R, general medical hospital, psychiatric hospital, outpatient clinic)
3. What would be an acceptable level of medical expertise and medical equipment available at the site of administration?
4. Given that the use of the product requires some degree of cooperation, would there be limitations in using the product in severely agitated patients?

5. What would be the estimated risk-benefit profile in patients with less severe agitation?
6. Can subjects with respiratory diseases other than asthma or COPD be safely administered ADASUVE?
7. Could patients be monitored effectively for respiratory signs and symptoms post-dose in the settings in which ADASUVE treatment is proposed?
8. For how long post-dose should patients be monitored for potential respiratory complications? The sponsor has proposed a 1-hour post-dose monitoring period; however, it is possible that not all respiratory adverse reactions will occur within this time frame (see **Sponsor's Conclusions on Risk of Pulmonary Toxicity in Asthma and COPD Subjects** and *Reviewer Comments*).
9. Can an effective REMS with ETASU be developed for this product? Can a REMS substantially mitigate the pulmonary risks associated with ADASUVE?

Other medications for treatment of acute agitation associated with schizophrenia and bipolar disorder, both approved (IM antipsychotics), and those used off-label (e.g., oral and IM benzodiazepines) are available. A final determination as to whether ADASUVE offers a reasonable alternative to these medications such that the potential benefit of ADASUVE in providing an effective, noninvasive, treatment with potentially rapid onset of therapeutic effect outweighs the risks of pulmonary toxicity in acutely agitated schizophrenic and bipolar patients will be made after Advisory Committee evaluation.

Francis E. Becker, M.D., F.A.C.P.
Medical Officer,
FDA CDER ODE1 DPP HFD 130

cc: T Laughren
M Mathis
R Levin
K Updegraff
T Michele
K Lehrfeld

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

/s/

FRANCIS E BECKER
11/08/2011

ROBERT L LEVIN
11/08/2011

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

DATE: October 7, 2010

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for complete response action for Staccato Loxapine for Inhalation for the treatment of agitation associated with schizophrenia and bipolar disorder.

TO: File NDA 22-549
[Note: This overview should be filed with the 12-11-2009 original submission of this NDA.]

1.0 BACKGROUND

Loxapine is a typical antipsychotic (primarily D2 antagonism) approved since 1975 for the treatment of schizophrenia. Staccato Loxapine for Inhalation is a single-use, hand-held drug device combination product intended to provide for rapid systemic delivery by inhalation of a thermally generated aerosol of loxapine. Oral inhalation through the Staccato device triggers the controlled rapid heating of a thin film of loxapine to form a drug vapor which is then inhaled. The vapor condenses to aerosol sized particles for delivery to the deep lung, with expectation of rapid systemic delivery. This new dosage form is intended to be used for the treatment of agitation associated with schizophrenia and bipolar disorder. It is a 505(b)(2) application that references the earlier applications for the innovator drug. Three intramuscular forms of atypical antipsychotics are approved for this indication in the US (Zyprexa, Geodon, and Abilify).

The studies in support of this application were conducted under IND 73248. An EOP2 meeting was held with the sponsor on 9-13-07. A meeting to discuss PK comparability data was held on 12-3-08. Additional advice on the pulmonary safety studies was conveyed to the sponsor in a 4-17-09 communication. A preNDA meeting was held on 7-14-09.

The primary clinical reviewer for this application was Dr. Frank Becker and the primary statistical reviewer was Dr. Yeh-Fong Chen. A secondary review of this application was conducted by Dr. Bob Levin. Data from the special pulmonary studies were conducted by Dr. Anya Harry from DPARP. CMC reviews were conducted by David Claffey, Ph.D., ONDQA reviewer for DPP and by Craig Bertha, Ph.D., ONDQA reviewer for DPARP. The pharm/tox review was conducted by Darren Fegley, Ph.D. from DPP. OCP reviews were conducted by Andre Jackson, Ph.D. and Donald Shuirmann, Ph.D. A QT team review was conducted by

Joanne Zhang. QuynhNhu Nguyen, a biomedical engineer from CDRH, reviewed the device manufacturing and performance data, and David Bar from CDRH, OC, also provided comments.

2.0 CHEMISTRY AND CDRH

There are multiple CMC issues for this product that has resulted in a CMC recommendation that it not be approved in this cycle.

-A preapproval inspection of the manufacturing site (Aug 2-11, 2010) resulted in a “withhold” recommendation.

-Dr. Claffey has noted the following deficiencies: (1) There are multiple problems with the stability data generated thus far, resulting in a recommendation for completely redoing the stability testing with the final version of the product in the final version of packaging that still needs to be determined. (2) Inappropriate storage of heat package stability samples. (3) Lack of in-process weight check for tray side for drug. (4) Lack of control over (b) (4) levels in drug film. (5) Capability of (b) (4) operation. (6) Thermogram test deficiencies.

--Dr. Bertha has noted the following deficiencies: (1) method validation for leachables in aerosol; (2) controls for emitted volatiles; (3) stability studies of unprotected product; (4) method for collection for delivered dose uniformity and mass balance; (5) more information about two device failures involving self-actuation.

-QuynhNhu Nguyen, found the following deficiencies: (1) The inspection deficiencies noted above raise concerns about the characterization of the aerosolization performance of the product and the in vitro performance data; (2) complete human factors validation study; (3) valid worst case testing.

3.0 PHARMACOLOGY

The pharmacology/toxicology part of this development program was designed to address several deficiencies in the current knowledge base for this well known drug, and to address specific issues related to the safety of inhalation delivery of loxapine. The pharm/tox group concluded that there were no deficiencies in the pharm/tox data provided that would preclude an approval action for this application.

4.0 BIOPHARMACEUTICS

Andre Jackson reviewed 4 clinical pharmacology studies for this product:

-AMDC-004-101: a dose escalation study (0.625, 1.25, 2.5, 5.0, and 10 mg) in healthy volunteers.

-AMDC-004-102: a multiple dose pk study in stable schizophrenic patients.

-AMDC-004-103: a 2-treatment, 4-period, dose-stratified replicate-design study to assess the single-dose bioequivalence of the Commercial Product Design vs the Clinical Version (studied in the clinical trials). This was the pivotal BE study in this program.

-AMDC-004-106: a SD pk study of the 10 mg product in smokers vs nonsmokers.

Dr. Jackson concluded that the sponsor had established dose proportionality. Regarding the BE study (103), he noted that this was not a “traditional” study, in the sense that the AUC metric was AUC(0-2 hrs), and that the sponsor combined data for the 5 and 10 mg doses. Individual analyses of the 5 and 10 mg doses revealed BE for the 5 mg, but for the 10 mg dose, exposure was slightly greater for the commercial product (CI: 1.095-1.535). [Comment: Although this CI does not meet the standard for strict BE, clinically it is not a problem. First, the only available product would be the commercial product. Second, from a safety and efficacy standpoint, this slight difference is of no consequence.] Thus, Dr. Jackson concluded that the BE data are acceptable.

Dr. Schuirmann also reviewed data for study 103. He noted that whether or not these data support BE for the clinical and commercial products satisfy usual BE standards depends on excluding data for an outlier, a subject who had dramatically lower exposures for the clinical product only. Since the clinical product would never be available, it is generally agreed that this should not be an issue. Dr. Schuirmann defers judgment of combining the 5 and 10 mg doses to OCP and the clinical group.

In sum, the sponsor has established BE for the clinical product, and at least one version of the commercial product.

5.0 CLINICAL DATA

5.1 Efficacy Data

Our efficacy review focused on two multicenter (all US sites), randomized, double-blind, parallel group, placebo-controlled trials of Staccato Loxapine at doses of 5 and 10 mg. Study CSR 004-301 was conducted in agitated schizophrenic inpatients, and Study CSR 004-302, a nearly identical study, was conducted in agitated bipolar 1 disorder inpatients. Both trials were conducted in adult patients (18-65), and patients were randomized (1:1:1) to Staccato Loxapine 5 mg, 10 mg, or placebo. [Note: It should be noted that patients were recruited for these trials from community referrals, and they all had extensive screening and device training prior to randomization. This is not the population most likely to be given this product, i.e., acutely agitated patients presenting in an ER setting. Thus, it is difficult to know whether or not these results could be extrapolated to the setting in which they would likely be used.] There was a third study (CSR 004-201), a smaller phase 2 study involving patients with schizophrenia, schizophreniform disorder, and schizoaffective disorder involving both the 5 and 10 mg doses. The primary endpoint was change from baseline to 2 hours in the PANSS Excited Component (PEC) for the 2 doses combined vs placebo, and the study was positive on this endpoint. It was also positive on the comparison of 10 mg vs placebo, but not for 5 mg vs placebo. The study was not intended to be a primary source of support for the intended claim, and thus the results were not reviewed in detail, and will not be further discussed in this memo.

Patients could be given up to 3 doses in a 24-hour period (with doses 2 and 3 being given only if needed; the 2nd dose \geq 2 hours after dose 1, and the 3rd >4 hours after dose 2). The primary endpoint was the change from baseline to 2 hours in the PEC following dose 1. A key secondary

endpoint was CGI-I at this same 2 hour time point. Other key secondary endpoints for the 10 mg dose were PEC change scores at 10, 20, 30, and 45 minutes. There were multiple tertiary endpoints. The primary analysis was ANCOVA and correction for multiple doses was done with Dunnet's procedure. [Note: The sponsor's proposed procedure for controlling type I error was not fully adequate. However, the p-values on key outcomes were so small that the biometrics group was willing to overlook this deficiency.]

-Study CSR 004-301: The change from baseline to 2 hours in the PEC following dose 1 was -5.5 for placebo, -8.1 for the 5 mg dose ($p=0.0004$), and -8.6 for the 10 mg dose ($p<0.0001$). The p-values for all other time points checked for the 10 mg dose (10, 20, 30, 45, 60, and 90 minutes) were also highly significant in favor of drug. The CGI-I results also highly significantly favored the drug groups over placebo: $p=0.0015$ for 5 mg and $p<0.0001$ for 10 mg. Subgroup analysis for age, gender and race generally revealed consistent findings for these groups.

-Study CSR 004-302: The change from baseline to 2 hours in the PEC following dose 1 was -4.9 for placebo, -8.1 for the 5 mg dose ($p=0.0001$), and -9.0 for the 10 mg dose ($p<0.0001$). The p-values for all other time points checked for the 10 mg dose (10, 20, 30, 45, 60, and 90 minutes) were also highly significant in favor of drug. The CGI-I results also highly significantly favored the drug groups over placebo: $p<0.0001$ for both the 5 and 10 mg groups. Subgroup analysis for age, gender and race generally revealed consistent findings for these groups.

DSI inspected 2 sites, and found no deficiencies that would impact on data integrity.

-Efficacy Conclusions: I agree with Drs. Becker and Chen that the sponsor has demonstrated efficacy for Staccato Loxapine for the acute treatment of agitation associated with schizophrenia and with bipolar 1 disorder. There was a slight numerical advantage for the 10 mg dose compared to the 5 mg dose, but the difference was small, and of questionable clinical significance. Thus, if this product were to be approved, it would be hard to argue for any advantage for the 10 mg dose over the 5 mg dose. Although the sponsor sought in labeling to claim efficacy on the PEC at each time point tested, the study protocols only provided for such testing for the 10 mg dose. This is true, and the statistical reviewer objects to the inclusion of this information for the 5 mg group, however, the p-values for both doses are so highly significant for all of these time points, that I would not object to the inclusion of such descriptive information in labeling. However, a major caveat for the efficacy data is the fact that the studies were conducted in a carefully conducted and trained population. The "popping" sound and flash associated with administration of this product may compromise its efficacy in a more realistic clinical setting.

5.2 Safety Data

The adverse event profile for Staccato Loxapine was typical of that expected for this class of drugs. The most common ($\geq 2\%$) and greater than placebo AEs included dysgeusia (altered taste sensation), sedation, fatigue, and throat irritation. However, a major concern is the pulmonary AEs associated with use of this product.

Pulmonary Safety Concerns for Staccato Loxapine: Dr. Anya Harry from DPARP has been consulting with DPP on this development program from early on, and based on DPARP's input, we had informed the sponsor of the need to carefully evaluate various aspects of pulmonary safety. Based on this advice, the sponsor conducted 3 studies focusing on pulmonary safety. These included a study in healthy controls, a study in patients with asthma, and a study in patients with COPD. Overall, the pulmonary safety database included 135 subjects in these 3 special studies who underwent a full pulmonary evaluation, and over 1500 other patients and volunteers for whom respiratory related AEs were reported. For the special pulmonary studies, subjects received two doses of Staccato Loxapine 10 mg with 8-10 hours between dosing, and serial pulmonary evaluations were carried out for 32 to 34 hours after dosing. These assessments included serial spirometry, oxygen saturation measured by pulse oximetry, vital signs, rescue medication use.

Across these 3 trials, FEV1 measures were decreased for Staccato Loxapine treated subjects compared to placebo. These decreases were particularly significant in the study of asthma patients. Furthermore, even greater decreases, which did not quickly return to normal, were observed after the second dose compared to the first. In addition, it was observed that patients exposed to the Staccato Placebo device also experienced a modest decrease in lung function, suggesting that even the device itself has a role in causing bronchospasm. The sponsor also tracked airway related AEs and it was observed that both asthma and COPD patients had an increase in such events (compared to healthy subjects), and a number of such patients were unable to complete the study through 34 hours of assessment. Based on these findings, DPARP has advised that, unless this product represents a significant advance over available treatments, the risk benefit profile may not support an approval action. The concern is that pulmonary problems are commonly comorbid in the psychiatric population of interest, particularly given the high incidence of smoking in schizophrenic and bipolar patients (estimates of 88% for schizophrenia and 70% for bipolar). In many cases of acute agitation, the history of pulmonary problems may be unknown.

QT Study: The QT Team reviewed the QT study for this product (Study 004-107), and agreed with the sponsor's conclusion that no significant QTc prolongation effect was detected.

6.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We did not to take this application to the PDAC.

7.0 LABELING AND COMPLETE RESPONSE LETTER

7.1 Labeling

Since the consensus among the review team was that the safety concerns for this product are sufficient to preclude an approval action at this point, we have not prepared a draft of labeling at this time.

7.2 CR Letter

The CR letter provides details on the multiple significant deficiencies, and as noted, does not provide draft labeling at this time, given the numerous problems that would need to be addressed before we could move forward with this application.

8.0 CONCLUSIONS AND RECOMMENDATIONS

I agree with the review team that the deficiencies for this application are sufficient to justify a CR action at this time. Primary clinical concerns include both the pulmonary safety issues, and the fact that this product has not been tested adequately in the typical emergency room setting, i.e., naïve patients with a less than optimal medical history, and the population most likely to be administered this product. As Dr. Becker has noted, there are alternative products available for the treatment of acute agitation in schizophrenia. In addition, there are multiple CMC and CDRH concerns that need to be addressed.

cc:

Orig NDA 22549

HFD-130

HFD-130/TLaughren/MMathis/RLevin/FBecker/KUpdegraff

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/s/

THOMAS P LAUGHREN
10/07/2010

Cross-Discipline Team Leader Review Memo

Date	September 30, 2010
From	Robert L. Levin, M.D.
Subject	Cross-Discipline Team Leader Review
NDA	22-549
Submission Date	December 11, 2009
Cross-referenced NDAs	17-525, 17-658, and 18-039 (Lederle Labs) Loxapine oral tablets, oral solution, and intramuscular injection
Related IND	73-248 <i>Staccato</i> [®] Loxapine for Inhalation for the treatment of acute agitation associated with schizophrenia or bipolar disorder, manic phase
Proprietary / Established (USAN) names	ADASUVE [®] <i>Staccato</i> [®] Loxapine for (oral) Inhalation
Dosage forms / strength	Combination Drug-Device Product – Single Use Inhalation Device Loxapine 5 mg and 10 mg
Proposed Indication(s)	1. Acute Agitation associated with Schizophrenia 2. Acute Agitation associated with Bipolar Disorder, Mania
Recommended:	Complete Response

1. Introduction to the Review

Alexza Pharmaceuticals, Inc. has submitted NDA 22-549 as a 505(b)(2) marketing application, referencing the innovator drug product, Loxitane oral tablets, oral solution, and intramuscular injection (Lederle Labs, NDA# 17-525, 17-658, and 18-039). The sponsor has developed *Staccato* Loxapine for the treatment of agitation associated with schizophrenia or bipolar disorder. *Staccato* Loxapine is based on the proprietary *Staccato* delivery system developed by Alexza Pharmaceuticals, Inc. (Alexza).

Staccato Loxapine is a new dosage form of loxapine, an approved first generation antipsychotic drug that has been available in the U.S. since 1975 for the treatment of schizophrenia. Loxapine is a dibenzoxazepine compound. It binds with high affinity to the dopamine D₂ receptor and acts as an antagonist at this receptor. Loxapine also binds at the serotonin 5-HT_{2a} receptor. Although no longer marketed, an intramuscular formulation of loxapine had been available for the treatment of acute agitation.

Staccato[®] Loxapine for [oral] Inhalation is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery of loxapine through absorption at the deep lung. Oral inhalation through the device initiates the controlled, rapid heating (up to 400°C) of a thin film of excipient-free loxapine, resulting in a thermally generated

drug vapor, which rapidly condenses into aerosol particles. The particles are of an appropriate size for delivery to the deep lung where the drug is rapidly absorbed.

This memorandum will consider in detail the critical pulmonary safety, CMC, and device issues that have led to my recommendation for a Complete Response action.

2. Background/Regulatory History/Foreign Regulatory Actions

Alexza submitted the initial IND (73-248) for *Staccato* Loxapine on August 31, 2005. The target indication was acute agitation associated with schizophrenia or bipolar disorder. The initial IND submission contained Protocol AMDC-004-101, which was a phase 1 pharmacokinetic study in healthy subjects. The two pivotal efficacy and safety protocols included: 1) Protocol AMDC-004-301, the controlled efficacy and safety study in schizophrenia, which was submitted on December 7, 2007; and 2) Protocol AMDC-004-302, the controlled efficacy and safety study in bipolar mania, which was submitted on June 16, 2008.

The clinical program was discussed with the sponsor at the end of Phase 2 (EOP2) meeting for *Staccato* Loxapine on September 13, 2007. Agreement was reached on the design of the Phase 3 studies. The design of the pulmonary safety program was also discussed at the EOP2 meeting. In an FDA communication dated April 17, 2009, the Division provided additional recommendations regarding the design of pulmonary safety and the design of a thorough study. The Division provided comments and recommendations on the sponsor's proposed statistical analysis plan in several communications (April 6, 2007; November 5, 2008; March 23, 2009; and April 24, 2009) and at the Pre-NDA meeting on July 14, 2009.

In the Type C Meeting on December 3, 2008 the Division and the sponsor discussed the pharmacokinetic comparability data (in vitro and in vivo) between the commercial and clinical versions of *Staccato* Loxapine. During the Pre-NDA Meeting on July 14, 2009, we continued the discussion about the pharmacokinetic data from the bioequivalence study (AMDC-004-103). The Division requested additional PK data from the bioequivalence data and provided further feedback regarding the analysis of the bioequivalence study data.

3. Chemistry Manufacture and Controls (CMC) Review – David Claffey, Ph.D.

David Claffey Ph.D. performed the CMC review for the Division of Psychiatry Products. Dr. Claffey recommends a Complete Response action, due to a number of critical problems and deficiencies in the application. I agree with his conclusions and recommendations.

3.1 Drug Substance

Dr. Claffey has concluded that the drug substance data provided in DMF (b) (4) are inadequate to support this application. The original NDA (17-525) for loxapine (as the

succinate) was approved in 1975 for orally administered capsules and tablets. NDA 17-658 was approved in 1976 for the loxapine HCl salt. NDA 18-039 was approved in 1979 for an intramuscular formulation of the HCl salt. All of these applications have been discontinued for business reasons. Several generic products have been approved and remain active for loxapine succinate orally administered capsules (ANDA 72- 206) with strengths up to 50 mg. The proposed product incorporates the (b) (4) manufactured all lots that were used in the pivotal phase 3 studies (Clinical Version 2). All subsequent lots (for Commercial Versions of the drug product) were manufactured by (b) (4) (DMF (b) (4) The drug product manufactured from drug substance from both suppliers were comparable.

3.2 Drug Product

As noted above, the proposed drug product is a hand-held, single-dose, single-use drug/device combination product. Oral inhalation through the product initiates the heating of a film of excipient-free loxapine coated on a heat package component to form a vapor which condenses into aerosol particles of a specified particle size distribution appropriate for deep lung deposition. Absorption of the drug through the lung provides peak plasma levels in the systemic circulation shortly after administration.

The principal components of the device are presented in the sponsor's figure below:



(b) (4)

(b) (4)

Immediately prior to administration, the health care provider pulls the activation tab (b) (4)

causes an LED light on the device to illuminate. This indicates that the product is ready for administration. The patient is instructed to exhale fully then to inhale through the mouth piece with a steady deep breath, then to remove the mouth piece and to hold their breath briefly. Successful actuation is signaled by the extinction of the green LED light. Actuation is accompanied by a clicking sound and a prominent flash of light, which are produced by the incendiary reaction within the heat package.

Reviewer's note (RL): Four FDA reviewers have used the Staccato placebo device. The users found both the clicking noise and the bright flash to be alarming or startling. In some cases, these startling phenomena prevented the users from completing a full inhalation. The reviewers have concluded that these effects of the device are likely to be an impediment to using the device as intended in some patients, especially if the patient has not been warned or trained to use the device. These device and use features are highly problematic, given that the intended population would be acutely agitated patients who psychotic and/or manic.

(b) (4)

(b) (4)

Dr. Claffey notes that the drug product specification includes typical tests such as appearance, identity, and assay as well as more specific tests for this product such as emitted dose, emitted dose uniformity, aerosol particle size distribution and aerosol particulates. Impurity levels (including (b) (4) levels) are measured in the aerosol rather than the drug film. The proposed limits are in agreement with ICH Q3B recommendations. Three critical quality attributes were identified: emitted dose, aerosol purity and aerosol particle size distribution. These attributes were tested during design verification testing after modifications were made to the product during development.

Dr. Claffey also notes that the NDA review was complicated by the fact that the sponsor had developed numerous versions of the device and had not clearly specified the changes initially. At the time of the NDA filing, the sponsor had referred to only a single version. Dr. Claffey requested additional information from the sponsor to clarify the changes that had occurred; as a result of the requests, the sponsor described the modifications and applied version numbers. These included: Clinical Version 1, Clinical Version 2, Commercial Version 1, Commercial Version 2, and Commercial Version 3 (or 2.1). Subsequently, during the review cycle the sponsor proposed additional changes; a version number for this device has not been assigned.

Clinical Version 1 was used for the phase 1 and phase 2 clinical studies. Clinical Version 2 was used in the two pivotal phase 3 studies. Dr. Claffey notes that the sponsor completely redesigned the device after completion of the phase 3 studies to give Commercial Version 1. The changes allowed for (b) (4)

The sponsor has stated that these changes (b) (4)

(b) (4) A bioequivalence study was conducted comparing the pharmacokinetics of Commercial Version 1 and Clinical Version 2 (the device used in the pivotal clinical studies). In addition, the sponsor conducted in vitro characterization studies to link the clinical performance of Commercial Version 1 with that of Clinical Version 1. Several changes resulted in Commercial Version 2. These changes included (b) (4) Commercial

Version 2 was used in the clinical safety studies (pulmonary and the QT study) as well as registration stability studies. Modification of (b) (4)

(b) (4) resulted in Commercial Version 3 (a.k.a. Commercial Version 2.1). Modification to Commercial Version 2.1 during the review cycle included a change in (b) (4)

3.3 Pre-approval Inspection of Facilities and Quality Issues Observed

The facilities inspection has been completed. Dr. Claffey accompanied the investigators at the final drug manufacturing site, Alexza Pharmaceuticals, Mountain View, CA from August 2-11, 2010. There were a number of significant problems observed that have contributed to the recommendation for a complete response action. The San Francisco District Office issued a withhold recommendation at the conclusion of the preapproval inspection.

A major area of concern upon inspection was whether there was adequate integrity of the registration stability data. Dr. Claffey has concluded that the lots used for the registration stability testing no longer adequately represent the proposed commercial drug product. In addition, the data cannot be used as the primary stability data to assign an expiry period.

The inspectors observed [REDACTED] (b) (4)

The inspectors observed that the registration stability samples [REDACTED] (b) (4)

[REDACTED] This is a violation of cGMP (21 CFR 211.166(a) (4) and a breach of the stability protocol. The inspector and Dr. Claffey had additional significant concerns: 1) there was inappropriate storage of heat package stability samples; 2) there was a lack of in-process weight check for the tray side for the drug substance; 3) there was a lack of control of [REDACTED] (b) (4) levels in the drug film; 4) there is questionable capability of the drug [REDACTED] (b) (4) operation; and 5) there was insufficient control over heat package heating (thermogram test).

3.4 Unresolved CMC Issues

Dr. Claffey has concluded that he cannot make a recommendation for approval until the outstanding issues outlined below are resolved:

1. Lack of integrity of the registration stability data.
2. Inappropriate storage of heat package stability samples
3. Lack of in-process weight check for tray side for drug

4. Lack of control over (b) (4) levels in drug film
5. Questionable capability of the (b) (4) operation
6. Results of thermogram testing: insufficient control over heat package heating
7. The DMF (b) (4) is not acceptable
8. The Office of Compliance is in the process of finalizing their recommendation.
9. The CDRH review team has concluded that the application is not acceptable.

4. CMC Consultant - Craig M. Bertha, Ph.D. – Division of Pulmonary and Allergy and Rheumatology Products

The Division consulted Dr. Bertha in order to seek expertise from CMC reviewers familiar with inhalation products. Dr. Bertha reviewed the extractables/leachables data, drug characterization studies, the delivered dose uniformity (DDU) data, and the aerodynamic particle size distribution (ASPD) methods. In addition, he evaluated and compared the *in vitro* dose performance data across the versions of the device. Overall, Dr. Bertha has recommended that this application be approved from a CMC perspective related to the aspects of the drug uniquely associated with products for oral inhalation.

5. CDRH Devices Review - QuynhNhu Nguyen, Biomedical Engineer

Dr. Nguyen conducted her review in collaboration with Dr. Claffey. Dr. Nguyen' review focused on the verification and validation measures conducted with the product. These measures include *in-vitro* performance testing, electromagnetic compatibility, electrical, mechanical, and thermal safety, biocompatibility, sterilization/shelf life/reuse, and software information. Dr. Nguyen has concluded that the device manufacturing and performance are unacceptable, and she recommends a Complete Response Action. I agree with here conclusions and recommendations.

There were many evolutionary changes during the development of the product. CDRH reviewed the verification and validation testing that were conducted on the finished products. Comparative *in vitro* data on the device versions, (in particular Clinical Version 2 and Commercial Version 1), were provided in the submission for the key performance parameters of emitted dose content uniformity, aerosol particle size distribution and aerosol impurities. Data for this comparison were derived from verification and/or release test results from various lots of the device versions. The results for the key performance parameters indicate acceptable agreement between the two device versions and support the conclusion that the devices are comparable. In addition, the two device versions were evaluated to compare two key user interface characteristics: 1) the inspiratory resistance of the device, and 2) the performance of the breath actuation mechanism. Inhalation resistance was tested as part of design verification testing for the commercial version. Pre-defined inhalation resistance acceptance criteria, consistent with the clinical version performance, were met. The breath actuation mechanism for the Commercial Version 1 consists of (b) (4) s the Clinical Version. An actuation reliability study, product characterization studies, and registration stability studies were conducted with

Commercial Version 2. The differences between Commercial Version 2 and Commercial Version 2.1 do not impact the aerosol performance of the product.

5.1 CDRH Inspection Findings

The CDRH Office of Compliance conducted a review of the manufacturing portion of the application. There were a number of important findings. Dr. Nguyen has outlined the four key inspection findings that would have a direct impact on the analysis of the performance data submitted. The findings pertain to the manufacturing and testing processes that would directly affect the characterization of the aerosolizing performance of the product. *Observation 2* of the inspection indicates that the laboratory controls did not include the establishment of scientifically sound and appropriate specifications and standards designed to assure that components and drug products conform to appropriate standards of identity, strength, quality and purity. *Observation 4* states that control procedures were not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and drug product. *Observation 9* states laboratory records did not include complete data derived from all tests, examinations, and assays necessary to assure compliance with established specifications, and standards. *Observation 10* states that samples of drug products for determination of conformance to written specifications are not representative.

5.2 Human Factors Validation

Dr. Nguyen notes that the sponsor has not conducted a complete human factors validation study using the product to be marketed. The small scale user studies and actuation studies conducted during development do not constitute an acceptable human factors validation study. The CDRH review team recommends that the sponsor conduct a human factors validation study with representative intended user groups (patients and healthcare providers). In her review, Dr. Nguyen has outlined the factors that should be considered as well as the required data and analyses regarding such a study.

5.3 Heat Package Worst Case Testing

Dr. Nguyen has concluded that the sponsor conducted an inadequate worst-case scenario for malfunction of the heat package. Perfect holes of 1mm were drilled in specific areas of the heat package. The sponsor selected locations of the heat package that are in the direction of the mouth piece. Dr. Nguyen states that while this approach has some merit, it is unrealistic. CDRH considers that the worst-case testing should be evaluated by breaking the (b) (4) seam that holds the tray and the lid together. This can induce a tremendous amount of heat that escapes from the heat package and travels through the airway of the product. This heat can potentially contact the patient's mouth, pharynx, and trachea, and lungs, and/or burn the patient or healthcare provider's hands. It would be a requirement to conduct an evaluation that measures the effects of serious compromises to the device (i.e. improperly/partially welded heat packages).

6. Nonclinical Pharmacology/Toxicology

Darren Fegley, Ph.D. conducted the pharmacology/toxicology review. Dr. Fegley has concluded that there are no unresolved pharmacology/toxicology issues. I agree with his conclusion. Furthermore, no clinical safety issues have been identified from the non-clinical findings. The non-clinical studies that supported the approval of the innovator product in combination with published literature, and bridging studies submitted by the sponsor are adequate to support the current submission.

Dr. Fegley states that the sponsor has conducted non-clinical studies conducted by the Sponsor to support the safety of inhalation delivery of loxapine include single and repeat dose inhalation toxicology and toxicokinetic studies in rats and dogs, a cardiovascular and respiratory safety pharmacology study in dogs, pharmacokinetic studies in rats and dogs and *in vitro* metabolism studies. In addition, *in vitro* genotoxicity studies were carried out with loxapine, a loxapine metabolite (8-OH-loxapine), and two loxapine aerosol impurities (b) (4)

The sponsor conducted multiple-dose, nasal inhalation studies in rats and dogs. Treatment resulted in CNS signs consistent with the pharmacology of loxapine. Lethargy, weakness, and ataxia were prominent. In cardiovascular and respiratory studies in dogs, rapid IV infusion high doses of loxapine (1.5 mg/kg) resulted in transient decreases in blood pressure. There was no effect on the QTc or other intervals. There was no effect on respiratory parameters. The sponsor studies the genotoxicity of loxapine in *in vitro* studies. The sponsor also reviewed the published literature regarding in *in vitro* and *in vivo* studies. Dr. Fegley has concluded that, based on a weight of evidence, loxapine is non-mutagenic.

The sponsor did not conduct new non-clinical reproductive and developmental toxicity studies of loxapine. The studies contained in the approved NDA demonstrated no effects on male reproductive performance or sperm morphology in rats or rabbits. No teratogenesis was observed in rats or rabbits. Loxapine disrupted estrous cycling in females rats, which is consistent with the known neuroendocrine effects of neuroleptics. High doses of loxapine, which resulted in marked maternal toxicity, caused an increase in resorptions, a low rate of dystocia, and reduced fetal weights indicative of developmental delay. Early neonatal death was observed when treated rats were allowed to deliver litters.

7. Clinical Pharmacology/Biopharmaceutics

Andre Jackson, Ph.D. performed the Clinical Pharmacology/Biopharmaceutics review. The primary review issue was whether the sponsor had demonstrated bioequivalence (or comparability) between the device version used in the pivotal trials (Clinical-2) and the device version used to be marketed (Commercial-1). The bioequivalence study (AMDC-004-103) was a 2-treatment, 4-period, dose-stratified, replicate-design study to assess the single-dose bioequivalence study of the Clinical and Commercial versions of the Staccato Loxapine drug/device product. Dr. Jackson also reviewed 2 other clinical pharmacology

studies. Study AMDC-004-101 was a single-center, randomized, double-blind, placebo-controlled, dose escalation study of 0.625, 1.25, 2.5, 5, and 10 mg administered as one or two inhalations in healthy subjects. Study AMDC-004-102 was pharmacokinetic, safety, and tolerability study of multiple doses of Staccato Loxapine in subjects on chronic, stable antipsychotic treatment. Dr. Jackson has concluded that the data from the clinical pharmacology studies is acceptable. I agree with his conclusions.

Dr. Jackson notes that the sponsor conducted the bioequivalence analysis in Study 004-103 by combining data from the 5 mg and 10 dose groups. He also notes that since loxapine exhibits dose proportional pharmacokinetics, combining the doses is scientifically acceptable. However, sufficient data were available at each dose level to independently assess equivalent exposures. The primary endpoint was $AUC_{(0-2h)}$ for the comparison of the commercial and clinical formulations of the product. In a separate analysis of the 5 mg dose comparing the Commercial Version-1 and the Clinical Version-2, the exposures were equivalent for $AUC_{(0-2hr)}$, with a 90% CI=[0.999-1.238]. In the separate analysis of the 10 mg dose comparing the Commercial-1 and Clinical-2 versions, the exposure for $AUC_{(0-2hr)}$ were not equivalent (90% CI=[1.095-1.535]). Dr. Jackson notes that although the upper limit of 1.535 exceeds the established limit for conventional equivalence, this does not constitute a safety concern, since the oral capsule formulation of loxapine administered in doses of 60-100 mg/day is much higher than the 10 mg dose of Staccato Loxapine.

Dr. Jackson states that there was not a dose-response efficacy relationship between 5 mg and 10 mg in the efficacy studies. Presumably, Dr. Jackson is pointing to the primary endpoint at 2 hours. I agree that there is not clear dose-relationship at this time point. However, for all other time points, the 10 mg dose demonstrated efficacy, and the 5 mg dose did not. Although these other time points were designated as secondary, my opinion is that the efficacy findings at the time points other than 2 hours are significant, when comparing the 2 doses.

8. Pulmonary Safety Studies

Anya Harry, M.D., Ph.D. performed the review of the pulmonary toxicity studies. The sponsor conducted 3 pulmonary safety studies: one in healthy subjects (004-104), one in patients with asthma (004-108), and one in patients with chronic obstructive pulmonary disease (004-108). Dr. Harry notes that there are highly clinically significant findings of drug-related abnormalities in pulmonary function test results in the studies. The abnormalities were particularly marked and clinically significant in patients with asthma and COPD. In addition, there were clinically significant respiratory signs and symptoms including bronchospasm, dyspnea, wheezing, chest discomfort, and cough). Furthermore, a significant proportion of asthma and COPD patients required rescue treatment with bronchodilator medication. As a result of these significant pulmonary safety findings, Dr. Harry has recommended a complete response action. I agree with Dr. Harry's conclusions and recommendations. The pulmonary safety findings are highly clinically significant. My opinion is that treatment with Staccato Loxapine would not be reasonably safe in patients with schizophrenia, who have an extremely high prevalence of chronic smoking along with a relatively high risk of pulmonary disease burden.

Dr. Harry also states:

“We are particularly concerned regarding the safety of Staccato Loxapine in patients whose pulmonary history may not be known during treatment for acute agitation, as well as the ability of health care or home personnel to recognize and respond to post-dosing respiratory distress.”

“Staccato placebo treatment also resulted in a modest decrease in lung function, suggesting that the Staccato device may play a role in causing bronchospasm.”

Dr. Harry has provided a summary table of findings from the 3 pulmonary safety studies below:

Post-dose Staccato loxapine (10 mg)	Healthy Subjects – Study 004-104	Placebo Study 104	Asthma patients – Study 004-105	Placebo Study 105	COPD patients – Study 004-108	Placebo Study 108
Mean decrease in FEV1	104 ml (2.5%)	103 ml (2.4%)	303 ml/ 537 ml (19%)		125 ml (8%)	
Mean baseline FEV1	4 L	4 L	2.9 L	3.33 L	1.6 L	1.6 L
FEV1 decrease > 10%	27%	27%	85%	12%	80%	67%
FEV1 decrease > 15%	19%	4%	62%	4%	56%	33%
FEV1 decrease > 20%	4%	0	42%	4%	40%	11%
Rescue medication	0	0	54%	12%	40%	22%
Significant respiratory signs or symptoms	0	0	69%	12%	58%	22%

Pulmonary function testing revealed that the forced expiratory volume in one second (FEV1) was significantly decreased in subjects treated with Staccato Loxapine 10 mg, compared to placebo. A decrease in FEV1 constitutes an obstruction to air escape. A decrease greater than 10% is considered clinically significant.

In healthy subjects, there was a loss of ~100 ml in FEV1 after single-dose treatment with either loxapine or placebo. This 100 ml represents a 2.5% decrease from baseline FEV1. To interpret the clinical significance of the change and place it in perspective, Dr. Harry compares this change to the transient decrease in FEV1 observed after a broncho-

provocation diagnostic test may. Among the various tests, a decrease in FEV1 of 10-20% is considered significant, depending on the particular test. The 2.5% decrease in FEV1 in healthy subjects (for both loxapine and placebo treatment) falls short of the 10-20% decrease in FEV1 defined as clinically significant in these bronchoprovocation tests.

Because these are mean numbers for the entire treatment group, it may be more relevant to look at number of patients with significantly decreased values as in the “responder analysis.” In addition, it is important to consider individual subjects who developed respiratory signs and symptoms or who required rescue treatment with bronchodilator medication. Respiratory signs and symptoms observed included bronchospasm, dyspnea, wheezing, chest discomfort, and cough.

In healthy subjects (Study 004-104), 27% of subjects had an FEV1 decrease > 10%, 19% had a decrease >15%, and 3% of subjects had a decrease > 20%. There were no reported significant respiratory signs or symptoms, and none of the subjects required rescue treatment with a bronchodilator. Loxapine treatment did not affect oxygen saturation of vital signs.

In asthma patients (Study 004-105), 85% had an FEV1 decrease >10%, and 42% had a decrease >20%. In addition, 69% had significant respiratory signs or symptoms, and 54% required rescue medication. There were considerably more discontinuations from the study before the second dose in the loxapine group than in the placebo group (62% of subjects discontinued before receiving the second dose). Dr. Harry states that the pulmonary safety results in the asthmatic subjects are quite concerning (representing airway obstruction. It is even more concerning that the decreases were markedly larger and did not show recovery after the second dose, which was given 8 hours after the first dose. The proposed dosing interval for Staccato Loxapine is every 2 hours up to 3 times per day, which would imply repeat dosing prior to FEV1 recovery. In addition, this product will be used in acutely agitated patients who may be unable to give a clear history of asthma and may be noncompliant with asthma controller medications. Further, patients who are sedated may be unable to report respiratory symptoms following dosing.

Sedation plus obstruction: intubation. The potential complications that could occur in an asthmatic patient that may develop bronchospasm as well as a prolonged sedative effect could result in the need for intubation and

Dr. Harry also expressed concern that asthmatics with greater severity of disease were not well represented in the study:

“It is concerning that the population size decreases significantly in the loxapine treated asthmatic group vs. the placebo asthma group, with only 10/26 patients completing both doses in the loxapine group. This was also seen in the COPD group study where 19/26 or 73.1% of loxapine treated subjects received Dose 2, while 26/27 or 96.3% of placebo treated subjects received Dose 2. It is unclear if 10 of 26 patients with asthma is a sufficient sample size to evaluate the effects of multiple dosing with Staccato Loxapine on the pulmonary safety in this target population.”

In subjects with COPD (Study 004-108), treated with loxapine, 80% had an FEV1 decrease >10%, and 40% had a decrease > 20%. In COPD patients, 58% had significant respiratory signs or symptoms, and 23% required rescue medication with a bronchodilator. A high proportion of subjects discontinued before receiving the second dose. A greater proportion of current smokers in the Staccato Loxapine group had a clinically significant FEV1 decrease than current smokers in the placebo group. There were no significant differences observed between current smokers and former smokers within the Staccato Loxapine group

Dr. Harry states that the findings are not surprising that smaller decreases in FEV1 were seen in the COPD population compared to the asthma population, since by definition COPD patients have some degree of fixed rather than reversible airway obstruction. In addition, starting from a lower baseline, a smaller decrease may be sufficient to cause respiratory compromise. Since many patients with schizophrenia and bipolar disease smoke, it is likely that a large portion of patients receiving this drug will have some degree of respiratory disease at baseline.

Dr. Harry expresses concern about the COPD subjects' severity of disease. The sponsor claims that the population for the study was moderate to severe COPD patients. However, the average baseline post-bronchodilator FEV1 (1.8L, 52% predicted) was significantly higher than in most COPD trials, indicating milder disease. For example, the mean post-bronchodilator FEV1 in the Spiriva HandiHaler UPLIFT trial was 1.3L (47% predicted) and in the Advair TORCH trial was 1.2L (44% predicted)

The findings in healthy subjects suggest that the inhalation of loxapine induces some degree of airway hyperresponsiveness. In addition, given the findings in placebo-treated subjects, it appears that treatment with the device itself results in a degree of pulmonary toxicity.

Furthermore, in subjects who received a second dose, there were greater decreases, compared to the first dose, which did not return to baseline at 32 hours post-dose. Thus, Dr. Harry has concluded that the true nadir of the FEV1 following Staccato Loxapine treatment is not known, since rescue albuterol was given immediately per protocol to any subject who had respiratory symptoms or a decrease in FEV1. In addition, there was a higher proportion of subjects who discontinued from the study after receiving a second dose, compared to subjects treated with a single dose.

9. Thorough QT Study

The Cardiorenal QT Interdisciplinary Review Team reviewed the data from the sponsor's dedicated thorough QT study (AMDC-004-107) with *Staccato* Loxapine for Inhalation. The team concluded that there is no QT prolongation effect with treatment with Staccato loxapine (10 mg). I agree with this finding.

The QT study was a single-center, randomized, double-blind, double-dummy, placebo-controlled and moxifloxacin-controlled, 3-period crossover study in 48 healthy subjects. The dose of loxapine inhalation was 10 mg, and the dose of moxifloxacin was 400 mg.

Each subject received 3 treatments in 1 of 6 sequences. Treatment A consisted of: oral placebo and Staccato Loxapine 10 mg. Treatment B consisted of: oral placebo and Staccato placebo. Treatment C consisted of moxifloxacin 400 mg p.o. and Staccato placebo. The study was conducted at a single clinical center with significant experience in conducting a thorough QT study. The sponsor used a blinded core laboratory, employing a manual methodology and a single cardiologist to read the ECGs. The cardiologist was blinded to treatment, period, and sequence. All ECGs were interpreted centrally by U.S. board certified Cardiologists at Cardiacore in a blinded manner.

The primary outcome was the difference from the pre-dose baseline at each time point in the individual subject-corrected QT interval (QTcI). The primary endpoint was based on least squares mean (LSmean) corrected for baseline QTcI, Sequence, Period, Time, Treatment group, and the interaction of Time and Treatment group according to the repeated measures model.

The IRT reviewers concluded that no significant QTc prolongation of Staccato Loxapine (10) was detected in the thorough QT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between Staccato Loxapine (10) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The maximum $\Delta\Delta\text{QTcI}$ occurred at 1 hour post-dose. At 1 hour post-dose, the $\Delta\Delta\text{QTcI}$ for loxapine 10 mg was 5.7 ms [90% CI (ms) = 3.0- 8.4]. The largest lower bound for moxifloxacin occurred at 3 hours post-dose. At 3 hours post-dose, the $\Delta\Delta\text{QTcI}$ for moxifloxacin was 9.6 ms [90% CI (ms) = 6.7- 12.5]. The IRT concluded that the study demonstrated adequate assay sensitivity.

10. Clinical Microbiology

There are no clinical microbiology issues for this application.

11. Clinical

11.1 Efficacy

Francis Becker, M.D. performed the clinical review. He has concluded that the two pivotal efficacy studies demonstrated the efficacy of *Staccato* Loxapine in the treatment of agitation in subjects with a diagnosis of schizophrenia or bipolar disorder. I agree that the 2 studies demonstrated efficacy. In addition, Dr. Becker concluded that there was a dose-response relationship for efficacy in both studies, as demonstrated by the differential treatment effects between the 5 mg and 10 mg doses for most of the time points assessed. Both doses demonstrated efficacy at the primary endpoint (2 hours post-dose). However, the 10 mg dose was efficacious at all time points measured before 2 hours; whereas the 5 mg dose demonstrated efficacy only at 2 hours. Furthermore, it is clinically meaningful that there was measurable efficacy at early time points for the 10 mg dose. Dr. Becker notes that the dose-response relationship was demonstrated by the changes in PEC scores, the changes in CGI-I scores, and the differential use of rescue medications between the 10 mg and 5 mg groups. I agree with Dr. Becker's conclusion about the dose-response

relationship favoring the 10 mg dose. In my opinion, these findings are clinically significant.

11.1.1 Study AMDC-004-301 (Schizophrenia)

Study AMDC-004-301 was a phase 3, multicenter (24 U.S.), randomized, placebo-controlled, fixed-dose study of Staccato Loxapine (5 and 10 mg) in the treatment of acute agitation in subjects with schizophrenia. The Clinical-2 version of the device was used. The study included 344 adult subjects (18-65 years-old) with acute agitation and a diagnosis of schizophrenia. Subjects were randomized to treatment with fixed-dose Staccato Loxapine (5 mg or 10 mg) or Staccato placebo. If there was an inadequate response after the first dose, subjects could receive up to 2 additional doses as needed within 24 hours; however, the primary endpoint was assessed only after the first dose. The study was conducted from February 22, 2008 to June 27, 2008.

The protocol states that patients could be enrolled from the following settings: 1) patients admitted to a hospital setting or research unit for the purpose of the trial, 2) patients already hospitalized for treatment of Schizophrenia who had acute agitation, 3) patients treated at a psychiatric emergency room setting that allowed extended stays in a secluded observation room for the period of the trial. However, the sponsor notes that the vast majority of subjects were enrolled at outpatient research units for the purposes of the studies (004-301 and 004-302). In addition, subjects underwent training on using the device for up to two weeks. Thus, it is possibly that the results of the studies may not be completely generalizable to the populations of patients who would be the primary candidates for such treatment: highly agitated schizophrenic or bipolar patients in an emergency room or acute inpatient unit. Otherwise, the psychiatric and medical inclusion and exclusion criteria were acceptable.

11.1.1.2 Efficacy Findings in Study AMDC-004-301

The primary efficacy measure was the Positive and Negative Syndrome Scale (PANSS). The primary endpoint was the mean change from baseline in the PANSS Excited Component (PEC) score at 2 hours after the first dose. This endpoint was prospectively agreed upon with the division. The PANSS Excited Component consists of 5 items from the PANSS: 1) poor impulse control, 2) Tension, 3) Hostility, 4) Uncooperativeness, and 5) Excitement. In order to qualify for treatment, a subject must have been judged to be clinically agitated. They must have had a pre-treatment score of ≥ 14 on the PEC. In addition, they must have had a score \geq on at least one of the 5 items of the PEC.

The table below outlines the primary efficacy findings in Study AMDC-004-301. The study demonstrated the efficacy of Staccato Loxapine at 2 hours post-dose for both doses studied (5 and 10 mg). The changes in PEC score at 2 hours were -5.8, -8.0, and -8.7 for placebo, 5 mg, and 10 mg, respectively. For the 5 mg dose, the treatment effect (compared to placebo) was statistically significant ($p= 0.0004$). For the 10 mg dose, the treatment effect was statistically significant ($P<0.0001$). The overall treatment effect was statistically significant ($P< 0.0001$).

Table 1. Primary Efficacy Endpoint: Change in PEC Score 2 Hours after Dose 1 (ITT Population with LOCF): Trial AMDC-004-301

PEC Score	<i>Staccato</i> Placebo (N=115)	<i>Staccato</i> Loxapine 5 mg (N=116)	<i>Staccato</i> Loxapine 10 mg (N=113)
Mean Baseline PEC Score	17.4	17.8	17.6
Mean change* in PEC score from baseline to 2 hours after Dose 1	-5.8	-8.0	-8.7
p-value for overall treatment effect	p<0.0001	----	----
p-value for active/placebo comparisons	----	p=0.0004	p<0.0001

*LS mean (was used in the primary efficacy analysis)

The key secondary endpoint was the Clinical Global Impression- Improvement (CGI-I) scale score at 2 hours post-dose. The treatment effects at 2 hours, as measured by the CGI-I, were statistically significant for the 5 mg and 10 mg doses. The overall treatment effect was also statistically significant, as shown in the table below.

Table 2. Key Secondary Efficacy Endpoint: CGI-I Score 2 Hours after Dose 1 (ITT Population with LOCF): Trial AMDC-004-301

CGI-S or CGI-I Score	<i>Staccato</i> Placebo (N=115)	<i>Staccato</i> Loxapine 5 mg (N=116)	<i>Staccato</i> Loxapine 10 mg (N=113)
Baseline (mean CGI-S score)	3.9	4.0	4.1
2 hours (mean CGI-I score)	2.8	2.3	2.1
p-value for overall treatment effect	p<0.0001	-----	-----
p-values for active/placebo comparisons	-----	p=0.0015	p<0.0001

The sponsor explored other secondary endpoints. These included the change in PEC at 10, 20, 30, and 45 minutes post-dose, as well as the change at 1.0, 1.5, 4, and 25 hours (using a stepwise statistical procedure). For the 10 mg dose, the treatment effect was statistically significant at all time points tested, as early as 10 minutes post-dose. For the 5 mg dose, the treatment effect was statistically significant only for the primary endpoint (2 hours). These findings indicate that there is a dose-response relationship for efficacy. In my opinion, the positive findings for the 10 mg dose at early time points (10, 20, 30, 45, 60, and 90 minutes) are clinically important.

Table 3. Change in the PEC Score at Assessments through 24 Hours after Dose 1 (ITT Population with LOCF): Trial AMDC-004-301

PEC Score	<i>Staccato</i> Placebo (N=115)	<i>Staccato</i> Loxapine 5 mg (N=116)	<i>Staccato</i> Loxapine 10 mg (N=112)
Baseline (mean)	17.4	17.8	17.6
+10 min (mean Δ)	-1.7	-3.1	-3.4
p-value		NA	p<0.0001
+20 min (mean Δ)	-2.9	-5.2	-6.1
p-value		NA	p<0.0001

+30 min (mean Δ) p-value	-4.1	-6.8 NA	-7.6 p<0.0001
+45 min (mean Δ) p-value	-4.8	-7.4 NA	-8.7 p<0.0001
+1 hour (mean Δ) p-value	-5.2	-7.7 NA	-9.2 p<0.0001
+1.5 hours (mean Δ) p-value	-5.3	-8.2 NA	-9.1 p<0.0001
+2 hours; primary endpoint (LS mean Δ) p-value	-5.8	-8.0 P=0.0004	-8.7 p<0.0001
+4 hours (mean Δ) p-value	-6.3	-8.2 NA	-9.5 p<0.0001
+24 hours (mean Δ) p-value	-4.4	-6.2 NA	-6.9 p<0.0001

11.1.2 Study AMDC-004-302 (Bipolar disorder)

Study AMDC-004-302 had a nearly identical design as Study 004-301. This was a phase 3, multicenter (17 U.S.), randomized, placebo-controlled, fixed-dose study of Staccato Loxapine (5 and 10 mg) in the treatment of acute agitation in subjects with bipolar disorder. The Clinical-2 version of the device was used. The study included 314 adult subjects (18-65 years-old) with acute agitation and a diagnosis of bipolar I disorder, manic or mixed episode. As in Study 004-301, subjects were randomized to treatment with fixed-dose Staccato Loxapine (5 mg or 10 mg) or Staccato placebo. If there was not an adequate response after the first dose, subjects could receive up to 2 additional doses as needed within 24 hours. The primary efficacy endpoint was the change in the PEC score at 2 hours post-dose after the first dose only. The PEC criteria for warranting treatment were the same as in Study 004-301. The study was conducted from July 24, 2008 to November 2, 2008.

11.1.2 Efficacy Findings in Study 004-302

The mean changes in PEC scores at 2 hours were -4.7, -8.2, and -9.2 for the placebo, 5 mg, and 10 mg groups, respectively. For the 5 mg group, the treatment effect (compared to placebo) was -3.5 points on the PEC component. This was statistically significant (p< 0.0001). For the 10 mg dose, the treatment effect (compared to placebo) was -4.5. This was also statistically significant (p< 0.0001).

Table Primary Efficacy Endpoint: Change in PEC Score 2 Hours after Dose 1 (ITT Population with LOCF): Trial AMDC-004-302

PEC Score	<i>Staccato</i> Placebo (N=105)	<i>Staccato</i> Loxapine 5 mg (N=104)	<i>Staccato</i> Loxapine 10 mg (N=105)
Mean Baseline PEC Score	17.7	17.4	17.3
Mean change* in PEC score from baseline to 2 hours after Dose 1	-4.7	-8.2	-9.2
p-value for overall treatment effect	p<0.0001	----	----

p-value for active/placebo comparisons	----	p<0.0001	p<0.0001
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*LS mean (was used in the primary efficacy analysis)

The key Secondary endpoint is the change in CGI-I score at 2 hours. As illustrated in the table below, the changes in CGI-I scores (compared to placebo) were statistically significant for the 5 mg and 10 mg doses.

Table Key Secondary Efficacy Endpoint: CGI-I Score 2 Hours after Dose 1 (ITT Population with LOCF): Trial AMDC-004-302

CGI-S or CGI-I Score	<i>Staccato</i> Placebo (N=105)	<i>Staccato</i> Loxapine 5 mg (N=104)	<i>Staccato</i> Loxapine 10 mg (N=105)
Baseline (mean CGI-S score)	4.1	4.0	4.0
2 hours (mean CGI-I score)	3.0	2.1	1.9
p-value for overall treatment effect	p<0.0001	-----	-----
p-values for active/placebo comparisons	-----	p<0.0001	p<0.0001

The sponsor explored other secondary endpoints. These included the change in PEC at 10, 20, 30, and 45 minutes post-dose, as well as the change at 1.0, 1.5, 4, and 25 hours (using a stepwise statistical procedure). For the 10-mg dose, the treatment effect (compared to placebo) was statistically significant at each time point, as early as 10 minutes. The sponsor did not perform a statistical analysis for the 5-mg dose. However, there appear to be numerical trends toward a treatment effect for the time points assessed.

Table Change in the PEC Score at Assessments through 24 Hours after Dose 1 (ITT Population with LOCF): Trial AMDC-004-302

PEC Score	<i>Staccato</i> Placebo (N=105)	<i>Staccato</i> Loxapine 5 mg (N=104)	<i>Staccato</i> Loxapine 10 mg (N=105)
Baseline (mean)	17.7	17.4	17.3
+10 min (mean Δ)	-1.8	-3.6	-4.0
p-value		NA	p<0.0001
+20 min (mean Δ)	-3.2	-5.8	-6.7
p-value		NA	p<0.0001
+30 min (mean Δ)	-3.9	-7.5	-8.0
p-value		NA	p<0.0001
+45 min (mean Δ)	-4.6	-8.1	-8.8
p-value		NA	p<0.0001
+1 hour (mean Δ)	-5.0	-8.8	-8.8
p-value		NA	p<0.0001
+1.5 hours (mean Δ)	-5.0	-8.3	-8.8
p-value		NA	p<0.0001
+2 hours; primary endpoint (LS mean Δ)	-4.7	-8.2	-9.2
p-value		p<0.0001	p<0.0001
+4 hours (mean Δ)	-6.1	-8.3	-9.3
p-value		NA	p<0.0001
+24 hours (mean Δ)	-4.5	-6.1	-6.0
p-value		NA	p<0.0001

11.2 Pediatric use/PREA waivers/deferrals

The use of Staccato Loxapine has not been studied in pediatric patients. In accordance with the Pediatric Research Equity Act, the sponsor submitted a request for a partial waiver for pediatric studies in children younger than 10 years of age and a deferral of the requirements for pediatric studies in the age group of 10 to 17 years-old. The sponsor reasoned that the necessary studies would be impossible or highly impractical children younger than 10 years-old, due to the small number of patients in this subgroup with a diagnosis of schizophrenia and bipolar disorder. The sponsor requested a deferral of studies in children and adolescents aged 10 to 17 years-old reasoning that: 1) the drug is ready for approval for use in adults before the pediatric studies are complete; and 2) the required lower dose strengths of the *Staccato* Loxapine commercial product have not been optimized for use in children and adolescents.

A PeRC PREA subcommittee meeting was held on August 11, 2010. The Division requested a full waiver from all pediatric studies, due to the pulmonary toxicity observed in the pulmonary safety studies. The committee granted the full waiver. The committee requested that labeling discuss that the absence of pediatric data is due to safety concerns.

11.2 Safety Review

Francis Becker, M.D conducted the safety review. Dr. Becker has concluded that treatment with Staccato Loxapine in patients with schizophrenia or bipolar would not be reasonably safe, due to the serious pulmonary function test abnormalities. In addition, a significant proportion of subjects in the pulmonary safety studies developed clinically significant respiratory symptoms requiring rescue treatment with bronchodilator medication in some cases. Patients with schizophrenia and bipolar disorder have a high rate of smoking; thus, they are at relatively high risk of developing chronic obstructive disease. Thus, these patient populations would have a relatively high risk of developing pulmonary toxicity if exposed to *Staccato* Loxapine for Inhalation. I agree with Dr. Becker's conclusion. In my opinion, treatment with *Staccato* Loxapine would not be reasonably safe, due to the pulmonary toxicity findings in the clinical program. In general I agree with Dr. Becker's conclusions regarding the overall safety analysis.

11.2.1 General Safety Considerations

The sponsor conducted adequate safety assessments and submitted adequate safety data for assessing the safety profile of treatment with Staccato Loxapine. The types and frequency of safety assessments was adequate, given that the clinical studies used one or two administrations of Staccato Loxapine per subject. The safety assessments included the following: adverse events monitoring, vital signs, ECG, pregnancy testing, extrapyramidal symptoms monitoring, clinical laboratory testing, urine drug screen, and alcohol screening.

In addition, there was adequate exposure to Staccato Loxapine in the safety database to support the application. Overall, in the 13 clinical studies, 1,147 subjects were exposed to Staccato Loxapine in the clinical development program. The majority of subjects (73%) were treated with single doses of Staccato Loxapine. Approximately 20% were treated with 2 doses. Approximately 5%, were treated with 3 doses, and 2%, and were treated with 4 doses. The doses ranged between 0.625 mg and 10 mg. In the 2 pivotal studies, a total of 438 subjects were treated with Staccato Loxapine (229 subjects in the schizophrenia study and 209 in the bipolar disorder study). Overall, 220 subjects were treated with 5 mg, and 218 were treated with 5 mg. In the phase 2 study (004-201), a total of 209 schizophrenic or schizoaffective disorder subjects were exposed to Staccato Loxapine (104 subjects were treated with 5 mg, and 105 were treated with 10 mg).

The main safety concern is the significant pulmonary toxicity observed in the pulmonary safety studies, especially in subjects with COPD and asthma. However, even in subjects without a history of pulmonary disease, there some significant abnormalities of pulmonary function. On the surface, treatment with *Staccato* Loxapine appeared to be reasonably safe in the 2 pivotal studies. However, one subject in the pivotal trials discontinued due to bronchospasm. One subject had wheezing. Pulmonary function was not formally assessed in the pivotal studies. It is possible that some subjects could have had abnormalities in pulmonary function tests due to treatment with Staccato Loxapine. It is also possible that ascertainment of such signs and symptoms differed between the pivotal studies and the pivotal studies, due to the different levels of monitoring for respiratory signs and symptoms. Potentially, this could have resulted in an underestimate of pulmonary toxicity in the pivotal studies and other clinical studies (phases 1 and 2). While the pulmonary toxicity was drug-related in the pulmonary safety studies, there was also a degree of toxicity with the placebo device. Thus, it would be important to explore the factors that contribute to pulmonary toxicity with use of the product.

11.2.2 Major Safety Findings

The major safety findings were the highly significant pulmonary toxicity findings discussed above. There was one death in the clinical program, which was not drug-related (a drug overdose in a placebo-treated subject). There were three non-fatal serious adverse events, none of which appeared to be related to *Staccato* Loxapine treatment. Five subjects in the *Staccato* Loxapine treatment group were discontinued due to adverse events. In two of these cases the adverse event leading to discontinuation were probably related to *Staccato* Loxapine treatment (urticaria and bronchospasm). In the pivotal trials, several adverse events were probably drug related: dysgeusia, sedation, fatigue, throat irritation, akathisia, tremor, dyskinesia, and dystonia. Dysgeusia was dose-related. In healthy subjects, sedation and dizziness were drug-related. There were no significant changes in vital signs, ECG, or clinical laboratory testing.

There is no foreign premarketing or postmarketing experience with Staccato Loxapine. The sponsor did not provide a safety update, because there were no ongoing studies.

12. Statistical

Yeh-Fong Chen, Ph.D. performed the statistical review. Dr. Chen confirmed the sponsor's findings, and she has concluded that both pivotal studies demonstrated the efficacy of Staccato Loxapine (for 5 mg and 10 mg at 2 hours) in the treatment of acute agitation in patients with schizophrenia or bipolar disorder. I agree with Dr. Chen's conclusions.

For both studies (004-301 and 004-302), the primary efficacy measure was the absolute change in the Positive and Negative Syndrome Scale (PASS). The primary endpoint was the PANSS Excited Component (PEC) at 2 hours post-dose, compared with placebo. The key secondary efficacy endpoint was CGI-I score at 2 hours post-dose, compared with placebo. Dr. Chen confirmed the sponsor's analysis results for the primary (PEC) as well as the key secondary (CGI-I) efficacy outcomes at 2 hours post-dose in both studies and for both doses (5 and 10 mg). Dr. Chen notes that the 5 mg dose did not demonstrate efficacy for any time points other than 2 hours. On the other hand, the 10 mg dose demonstrated efficacy for all time points assessed.

13. Advisory Committee Meeting

We did not convene an advisory committee meeting, because the review issues were clear. Furthermore, loxapine is a drug with which there is considerable experience.

14. Financial Disclosure

There are no unresolved issues regarding financial disclosures.

14. Labeling

We have not conducted a labeling review or discussed labeling with the sponsor, because we plan to take a complete response action. There are numerous significant concerns about the application among various disciplines of the review team.

15. DSI Inspections

We selected two sites that had a large number of subjects enrolled in both clinical studies (AMDC-004-301– schizophrenia and AMDC-004-302– bipolar, mania). We had no specific concerns about any of the clinical sites before choosing the sites to be inspected.

Anthony Orenca, M.D. conducted the DSI review. Richard L. Jaffe, M.D. was the principal investigator at site #10: Belmont Center for Comprehensive Treatment, 4200 Monument Road, Philadelphia, PA. Dr. Jaffe enrolled subjects in studies AMDC-004-301 and AMDC-004-302.

Dr. Orenca concluded, that for Dr. Jaffe's site, the final classification was: No Action Indicated (NAI). Dr. Jaffe enrolled 15 subjects in study 301 and 18 subjects in study 302. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, correspondence, informed consent documents, and sponsor-generated

correspondence. Dr. Orenca stated that there were no limitations of the inspection. He also concluded that the data in support of clinical efficacy and safety from this clinical site, from both pivotal studies [301 and 302], appear acceptable for this specific indication. Thus, DSI has no significant concerns regarding the data from this site.

Adam F. Lowy, M.D. was the principal investigator at sites #12 and #17: Comprehensive Neuroscience, Inc., Psychiatric Institute of Washington, 4228 Wisconsin Ave., N.W., Washington, D.C. 20016. Dr. Lowy enrolled 5 subjects in study AMDC-004-301 and 14 subjects in AMDC-004-302. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, correspondence, informed consent documents, and sponsor-generated correspondence. Dr. Orenca stated that there were no limitations of the inspection. Dr. Orenca noted that there were some regulatory deficiencies with respect to Study AMDC 004-301; however, the findings are considered minor and isolated in occurrence, and it is unlikely that these would impact data reliability. Dr. Orenca concluded that the data, in support of clinical efficacy and safety from this clinical site for both pivotal studies, appear acceptable for this specific indication. Dr. Orenca concluded, that for Dr. Lowy's site, the final classification was: Voluntary Action Indicated (VAI).

Overall, Dr. Orenca concluded that there were no significant regulatory violations that would impact data integrity from the 2 clinical sites inspected. The inspection documented general adherence to Good Clinical Practices regulations governing the conduct of clinical investigations. The data are considered reliable in support of the application.

16. Conclusions and Recommendations

16.1 Recommended Regulatory Action

I recommend a Complete Response action, due to the considerable risk of pulmonary toxicity with use of Staccato Loxapine for Inhalation. Three pulmonary safety studies demonstrated that there were significant abnormalities in pulmonary function test parameters for healthy subjects, subjects with asthma, and subjects with COPD. The abnormalities were marked in the asthmatic and COPD patients. The primary findings from pulmonary testing were decreases in forced expiratory volume in one second (FEV1). A significant decrease in FEV1 indicates that there is an obstruction to air escape. A decrease in FEV1 of > 10% is considered clinically significant. In healthy subjects, 27% had a decrease > 10% in both the Staccato Loxapine and the Staccato placebo groups. This suggests that both delivery of loxapine to the lung and the use of the Staccato device may play a role in the development of pulmonary toxicity and bronchospasm. In healthy subjects, 19% treated with Staccato Loxapine and 4% treated with Staccato placebo had decreases in FEV1 >15%. In addition, 4% of healthy subjects treated with Staccato Loxapine had a decrease in FEV1 > 20%. To put these data in perspective, Dr. Harry notes that standard bronchoprovocation tests cause decreases in FEV1 of 10-20%.

In subjects with asthma and COPD the proportions of subjects with significant decreases in FEV1 were much higher. In asthma subjects, 85%, 62%, and 42% had decreases in FEV1 >10%, >15%, and >20%, respectively. In COPD subjects, 80%, 56%, and 40% had decreases in FEV1 >10%, >15%, and >20%, respectively. Moreover, a high proportion (40-69%) of asthmatic and COPD subjects had significant respiratory signs/symptoms or required rescue treatment with bronchodilator medication. Respiratory signs and symptoms included bronchospasm, dyspnea, wheezing, chest discomfort, and cough.

Subjects treated with a second dose had greater decreases in FEV1 (compared to their first dose) which did not return to baseline at 32 hours post-dose. In addition, a significant proportion of asthmatic and COPD subjects discontinued before receiving the dose, due to a decreased FEV1 or need for rescue treatment of respiratory symptoms. As a result, Dr. Harry notes that the true nadir of the FEV1 following Staccato Loxapine treatment is not known.

Additional factors could contribute to an excessive risk of pulmonary toxicity in the intended population. Patients with schizophrenia and bipolar disorder have a high rate of tobacco smoking. Thus, many of these patients will have some degree of respiratory disease burden at baseline. As demonstrated in the pulmonary safety studies, exposure to Staccato Loxapine can result in acute obstructive exacerbations requiring rescue bronchodilator treatment in patients with baseline obstructive disease. Another concern is that acutely agitated patients with schizophrenia or bipolar disorder may be incapable of providing an accurate history of pulmonary disease. Similarly, healthcare professionals may not be able to perform an adequate respiratory examination during an acute episode of agitation. Moreover, sedation from Staccato Loxapine could obscure respiratory signs and symptoms. Finally, dosage and administration of proposed labeling indicates that Staccato Loxapine could be administered every 2 hours up to 3 times, which would allow repeat dosing prior to recovery of FEV1.

16.2 Recommended Comments to the Applicant in the Regulatory Action Letter

16.2.1 Pulmonary Toxicity

Comments

The primary clinical safety concern is the pulmonary toxicity associated with *Staccato* Loxapine treatment. Clearly, the toxicity is drug-related. However, an additional component of the toxicity appears to be related to use of the device itself. In the 3 pulmonary safety studies, pulmonary function testing revealed clinically significant decreases in FEV1 that were greater than 10%, 15%, and 20% for individual subjects. A decrease in FEV1 of greater than 10% is considered clinically significant. Furthermore, standard bronchoprovocation tests induce a decrease in FEV1 of 10-20%. In healthy subjects, 27% of the loxapine and the placebo groups had a decrease in FEV1 >10%. Approximately 19% of healthy subjects treated with loxapine and 4% treated with placebo had decreases in FEV1 >15%. An additional 4% of healthy subjects treated with loxapine had decreases in FEV1 >20%.

In subjects with asthma or COPD, the FEV1 findings were marked. Moreover, a substantial proportion of subjects in the asthma and COPD studies had significant respiratory signs and symptoms requiring rescue treatment with bronchodilator medication. In asthma subjects, 85%, 62%, and 42% had decreases in FEV1 >10%, >15%, and >20%, respectively. In COPD subjects, 80%, 56%, and 40% had decreases in FEV1 >10%, >15%, and >20%, respectively. A high proportion (40-69%) of asthmatic and COPD subjects had significant respiratory signs/symptoms or required rescue treatment with bronchodilator medication. Respiratory signs and symptoms included bronchospasm, dyspnea, wheezing, chest discomfort, and cough.

Pulmonary toxicity was dose-related. Subjects treated with a second dose had greater decreases in FEV1 (compared to their first dose) which did not return to baseline at 32 hours post-dose. A significant proportion of asthmatic and COPD subjects discontinued before receiving the second dose, due to a decreased FEV1 and/or the need for rescue treatment of respiratory signs and symptoms. As a result, one cannot determine the true nadir of the FEV1 following treatment with *Staccato* Loxapine in the pulmonary safety studies.

Additional factors could contribute to an excessive risk of pulmonary toxicity in the intended population. Patients with schizophrenia and bipolar disorder have a high prevalence of tobacco smoking. Thus, many of these patients will have some degree of respiratory disease burden at baseline. Exposure to *Staccato* Loxapine can result in acute obstructive exacerbations requiring rescue bronchodilator treatment in patients with baseline obstructive disease. Another concern is that acutely agitated patients with schizophrenia or bipolar disorder may be incapable of providing an accurate history of pulmonary disease during the episode. Similarly, healthcare professionals may not be able to perform an adequate respiratory examination during an acute episode of agitation. Moreover, sedation from *Staccato* Loxapine could obscure respiratory signs and symptoms. Finally, the dosage and administration section of proposed labeling states that *Staccato* Loxapine could be administered every 2 hours up to 3 times, which would allow repeat dosing prior to recovery of FEV1.

In our opinion, labeling or a risk evaluation and mitigation strategy (REMS) would not provide a reasonable degree of safety regarding the risk of pulmonary toxicity in the intended population.

Requirements for Resolving the Deficiencies:

You would be required to submit adequate data on a formulation of the *Staccato* Loxapine product that demonstrates a lack of pulmonary toxicity.

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/s/

ROBERT L LEVIN
10/05/2010

CLINICAL REVIEW

Application Type NDA
Submission Number 22549 S-00
Submission Code N

Letter Date December 11, 2009
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Reviewer Name Francis E. Becker, M.D.
Review Completion Date September 17, 2010

Established Name Loxapine
Trade Name Staccato Loxapine for
Inhalation
Therapeutic Class Antipsychotic
Applicant Alexza Pharmaceuticals
Related IND 73248

Priority Designation Standard

Formulation Single-Use Inhaler: 5 mg, 10
mg
Dosing Regimen 5-10 mg Q 2 hrs PRN (max: 30
mg/day)
Indication Agitation
Intended Population Adults with Schizophrenia or
Bipolar Disorder

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the data provided, I recommend a Complete Response action be taken for *Staccato* Loxapine for Inhalation in the treatment of acute agitation associated with Schizophrenia or Bipolar Disorder. In an acute situation, *Staccato* Loxapine may prove difficult to use, and the risk of serious respiratory adverse events associated with its use in the target population is very high. Moreover, appropriate, alternative medication is available.

1.2 Risk Benefit Assessment

In two pivotal trials, *Staccato* Loxapine demonstrated efficacy in the rapid treatment of agitation associated with Schizophrenia (Trial **004-301**) and Bipolar Disorder (Trial **004-302**). Both the 5- and 10-mg doses met the primary efficacy endpoint (change in PEC score from baseline to 2 hours after Dose 1, active vs. placebo) and key secondary endpoint (CGI-I score 2 hours after Dose 1, active vs. placebo). In both trials, the effect size was larger in the 10-mg group compared to the 5-mg group, providing evidence for a dose-response pattern. In addition, device failure rates were very low.

However, most patients were recruited from referrals in the community, undergoing device training and extensive pre-treatment screening (up to 2 days or more in Trial **004-301**, and up to 24 hours in Trial **004-302**). No patients were recruited from psychiatric emergency rooms, yet psychiatric emergency rooms would likely be a common setting for use of *Staccato* Loxapine if it is approved. Patients presenting to a psychiatric emergency room may be less cooperative and are less likely to have an established relationship with the health care provider. Under such circumstances, it is unclear if device training would be as effective as it was in the pivotal trials and if *Staccato* Loxapine could be effectively administered.

In general, the adverse events (AEs) associated with *Staccato* Loxapine were either expected from the known adverse event profile of loxapine or related to the method of loxapine administration (inhalation). In the agitated patient population, the most frequently reported AEs in patients treated with *Staccato* Loxapine were dysgeusia (All *Staccato* Loxapine ~13%) and sedation (All *Staccato* Loxapine 10.5%). Most AEs (96.3%) were mild to moderate. Dysgeusia, sedation (including sedation combined with somnolence), fatigue, and throat irritation were identified as potential adverse reactions associated with *Staccato* Loxapine (incidence rate $\geq 2\%$ and greater than placebo in either the 5-mg or 10-mg *Staccato* Loxapine groups). Dysgeusia was the only adverse event that exhibited evidence for dose-dependency. Akathisia and tremor were observed rarely, each occurring in 2 patients (0.4%), and there was one report of neck dystonia combined with oculogyration.

However, significant pulmonary adverse events, particularly in subjects with asthma or COPD, were reported and are a major safety concern. In subjects with asthma (Trial **004-105**), eighteen (69%) loxapine-treated subjects and 3 (12%) placebo-treated subjects had notable respiratory signs or symptoms, defined as FEV₁ decrease from baseline of $\geq 20\%$, an airway AE, or use of rescue medication. In this trial, ~54% of loxapine-treated subjects had airway adverse events compared to 11.5% of placebo-treated subjects. The most common airway adverse events in subjects with asthma were bronchospasm (~27%), chest discomfort (~23%), wheezing (~15%), and dyspnea (11.5%). In subjects with COPD (Trial **004-108**), fifteen (~58%) loxapine-treated subjects had notable respiratory signs or symptoms compared to six (~22%) placebo-treated patients, and airway adverse events were reported for ~19% of loxapine-treated patients compared to ~11% of placebo-treated patients. Airway AEs that occurred in more than a single loxapine-treated subject in Trial **004-108** were dyspnea (3 subjects, 11.5%), cough (3 subjects, 11.5%), and wheezing (2 subjects, ~8%). No airway AEs occurred in more than a single placebo-treated subject in this trial.

In the controlled studies in agitated patients population (subjects from the 2 pivotal trials, **004-301** and **004-302**, and the phase 2 proof of concept trial, **004-201**), the most frequently reported respiratory system AEs in loxapine-treated subjects versus placebo-treated subjects were throat irritation (~2% vs. 0.4%), pharyngeal hypoaesthesia (0.6% vs. 0%), and wheezing (0.4% vs. 0%). The two subjects with AEs of wheezing did not require treatment. Bronchospasm was reported for one subject in the *Staccato* Loxapine 10 mg group in Trial **004-301**, resulted in early discontinuation, and required treatment with a bronchodilator. All the respiratory AEs were mild to moderate. In the trials of healthy volunteers, although there were no incidences of wheezing or bronchospasm, a high incidence of cough (~7% of loxapine-treated subjects compared to ~2% of placebo-treated subjects) was noted, which may be suggestive of underlying bronchospasm.

Thus, although a particularly high incidence of respiratory adverse events was not found in the pivotal trials or in the Phase 1 and 2 trials, it is noteworthy that subjects with clinically significant acute or chronic pulmonary disease, such as clinically apparent asthma, chronic bronchitis, or emphysema, were excluded from these trials. In the trials of healthy volunteers (**004-101**, **004-102**, **004-103**, **004-104**, and **004-107**), subjects who reported regular tobacco use within the last year were excluded. The only exception was in Trial **004-106**, a pharmacokinetic study of healthy smokers compared to nonsmokers, but in this trial subjects were excluded for FEV₁ < 80% of predicted or FVC < 80% of predicted.

The high rate of smoking in patients with Schizophrenia and Bipolar Disease has been well-documented. In one study, Hughes et al (*American Journal of Psychiatry* 1986, **143**: 993-997) reported that the prevalence of smoking among psychiatric outpatients was significantly higher than among either local or national population-based samples (52% versus 30% and 33%) and that smoking was especially prevalent among patients with Schizophrenia (88%) or Mania (70%) and among the more severely ill patients. In another study, Goff et al (*American Journal of Psychiatry* 1992, **149**: 1189-1194)

reported that 74% of a group of Schizophrenic outpatients smoked. Therefore, it is likely that excluding subjects with clinically significant pulmonary disease and subjects who reported regular tobacco use in the pivotal trials and the Phase 1 and 2 trials resulted in a better pulmonary safety profile than would be expected in the target population. Furthermore, in the 3 pulmonary safety studies, doses of *Staccato* Loxapine were given 8 to 10 hours apart, and subjects who required rescue medication for pulmonary events were excluded from further dosing in the trial. The sponsor's recommended dosing interval for *Staccato* Loxapine is 2 hours; therefore, airway adverse events and significant decreases in FEV₁ may prove to be more frequent and more severe in clinical practice than noted in the pulmonary safety studies.

Considering this extremely high rate of smoking in patients with Schizophrenia and Bipolar Disorder, a high rate of asthma and COPD would be expected, and it is unlikely that Schizophrenic or Bipolar patients presenting with acute agitation would be able to give a reliable medical history. In a case-matched, retrospective review, Roberts et al. (*Family Practice*; 24: 34-40) demonstrated that patients with Schizophrenia were less likely than asthma controls to have smoking status noted and in general were less likely to receive some important general health checks than patients without Schizophrenia. Thus, it would be extremely difficult for practitioners to exclude patients at risk for airway adverse events (ie, patients with asthma or COPD), especially in an emergency room setting. In the setting of a psychiatric inpatient ward or a psychiatrist's office, early recognition and prompt treatment of an airway adverse event in an already agitated patient may not be feasible, and appropriate rescue medication may not be readily available.

Appropriate, safer alternatives to *Staccato* Loxapine have already been approved. Intramuscular medication (aripiprazole, ziprasidone, and olanzapine) is available for treatment of acute agitation associated with Bipolar disorder or Schizophrenia. These medications have a reasonably rapid onset and have a safety profile similar to loxapine. However, the possibility of potentially serious respiratory adverse events is greatly decreased with intramuscular administration of these medications.

1.3 Recommendation for Postmarket Risk Evaluation and Mitigation Strategies

From a clinical perspective, safety issues associated with *Staccato* Loxapine are numerous and profound. REMS would not be adequate or sufficient to address these issues.

1.4 Recommendations for Postmarket Requirements and Commitments

Since my recommendation is for Complete Response action, no recommendations for postmarket requirements and commitments will be made at this time.

2 Introduction and Regulatory Background

2.1 Product Information

Staccato Loxapine for Inhalation is a single-use, hand-held, drug-device combination product designed to provide rapid systemic delivery by inhalation of a thermally generated aerosol of loxapine. *Staccato* Loxapine represents a new dosage form of loxapine, an antipsychotic used in oral form for the treatment of Schizophrenia.

The antipsychotic effects of loxapine are similar to those of other antipsychotics such as haloperidol, and are likely attributable to its action at dopamine D₂ receptors. There is limited evidence that loxapine shares some of its clinical effects with atypical antipsychotics such as clozapine and olanzapine, due to its unique binding profile, especially its action at 5-HT_{2A} receptors.

Although no longer marketed, an intramuscular form was previously approved for the management of acutely agitated patients. In some countries (e.g., France), IM loxapine is frequently used in the emergency room setting for the treatment of acute agitation.

According to the sponsor, oral inhalation through the *Staccato* Loxapine for Inhalation 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 sponsor claims that the resulting rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration.

This NDA is submitted by the sponsor to support the marketing approval of *Staccato* Loxapine for the indication of rapid treatment of agitation associated with Schizophrenia or Bipolar Disorder at the recommended dose of 10 mg. Since agitation in these psychiatric populations is an acute and intermittent condition, the sponsor expects that patients will be treated with *Staccato* Loxapine on an infrequent basis. The NDA is submitted as a 505(b)(2) marketing application since, in addition to the sponsor-conducted nonclinical and clinical studies, the application cross-references limited nonclinical information in the approved loxapine NDAs (NDA 17525 and NDA 18039) for which the applicant does not have right of reference.

2.2 Tables of Currently Available Treatments for Proposed Indications

The table below summarizes the approved treatments for acute agitation associated with Schizophrenia or Bipolar Disorder:

Table 1: FDA-Approved Treatment Regimens – Acute Agitation associated with Bipolar Disorder or Schizophrenia

Generic Name	Trade Name	Bipolar I Disorder	Schizophrenia	Dosage		
				Initial	Maximum	Route
Aripiprazole	Abilify	X	X	9.75 mg	30 mg/day	IM
Ziprasidone	Geodon		X	10-20 mg	40 mg/day	IM
Olanzapine	Zyprexa	X	X	10 mg	30 mg	IM

2.3 Availability of Proposed Active Ingredient in the United States

Loxapine has been available in the United States (US) since 1975. Following the initial approval for oral tablets and capsules (NDA 17-525; approved 2-25-75), an oral concentrate (NDA 17658; approved 5-4-76) and an intramuscular (IM) dosage form (NDA 18039; approved 10-26-79) were approved. Only loxapine capsules are currently marketed in the US.

For the treatment of Schizophrenia, oral loxapine is administered at an initial dose of 20 mg daily, with a usual maintenance range of 60 to 100 mg daily. A dosage greater than 250 mg daily is not recommended.

IM loxapine was previously approved for prompt symptomatic control in acutely agitated schizophrenic patients and in patients whose symptoms rendered oral medication temporarily impractical. IM loxapine was labeled for administration in doses of 12.5 to 50 mg at intervals of 4 to 6 hours or longer.

To the sponsor’s knowledge, marketing approval for loxapine has not been withdrawn for safety reasons.

2.4 Important Safety Issues with Consideration to Related Drugs

In general, the drugs categorized as atypical antipsychotics have similar pharmacodynamic profiles, benefits, and safety and tolerability profiles. Treatment with aripiprazole, olanzapine, and ziprasidone has been associated with development of the following adverse events: extrapyramidal symptoms, sedation, orthostatic hypotension, weight gain, and hyperglycemia. Treatment with some of the atypical antipsychotics has been associated with proarrhythmic effects (primarily prolongation of the QTc interval). Ziprasidone may pose a higher risk of QTc prolongation than other antipsychotics. In addition, elderly patients with dementia-related psychosis treated with atypical antipsychotics have been found to be at an increased risk of death compared to placebo. Therefore, atypical antipsychotics are labeled with a boxed warning for the treatment of dementia-related psychosis in elderly patients.

In summary, aripiprazole, olanzapine, and ziprasidone appear to have similar potential risks.

2.5 Summary of Presubmission Regulatory Activity

The clinical program was discussed at the end of Phase 2 (EOP2) meeting for *Staccato* Loxapine on September 13, 2007, and agreement was reached on the design of the Phase 3 studies. The design of the pulmonary safety program was also discussed at the EOP2 meeting. In an FDA communication dated April 17, 2009, further recommendations regarding design of pulmonary safety studies was provided to the sponsor as well as feedback regarding the planned QT/QTc study.

Statistical comments and recommendations on the statistical analysis plans for the different studies were provided in several FDA communications (April 6, 2007; November 5, 2008; March 23, 2009; and April 24, 2009) and at the Pre-NDA meeting on July 14, 2009.

In addition, pharmacokinetic comparability data (in vitro and in vivo) between the commercial and clinical versions of *Staccato* Loxapine were reviewed in the Type C Meeting with the Division on December 3, 2008. Additional pharmacokinetic and safety data from the bioequivalence study (Trial **004-103**) requested by the Division were subsequently submitted and additional feedback was provided at the Pre-NDA Meeting on July 14, 2009.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of this submission is acceptable.

3.2 Compliance with Good Clinical Practices

It appears that the clinical trials were conducted in compliance with good clinical practice. This included all International Conference on Harmonization (ICH) Good Clinical Practice Guidelines (GCP) Guidelines. In addition, all local regulatory requirements were followed. The final protocol, any amendments, and informed consent documentation were reviewed and approved by the Institutional Review Board(s) (IRB) at each of the investigational centers participating in the trial.

3.3 Financial Disclosures

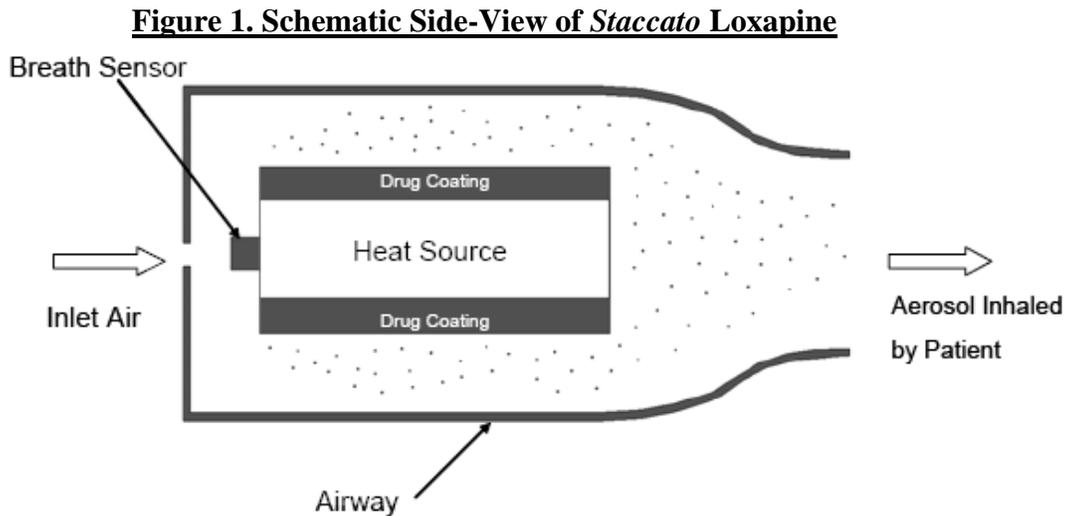
The sponsor has provided documentation certifying that each listed clinical investigator was required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor and did not disclose any such interests. There does not appear to be any instances of conflict of interest which affected the conduct or results of the trials.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Principal Components

The principal components of *Staccato* Loxapine are shown schematically in the figure below (electronically copied and reproduced from sponsor's submission):



The breath sensor is the breath-activation mechanism that initiates actuation of the heat source. The heat source (heat package) is comprised of a reactant coating on the interior surface of a stainless steel substrate. A battery activated starter is inserted into the heat package. The drug coating (excipient-free loxapine (b) (4)) is on the external surface of the stainless steel substrate. Inhalation through the product is detected by the breath sensor, causing the starter to initiate a gasless oxidation-reduction (redox) reaction of the reactants on the interior surface of the heat package. The redox reaction liberates heat, and the subsequent rapid heating of the substrate to ~400°C causes the loxapine film on the exterior surface to rapidly (<1 second) vaporize. The vapor cools in the airflow and

condenses to form aerosol particles with a mass median aerodynamic diameter of 1.0 to 3.5 μm .

Removal of a pull tab renders it ready for use, as indicated by illumination of a green light. (b) (4)

Device Modifications

During the course of development, the sponsor has made several changes to the drug product. According to the sponsor, the reasons for the changes were (b) (4). Numerous communications between FDA and the sponsor were initiated in order to clarify the exact nature of the changes, exactly which versions of the drug product were used in the different clinical trials, and which version is planned for marketing if the NDA is approved.

In a response to FDA query dated January 27, 2010, the sponsor reported that three device versions were used during clinical development: *Clinical Version 1*, *Clinical Version 2*, and *Commercial Version*. The sponsor reported that the *Clinical Version 1* was only used in the initial phase 1 study (004-101); *Clinical Version 2* was used in the majority of studies in the program (phase 2 and phase 3 studies); and the *Commercial Version* (intended for marketing) was used in the last 4 studies of the clinical program (PK study in smokers, thorough QT study, and 2 clinical safety studies in patients with compromised lung function). A bioequivalence study (004-103) compared the *Clinical Version 2* and the *Commercial Version*.

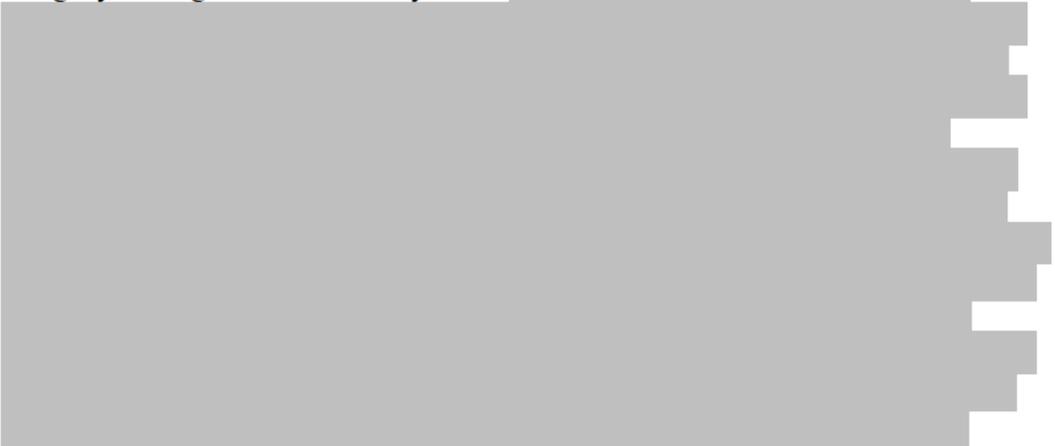
On further review, it became apparent that the *Commercial Version* to be marketed will contain several modifications, some of which were made between the bioequivalence study and the special safety studies, and some of which were not incorporated into the product at the time of any of the studies. In response to FDA request, the sponsor defined these versions as *Commercial Version 1* (used in the bioequivalence study), *Commercial Version 2* (used in the smoker PK study, thorough QT study, and the 2 clinical safety studies in patients with compromised lung function), and *Commercial Version 3* (planned for marketing). However, based on FDA feedback at a teleconference on January 29, 2010, the sponsor advised the agency that (b) (4)

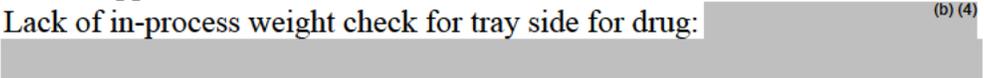
would be the only additional changes for marketing. This version is to be called *Commercial Version 2.1*.

A summary of the clinical studies and the device version used in each study is provided in the tables in **Section 5.1** below.

4.1.1 CMC Review (DPP): David Claffey, PhD

A thorough Chemistry Review was done by David J. Claffey, PhD, ONDQA. Dr. Claffey accompanied the investigator on the preapproval inspection at the final drug product manufacturing site, Alexza Pharmaceuticals, Mountain View, CA from August 2-11, 2010. As a result of this inspection, the San Francisco District Office issued a “withhold” recommendation, and Dr. Claffey has concluded that an approval recommendation from a CMC perspective can not be made until several deficiencies identified during the preapproval inspection are resolved. The main deficiencies are briefly outlined below:

- Integrity of Registration Stability Data: (b) (4)


Dr. Claffey therefore concluded that the lots used for the registration stability lots no longer adequately represent the proposed commercial drug product and cannot be used as primary stability data to assign an expiry period. A recommendation will be forwarded to the applicant that data be generated with the final commercial iteration of the product packaged in the final iteration of the commercial packaging (under cGMP conditions). Appropriate packaging material will need to be selected and relevant stability data will need to be accumulated and submitted to the application to support an expiry period for the drug product.
- Inappropriate storage of heat package stability samples: Data were provided in the application to support a (b) (4) retest period; however, it was discovered at the inspection that these data were derived from components already assembled and packaged to (placebo) drug product. No data to simulate the heat package’s storage in the warehouse prior to use in the drug product was provided. The inspection indicated that some lots of heat packages were found to have oxidation on their outside surfaces. The applicant will be asked to explain how they control for this application.
- Lack of in-process weight check for tray side for drug: (b) (4)


. It emerged during the inspection that the weight check was only carried out for the lid side and no check was in place for the tray side. This will be followed up with the applicant as a review issue.

- Lack of control over (b) (4) levels in drug film: It emerged during the inspection that (b) (4) . The applicant will be asked to account for these changes.
- Capability of (b) (4) operation: (b) (4) The applicant will be asked to provide an explanation.
- Thermogram test: During the inspection, it was found that (b) (4) This issue can have an important impact on product performance and needs to be resolved.

4.1.2 CMC Review (DPARP): Craig Bertha, PhD

The Initial Quality Assessment for NDA 22549 recommended that the assigned CMC reviewer, Dr. Claffey, consult with CMC reviewers that are familiar with the review of inhalation drug products for the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). Therefore, it was agreed that Craig Bertha, PhD, would review the extractables/leachables information and data, drug product characterization studies, the delivered dose uniformity (DDU) and aerodynamic particle size distribution (APSD) methods, and evaluate and compare the *in vitro* dose performance data across the pertinent versions of the drug product.

Dr. Bertha has identified several deficiencies including deficiencies in method validation data that support the ability of the various methods to quantify the leachables in the aerosol emitted from the drug product, lack of institution of controls for the various components of the device and packaging to ensure that the levels of emitted volatile compounds are always at acceptably low levels, failure to provide formal stability studies including some samples of unprotected product (i.e., without foil pouches), and revisions in the method for collection for the delivered dose uniformity and mass balance (recovery) requirements. Dr. Bertha has provided a draft information request letter in which in which further information and corrective actions for these deficiencies is requested.

In addition, two device failures of the Commercial Version 2 involved “self-actuation” of the device after the activation tab was removed but prior to the inhalation maneuver by the patient. (b) (4)

The sponsor has reported that “corrective action has been taken with the component vendor to ensure that these parts have been manufactured to meet

specification on an ongoing basis,” but no other details are available. Details about the specification in question as well as details regarding the corrective action are requested in the draft information request letter.

4.3 Preclinical Pharmacology/Toxicology

Summary of Nonclinical Program

The core sponsor nonclinical program includes safety pharmacology, pharmacokinetic and toxicology studies, with an emphasis on inhalation delivery. The sponsor did not conduct a program to address primary and secondary pharmacology, since loxapine has been marketed for many years and a great deal is known about its activity. The sponsor carried out several in vitro studies to characterize loxapine metabolism, plasma protein binding, drug transport, and drug-drug interactions, as this information was not previously reported. In order to support the safety of inhalation delivery of loxapine, the sponsor carried out single and repeat dose inhalation toxicology and toxicokinetic studies in rats and dogs.

Pharmacology

The in vivo pharmacological activity of loxapine is primarily related to its affinity and antagonist activity at dopamine and serotonin receptor subtypes, especially D₂ and 5HT_{2A}.

The primary metabolites of loxapine in rat, dog, and man are amoxapine, 7-OH-loxapine, 8-OH-loxaopine, and loxapine N-oxide. Amoxapine is a pharmacologically active tricyclic antidepressant, showing a different spectrum of receptor and pharmacological activities from loxapine, and 7-OH-loxapine is pharmacologically active at the D₂ receptor, with potency approximately 5 times greater than loxapine. 8-OH-loxapine and loxapine N-oxide are pharmacologically inactive.

Safety Pharmacology

The sponsor conducted a cardiovascular and safety study in conscious telemetered beagle dogs. At the high dose of 1.5 mg/kg (delivered intravenously), mild increases in respiratory rate were seen, and a transient and mild decrease in blood pressure followed by a transient and mild increase was the only biologically relevant cardiovascular change. There was no QT prolongation. In addition, the sponsor compared pharmacokinetic profiles of intravenous and inhalation administration in anesthetized dogs and found that IV bolus delivery mimicked exposure by inhalation. C_{max} seen with doses of 0.5 to 1.5 mg/kg in this study was more than 5 times greater than seen in healthy human volunteers administered a single 10 mg dose of *Staccato* Loxapine.

Pharmacokinetics of Loxapine following Inhalation Administration

Aerosolized loxapine was rapidly absorbed after inhalation administration to rats and dogs, with mean peak plasma levels reaching maximal concentrations near or at the end of the exposure period in both species. In the rat, a 5-fold decrease in dose-normalized loxapine exposure was observed after 10-minute nose-only inhalation as compared to 10-minute IV infusion, which was attributed to the respiratory deposition fraction for the inhalation route. In both rats and dogs, immediately following exposure, the concentrations fell in a manner consistent with rapid distribution, and there was no evidence of loxapine accumulation in repeat dose inhalation studies. The terminal half-life ($T_{1/2}$) for loxapine after inhalation ranged from 1.2 to 5.4 hours in rat, 0.8 to 6.6 hours in dog, and 7.6 to 8.2 hours in man. No new metabolites resulting from the inhalation route were identified, nor was there a marked shift in the relative proportions of previously identified metabolites in comparison to those resulting from either oral or intramuscular delivery of loxapine.

Inhalation Toxicity Studies Conducted by the Sponsor

In acute inhalation toxicity studies conducted in rats and dogs using nose-only and oral inhalation administration, respectively, pharmacological effects on CNS (lethargy or decreased activity, weakness, and tremors) were noted at mean doses of 6.7 mg/kg and higher in rats and 0.68 mg/kg and higher in dogs.

Repeat dose oral toxicity studies of up to 1, 15, and 12 months were conducted in mice, rats, and dogs, respectively. CNS effects such as decreased locomotor activity, sedation, catalepsy, ptosis, and/or convulsions were observed in all three species. In rats, audiogenic seizures increased with prolongation of treatment time. In dogs, the recovery time from onset of loxapine-induced decrease in locomotor activity shortened as dosing progressed.

Loxapine administered to rats by inhalation for 14 consecutive days, at doses of 1.7 to 13 mg/kg/d resulted in dose-related CNS clinical signs consistent with the extended pharmacology of loxapine. Histological changes related to the extended pharmacology of loxapine included mammary hyperplasia in both sexes, and ovarian follicular cysts and mucification of vaginal epithelium in females. The no-observed-adverse-effect level (NOAEL) was considered to be 1.7 mg/kg/d, the low dose in the study.

When administered via inhalation to beagle dogs for 28 days, loxapine-induced clinical signs noted at dose levels ranging from 0.12 to 1.8 mg/kg/day included decreased activity, weakness, tremors, and/or lack of coordination. Based on these observations, the mean achieved dose of 1.8 mg/kg/day was considered the NOAEL.

No local irritation was observed with repeated inhalation exposure at dose levels up to 1.8 mg/kg/d in the dog. In the rat with repeated inhalation exposure for 14 consecutive days, minimal squamous metaplasia of the larynx was seen at doses of 1.7, 6.4, and 13

mg/kg/d. This finding was considered a nonspecific effect due to particle impaction, and its incidence was greatly reduced by the end of the 14-day recovery period.

Genotoxicity

(b) (4)
8-OH-loxapine is the major metabolite of loxapine in humans via both inhalation and oral routes, but it is essentially pharmacologically inactive and is only a minor metabolite in rats and dogs.

Therefore, in addition to the assessment of genotoxicity of loxapine, genotoxicity studies were conducted by the sponsor with 8-OH-loxapine (a disproportionate metabolite), (b) (4) (an aerosol impurity), and the leachable (b) (4). No genotoxic potential was exhibited in any of the sponsor studies.

4.3.1 Division of Pharmacology/Toxicology

Pharmacology/Toxicology review was conducted by Darren Fegley, PhD. Dr. Fegley concluded that the non-clinical studies that supported the approval of the innovator product in combination with the published literature, and bridging studies submitted by the sponsor are considered adequate to support the current submission and that, from a Pharmacology/Toxicology Perspective, there are no issues that would prevent or delay the approval; of this NDA.

4.4 Clinical Pharmacology

The clinical development program for *Staccato* Loxapine included several trials that examined the pharmacokinetics and pharmacodynamics of loxapine following administration of *Staccato* Loxapine in relevant populations.

The pharmacokinetics of *Staccato* Loxapine for Inhalation was determined in 4 clinical pharmacokinetic (PK) studies:

1. **Study 004-101:** In this phase 1, randomized, double-blind, placebo-controlled, dose-escalation, safety and pharmacokinetic study, five dose levels of *Staccato* Loxapine were evaluated sequentially (0.625 mg, 1.25 mg, 2.5 mg, 5 mg, and 10 mg) in 50 adult male and female subjects, age 18 to 55 years, inclusive. For each dose level, 10 subjects were randomized, 8 subjects to *Staccato* Loxapine and 2 subjects to *Staccato* Placebo. Pharmacokinetics and safety were assessed for 24 hours following treatment.
2. **Study 004-102:** This was a phase 1, single-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the pharmacokinetics, safety, and tolerability of *Staccato* Loxapine at 3 dose levels. Qualifying subjects (male

- and female, age 18 to 65 years, inclusive) on a stable, oral, chronic antipsychotic medication regimen were randomized 1:1:1:1 to *Staccato* Loxapine (total doses of 15, 20, or 30 mg) or *Staccato* Placebo. Enrolled subjects decreased their oral antipsychotic medication to ½ of their regular dose 2 days before dosing and to ¼ of their regular dose 1 day before dosing. The total *Staccato* Loxapine or *Staccato* Placebo dose was administered in 3 divided doses given 4 hours apart. The 30-mg group received *Staccato* Loxapine 10 mg at each time point (0, 4, and 8 hours). The 20-mg group received *Staccato* Loxapine 10 mg at 0 hours, 5 mg at 4 hours, and 5 mg at 8 hours. The 15-mg group received *Staccato* Loxapine 5 mg at each time point.
3. **Study 004-106:** This was a phase 1, single-center, single-treatment, open-label study in which healthy male and female subjects, age 20 to 50 years, inclusive, received a single dose of *Staccato* Loxapine 10 mg to assess the pharmacokinetics of *Staccato* Loxapine in smokers compared to nonsmokers. Equal numbers of smokers and nonsmokers were enrolled in the study.
 4. **Study 004-107:** This was a double-blind, double-dummy, active- and placebo-controlled, 3-period crossover study investigating single doses of *Staccato* Loxapine 10 mg, a positive control with known QT/QTc prolongation (oral moxifloxacin, 400 mg), and oral and inhaled placebos. Treatments were designated as A (oral placebo with *Staccato* Loxapine), B (oral placebo with *Staccato* Placebo), and C (oral moxifloxacin with *Staccato* Placebo). Healthy subjects were randomized to 1 of 6 sequence groups and received all 3 treatments (A, B, and C), separated by a minimum 3-day washout period. Subjects were confined to the clinical research unit (CRU) during each treatment period.

Additionally, a clinical bioequivalence trial (**004-103**, described in **Section 5.3**) was conducted in healthy subjects to compare the pharmacokinetics following administration of the commercial version of *Staccato* Loxapine versus the clinical version (i.e. *Commercial Version 1* and *Clinical Version 2*: see **Section 4.1**).

Since sedation is a consistent effect of antipsychotics, sedation scales served as the primary pharmacodynamic (PD) measure. Changes in sedation score from baseline were examined in 6 studies. This included 3 of the 4 pharmacokinetic studies described above (**004-101**, **004-102**, and **004-106**) as well as the lung safety studies in normal volunteers (**004-104**), subjects with asthma (**004-105**), and subjects with COPD (**004-108**). The lung safety studies are described in detail in **Section 5**. Changes in sedation score from baseline were measured in Trial **004-101** using the Stanford Sleepiness Scale (SSS) and in 5 other trials (**004-102**, **004-104**, **004-105**, **004-106**, and **004-108**) using a 100-mm visual analog scale (VAS).

The final measure of PD was the examination of electrocardiogram (ECG) effects in the thorough QT study (**004-107**, described above).

4.4.1 Mechanism of Action

Loxapine, a tricyclic dibenzoxazepine compound, is a typical antipsychotic. Although the exact mechanism of action has not been established, 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 D₂ and serotonin 5-HT_{2A}.

4.4.2 Pharmacodynamics

Sedation

Based on the Visual Analog Scale (VAS) analysis, a clear sedation effect was observed in all 5 trials 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 trials (**004-102** and **004-106**) in which both PK and PD were measured, a strong sedation-exposure relationship was seen (ie, VAS-AUC_{0-2h} was strongly related to PK-AUC_{0-2h}).

Cardiac Repolarization

Trial **004-107** was performed to assess the potential for *Staccato* Loxapine to delay cardiac repolarization using the corrected QT interval (QTc) duration. The primary outcome measure for the study was the difference from the pre-dose baseline at each time point in the individual subject-corrected QT interval, QTcI. As shown in the table below (electronically copied and reproduced from sponsor's submission), *Staccato* Loxapine at a dose of 10 mg did not increase QTcI intervals, as demonstrated by the upper one-sided 95% confidence bound placed on the point estimate of the placebo-subtracted change of QTcI ($\Delta\Delta\text{QTcI}$) being less than 10 ms at all post-dose times.

Table 2: Staccato Loxapine QTcI, Difference from Placebo, Change from Baseline, Primary Analysis Model (QT Population) - Trial 004-107

Time Post-Dose	$\Delta\Delta\text{QTcI}$ <i>Staccato</i> Loxapine 10 mg	Upper 95% Confidence Bound
1 min	0.031	2.352
2 min	-0.119	2.203
5 min	1.817	4.139
9 min	3.613	5.934
15 min	2.156	4.477
30 min	4.499	6.820
1 hour	5.418	7.753
3 hour	4.560	6.895
6 hour	1.438	3.773
10 hour	1.667	4.014
22 hour	-1.404	0.917

Therefore, Trial **004-107** was a negative Thorough QT/QTc study as defined in the ICH E14 guideline, 2005. The study outcome was validated by the demonstrated assay sensitivity using the positive control moxifloxacin.

4.4.3 Pharmacokinetics

The pharmacokinetics of oral and intramuscular (IM) administration of loxapine is well-established in the literature. Following oral administration, loxapine is well-absorbed from the gastrointestinal tract and undergoes substantial first-pass metabolism with systemic bioavailability ~33%. The T_{\max} is approximately 1 to 3 hours following both oral and IM administration. High loxapine concentrations are found mainly in the liver, brain, spleen, and lungs.

Following oral administration, loxapine is extensively metabolized in the liver via hydroxylation, N-oxidation, and demethylation, resulting in the formation of multiple metabolites. Plasma levels of the major metabolite, 8-OH-loxapine, exceed the levels of the parent compound in most studies; however, 8-OH-loxapine is not pharmacologically active at the relevant dopamine receptors. Other metabolites include 7-OH-loxapine, N-oxides of loxapine and its metabolites, and amoxapine (N-desmethyl-loxapine) and its hydroxylated metabolites. 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 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, consistent with a hepatic first-pass effect following oral dosing. Loxapine and its metabolites are excreted mainly in the urine. The elimination half-life of oral loxapine is 3 to 8 hours and appears to be slightly longer after IM administration.

Loxapine is a substrate for multiple CYP450 enzymes in addition to flavin-containing monooxygenases (FMOs). Therefore, the risk of metabolic interactions caused by an effect of an individual isoform is minimized.

The individual pharmacokinetic studies in healthy nonsmoking subjects demonstrated similar loxapine pharmacokinetic parameters across individual studies following inhalation administration of either 5-mg or 10-mg doses of *Staccato* Loxapine. In all studies, plasma loxapine concentrations increased rapidly with a median T_{max} within 2 minutes, followed by a rapid decrease in plasma concentrations. A pooled analysis of loxapine PK parameters for all healthy subjects in Trials **004-103**, **004-106**, and **004-107** was done and is summarized in the table below (electronically copied and reproduced from sponsor's submission):

Table 3: Summary of Loxapine Pharmacokinetic Parameters Following Administration of *Staccato* Loxapine 5 or 10 mg in Healthy Subjects

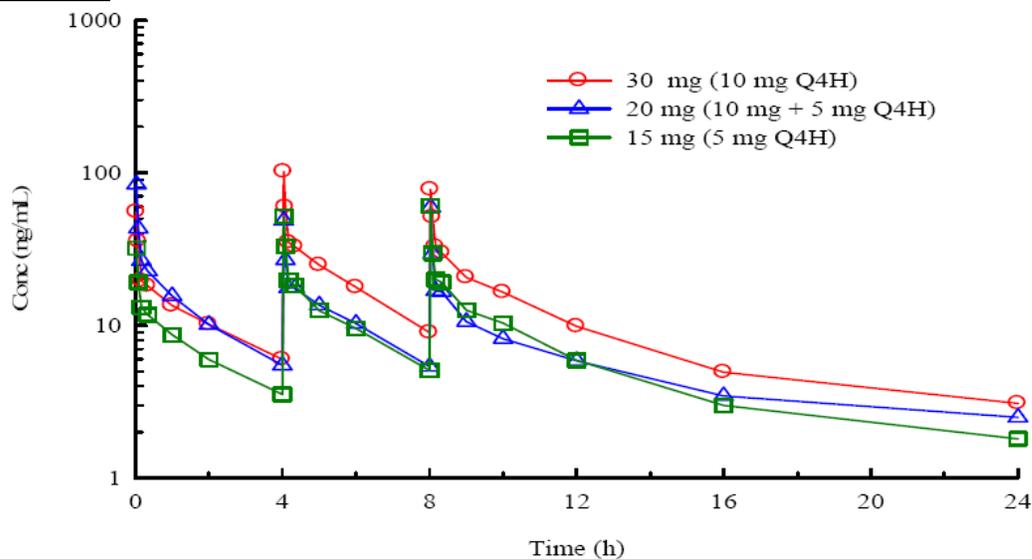
Parameter	5 mg (N=31)	10 mg (N=114)
AUC _{0-2h} (ng·h/mL) Mean ± SD	25.6 ± 7.31	66.7 ± 18.2
AUC _{inf} (ng·h/mL) Mean ± SD	70.1 ± 17.8	188 ± 46.6
C _{max} (ng/mL) Mean ± SD	116 ± 85.1	257 ± 219
T _{max} (min) Median (25%, 75%)	1.50 (1, 2)	1.13 (0.948, 1.98)
Half-life (h) Mean ± SD	7.64 ± 2.22	7.61 ±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

The PK profile of loxapine following administration of *Staccato* Loxapine to subjects on stable antipsychotic regimens was similar to that observed in healthy subjects. In both healthy subjects and subjects on stable antipsychotic regimens, the mean plasma loxapine concentrations were linear over the clinical dose range. Values for AUC_{0-2h}, AUC_{inf}, and C_{max} increased in an expected dose-dependent manner.

The early exposure to loxapine (AUC_{0-2h}) and the total exposure to loxapine (AUC_{inf}) were similar for smokers and nonsmokers (geometric mean ratios of ~92% and ~85%, respectively). Therefore, the sponsor recommends no dosage adjustment based on smoking status.

In Trial **004-102** (described in **Section 4.4**), subjects on chronic, stable antipsychotic regimens received 3 doses of *Staccato* Loxapine (either 5 mg or 10 mg) every 4 hours. Mean peak plasma concentrations were similar after the first and third dose of *Staccato* Loxapine, indicating minimal accumulation during the 4-hour dosing interval, as shown in the figure below (electronically copied and reproduced from sponsor's submission). Relative to C_{max} , there were small differences in loxapine concentration between 2 and 4 hours after dosing. Therefore, the sponsor concludes that a second dose of *Staccato* Loxapine could be administered as early as 2 hours following a first dose with minimal increase in C_{max} .

Figure 2: Mean Plasma Concentrations of Loxapine Following Administration of Repeated Doses of Staccato Loxapine to Subjects on Chronic, Stable Antipsychotic Therapy



Based on the completed studies, the PK of loxapine is expected to be similar in healthy subjects and in patients with Schizophrenia and Bipolar Disorder.

4.4.4 Office of Clinical Pharmacology (OCP)

The final results of the evaluation of clinical pharmacology data by the Office of Clinical Pharmacology (OCP) are not available at the time of this writing. However, statistical analysis was performed for OCP by Donald Schuirmann, Mathematical Statistician, regarding the bioequivalence study, Trial **004-103** (see **Section 5.3.1**). In this trial to determine bioequivalence between the Reference product (Clinical Version 2) and the Test Product (Commercial Version 1), data from the 5 and 10 mg dose groups were combined into one analysis. Dr. Schuirmann notes that if the data from the 5 mg dose group are analyzed by themselves, the study does not pass the usual bioequivalence test. Similarly, if the data from the 10 mg dose group are analyzed by themselves, the study does not pass the usual bioequivalence test.

If the data from both groups are combined into one analysis, the study does not pass the usual bioequivalence test if the data from subject #8 (defined by the sponsor as an outlier) is included. Subject #8 had AUC₀₋₂ values consistently low for Clinical Version 2 but not for Commercial Version 1. Therefore, it is not known if there is a population of persons who would respond similarly. However, since Clinical Version 2 will not exist in the market place, there is no issue of a subject beginning therapy on commercial product and then switching to Clinical Version 2, or vice versa, and so obtaining dangerously different blood levels after the switch. This may provide a justification for excluding the data from subject #8 in the analysis of the bioequivalence study.

4.5 Division of Scientific Investigation

The Division of Scientific Investigation (DSI) conducted an inspection of two U.S. clinical investigator sites: the site of Richard Jaffe, MD (Trial **AMDC-004-301** Site #10 and Trial **AMDC-004-302** Site #08) and the site of Adam Lowy, MD (Trial **AMDC-004-301** Site #17 and Trial **AMDC-004-302** Site #08). No significant regulatory violations that would importantly impact data integrity were noted. The inspection documented general adherence to Good Clinical Practices regulations governing the conduct of clinical investigations, and the data are considered reliable in support of the application.

4.6 Division of Pulmonary, Allergy, and Rheumatology Products

Consultation was obtained with Anya C. Harry, M.D., Ph.D., Division of Pulmonary, Allergy, and Rheumatology Products. Dr. Harry reviewed the three pulmonary safety studies described below (Trials **004-104**, **004-105**, and **004-108**) and noted that in all three trials, FEV₁ measures were decreased in *Staccato* Loxapine-treated patients compared to placebo. These decreases were particularly marked and clinically significant in patients with asthma. In addition, greater decreases, which did not quickly return to baseline, were found following the second dose of medication compared to the first. The largest FEV₁ changes in asthmatics on loxapine were 303 cc at 15 minutes (post-Dose 1) and 537 cc at 10 hours 15 minutes (15 minutes post-Dose 2). The largest FEV₁ changes in patients with COPD on loxapine were 125 cc at 10 hours 15 minutes (15 minutes post-Dose 2). Lastly, Dr. Harry noted that patients with underlying pulmonary disease had more airway-related adverse events: bronchospasm, cough, dyspnea, or chest discomfort.

The Division of Pulmonary, Allergy, and Rheumatology Products concluded that the significant drop in FEV₁ in asthmatics and in healthy subjects is concerning and that a decision as to whether or not a Complete Response is warranted should depend on a risk benefit evaluation in conjunction with DPP.

4.7 Interdisciplinary Review Team for QT Studies

Consultation was obtained with the Interdisciplinary Review Team for QT studies who reviewed the thorough QT Study (Trial **004-107**; see **Sections 4.4** and **4.4.2** above) and agreed with the sponsor's conclusion that no significant QTc prolongation effect of *Staccato* Loxapine (10 mg) was detected. In addition, the moxifloxacin profile over time was adequate to demonstrate that assay sensitivity was established in this trial.

4.8 Biostatistics

The statistical reviewer, Yeh-Fong Chen, Ph.D, confirmed the sponsor's efficacy analysis results for the two Phase 3 trials (**004-301** and **004-302**), concluding that the data supported the efficacy of *Staccato* Loxapine for both 5 mg and 10 mg. However, Dr. Chen noted that, besides at 2 hours, only the efficacy for 10 mg before an hour can be claimed in the labeling.

4.9 Center for Devices and Radiological Health (CDRH)

Consultation was also obtained with QuynhNhu Nguyen, Biomedical Engineer, Anesthesiology and Respiratory Device Branch (ARDB), Division of Anesthesiology, General Hospital, Infection Control, and Dental (DAGID), CDRH. Based on CDRH's review, the device manufacturing and performance were not found acceptable for the following three primary reasons:

1. The cited findings from the preapproval inspection (see **Section 4.1.1**) presented major concerns regarding manufacturing and testing processes that directly impact the characterization of the aerosolize performance of the product and the *in vitro* performance data that were submitted in the application.
2. A complete human factors validation study was not conducted with the product to be commercialized. CDRH recommends that this study be done with representative intended user groups (patients and healthcare providers). The human factors validation study should include a thorough analysis of use related hazards based on use interaction that can lead to potential hazards for the users and patients. It should also include a detailed analysis of use performance and the effectiveness of proposed mitigations that supports a conclusion that the device can be safely used by the intended user groups.
3. The sponsor conducted a heat package worse case testing scenario where perfect holes of 1mm were drilled in the direction of the mouth pieces. CDRH considers this approach to be unrealistic and recommends that worse case testing should be evaluated with the breaking of seam (b) (4) that holds the tray and the lid together. This can induce tremendous amount of heat that escapes from the heat package and travels through the airway of the product. This heat can potentially contact patient's mouth, pharynx, trachea, and lungs, and/or burn the patient or

healthcare provider's hands, so it is critical that such an evaluation be done prior to product approval.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical program to support the use of *Staccato* Loxapine for the treatment of agitation comprised 11 clinical trials which are listed in the Tables below:

Table 4: Biopharmaceutic, Pharmacokinetic, and Pharmacodynamic Studies

Study Number	Study Design	Drugs/Dose/Duration	Number and Type of Subjects	Device Version
004-101	Phase 1, randomized, double-blind, placebo-controlled, single-dose, dose escalation, safety, tolerability, and PK study	<i>Staccato</i> Loxapine 0.625 mg, 1.25 mg (2x0.625 mg), 2.5 mg, 5 mg, or 10 mg (2x5 mg) <i>Staccato</i> Placebo	50 healthy nonsmokers (10 in each dose level (8 active drug:2 placebo)	Clinical 1
004-102	Phase 1, randomized, double-blind, placebo-controlled, parallel-group multiple-dose, safety, tolerability, and PK study	<i>Staccato</i> Loxapine total doses 15, 20, or 30 mg in 3 divided doses 4 hours apart: 15 mg: 5/5/5 mg 20 mg: 10/5/5 mg 30 mg: 10/10/10 mg	32 subjects on stable, chronic antipsychotic medications (8 in each treatment group); 28 smokers, 4 nonsmokers	Clinical 2
004-103	Phase 1 randomized, 2-treatment, 4-period, dose-stratified, replicate-design to compare commercial and clinical versions of <i>Staccato</i> Loxapine	<i>Staccato</i> Loxapine commercial and clinical versions: each subject received a total of four 5 mg or four 10 mg doses	32 healthy subjects	Clinical 2 & Commercial 1
004-106	Phase 1, single-dose, single-treatment, open-label, PK study in smokers vs. nonsmokers	<i>Staccato</i> Loxapine 10 mg; Each subject received a single dose	35 healthy subjects: 17 smokers 18 nonsmokers	Commercial 2
004-107	Phase 1, double-blind, double-dummy, active-and placebo-controlled 3-period crossover QT study	A: <i>Staccato</i> Loxapine + oral placebo B: <i>Staccato</i> Placebo + oral placebo C: <i>Staccato</i> Placebo+ oral moxifloxacin (1 of 6 sequences containing A,B, & C)	48 healthy subjects	Commercial 2

Table 5: Safety Studies

Study Number	Study Design	Drugs/Dose/Duration	Number and Type of Subjects	Device Version
004-104	Phase 1, randomized, double-blind, placebo-controlled, 2-period crossover pulmonary safety study	<i>Staccato</i> Loxapine 10 mg or <i>Staccato</i> Placebo; in each of 2 treatment periods, subjects received 2 doses of same treatment within 24 hours (doses separated by 8 hours)	30 healthy nonsmokers	Clinical 2
004-105	Phase 1, randomized, double-blind, placebo-controlled, parallel-group, pulmonary safety study	Each subject was to receive 2 doses of <i>Staccato</i> Loxapine 10 mg or <i>Staccato</i> Placebo in 24 hours (doses separated by 10 hours)	52 subjects with mild to moderate persistent asthma	Commercial 2
004-108	Phase 1, randomized, double-blind, placebo-controlled, parallel-group, pulmonary safety study	Each subject was to receive 2 doses of <i>Staccato</i> Loxapine 10 mg or <i>Staccato</i> Placebo in 24 hours (doses separated by 10 hours)	53 subjects with COPD	Commercial 2

Table 6: Efficacy and Safety Studies in Agitation

Study Number	Study Design	Drugs/Dose/Duration	Number and Type of Subjects	Clinical Version
004-201	Phase 2A, randomized, double-blind, placebo-controlled, parallel-group, single-dose study	<i>Staccato</i> Loxapine 5 mg or 10 mg or <i>Staccato</i> Placebo; single dose in 24 hours	129 patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder, clinically agitated	Clinical 2
004-301	Phase 3, randomized, double-blind, placebo-controlled, parallel-group study	<i>Staccato</i> Loxapine 5 mg or 10 mg or <i>Staccato</i> Placebo; each patient received up to 3 doses in 24 hours, with Doses 2 and 3 administered only if needed	344 patients with Schizophrenia, clinically agitated	Clinical 2
004-302	Phase 3, randomized, double-blind, placebo-controlled, parallel-group study	<i>Staccato</i> Loxapine 5 mg or 10 mg or <i>Staccato</i> Placebo; each patient received up to 3 doses in 24 hours, with Doses 2 and 3 administered only if needed	314 patients with Bipolar I Disorder, manic or mixed, clinically agitated	Clinical 2

In addition, *Staccato* Loxapine is being developed for the acute treatment of migraine headache. Two phase 2 clinical trials have been completed for this indication and are listed in the table below:

Table 7: Efficacy and Safety Studies in Migraine Headache

Study Number	Study Design	Drugs/Dose/Duration	Number and Type of Subjects	Device Version
104-201	Phase 2A, randomized, double-blind, placebo-controlled, single-dose study in the clinic	<i>Staccato</i> Loxapine 1.25, 2.5, or 5 mg, or <i>Staccato</i> Placebo; 1 dose in 24 hours	168 patients with migraine headache with or without aura	Clinical 2
104-202	Phase 2B, randomized, double-blind, placebo-controlled, parallel-group, single-dose, outpatient study	<i>Staccato</i> Loxapine 1.25 or 2.5 mg, or <i>Staccato</i> Placebo; 1 dose in 24 hours	366 patients with moderate to severe migraine headache with or without aura	Clinical 2

5.2 Review Strategy

The review was conducted by analyzing the completed studies listed in the tables above. The review included clinical summaries, integrated summary of efficacy, integrated summary of safety, and analysis of individual trials including subject data, summary tables, and raw data provided by the sponsor. Particular attention was given to analysis of the pivotal trials (**004-301** and **004-302**), the proof of concept trial (**004-201**), the bioequivalence trial (**004-103**), the pulmonary safety trials (**004-104**, **004-105**, and **004-108**), and the overall safety data.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Trial AMDC-004-103

This was a Phase 1, randomized, single-center, 2-treatment, 4-period, dose-stratified, replicate-design trial to assess the safety, pharmacokinetics, and bioequivalence of the Commercial Product Design (*Commercial Version 1*) and the Current Clinical Version (*Clinical Version 2*) of *Staccato* Loxapine in healthy volunteers. This trial was initiated on August 11, 2008 and completed on October 6, 2008.

Objectives

The trial objectives were:

- To assess the pharmacokinetics of 5 mg and 10 mg Commercial Product Design of *Staccato* Loxapine
- To assess the single-dose bioequivalence of Commercial Product Design versus Current Clinical Version
- To assess the safety and tolerability of 5 mg and 10 mg of *Staccato* Loxapine delivered via Commercial Product Design

Trial Population

Trial subjects were healthy male and female nonsmokers between the ages of 18 and 55, inclusive. Female participants (if of child-bearing potential and sexually active) and male participants (if sexually active with a partner of child-bearing potential) agreed to use an acceptable birth control method throughout the trial and for 1 week following the end of the trial. A total of 32 subjects were enrolled to ensure that at least 24 subjects completed the trial.

Key Inclusion Criteria

1. Subjects who were in good general health as determined by a complete medical history, physical examination, ECG, spirometry, and clinical labs.

Key Exclusion Criteria

1. Subjects who reported regular tobacco use within the past year, or who have positive urine cotinine test or exhaled carbon monoxide test for recent smoking
2. Subjects with hypotension (systolic blood pressure \leq 90 mm Hg; diastolic blood pressure \leq 50 mm Hg) or hypertension (systolic blood pressure \geq 140 mm Hg; diastolic blood pressure \geq 90 mm Hg).
3. Clinically significant ECG abnormality.
4. Subjects with a history of unstable angina, syncope, coronary artery disease, myocardial infarction, congestive heart failure, stroke, transient ischemic attack, or a neurological disorder.
5. Subjects who had clinically significant acute or chronic pulmonary disease (eg, clinically apparent asthma, chronic bronchitis, or emphysema, or any use of bronchodilator in the past 6 months).
6. FEV₁ and/or FVC $<$ 80% of predicted at Visit 1.

Trial Design

Trial subjects were randomized to *Staccato* Loxapine 5 mg or 10 mg and received a total of 4 doses (2 doses of the commercial version, and 2 doses of the clinical version). Each dose was administered in a separate treatment period with a washout period of \geq 4 days between treatment periods. Subjects received only 1 dose level, either 5 mg or 10 mg, and were not crossed over between dose levels. Subjects were confined to the clinic from ~14 hours before each dose of *Staccato* Loxapine until at least 24 hours following dosing at each visit.

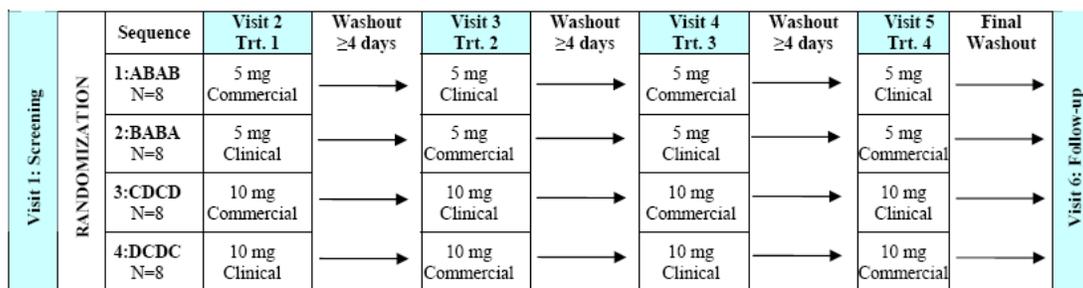
Screening evaluations could span up to a 3-week period, and baseline evaluations were performed in the hour before administration of initial study treatment (Day -1). As part of the screening process, subjects were trained in the use of the *Staccato* system and their ability to use the device properly was evaluated.

After screening and baseline evaluations confirmed eligibility, each subject was randomly assigned (1:1:1:1) to 1 of 4 different *Staccato* Loxapine treatment sequences, 8 subjects per sequence. The sequences were as follows:

- Sequence 1: commercial, clinical, commercial, clinical; 5 mg in each dose (designated ABAB)
- Sequence 2: clinical, commercial, clinical, commercial; 5 mg in each dose (designated BABA)
- Sequence 3: commercial, clinical, commercial, clinical; 10 mg in each dose (designated CDCD)
- Sequence 4: clinical, commercial, clinical, commercial; 10 mg in each dose (designated DCDC)

The evaluation period started with the administration of Dose 1 (Time 0) and continued for 24 hours. Subjects were then discharged and returned to the clinic a week later for the next treatment. This was repeated 2 additional times. A final visit was scheduled 5-9 days after discharge. Please see figure below for trial schematic (electronically copied and reproduced from sponsor’s submission):

Figure 3: Trial AMDC-004-103 Schematic



A=5-mg *Staccato* Loxapine commercial; B=5-mg *Staccato* Loxapine clinical; C=10-mg *Staccato* Loxapine commercial; D=10-mg *Staccato* Loxapine clinical

Device Malfunctions

Trial personnel were instructed in the identification and management of suspected device malfunctions as follows:

For the commercial version of *Staccato* Loxapine:

- If the solid green light does not light when the pull-tab is removed, dispense another device and return the initial device via the device complaint system.
- If the solid green light does not turn off when the subject inhales:
 1. Instruct the patient to inhale through the device 1 more time.
 2. If the green light still does not turn off, dispense another device and return the initial device via the device complaint system.

For the clinical version of *Staccato* Loxapine:

- If the solid green light does not light when the pull-tab is removed, dispense another device and return the initial device via the device complaint system.
- If the green light does not flash when the subject inhales:
 1. Instruct the patient to inhale through the device 1 more time.
 2. If the green light still does not flash, dispense another device and return the initial device via the device complaint system.

All suspect devices were to be returned to Alexza via the device complaint system.

Concomitant Medications

With the exception of acetaminophen or ibuprofen for pain, or ongoing doses of oral contraceptives, medications other than study drug were not allowed from 12 hours before dosing until 24 hours after dosing, unless medically required. Subjects who regularly consumed more than 5 cups of coffee or equivalent amounts of xanthine-containing substances per day were excluded from the trial.

Pharmacokinetic Assessments

Blood samples for the determination of loxapine, 7-OH-loxapine, and 8-OH-loxapine were collected at times specified in the table below. Plasma concentration-time profiles were produced for each subject. Pharmacokinetic parameters, including T_{max} , C_{max} , and C_{2h} , AUC_{0-2h} , AUC_{last} , $T_{1/2}$, and CL/F were estimated.

Safety Assessments

Safety assessments at screening (Day -21 to Day -2) included physical examination, ECG, spirometry (FEV₁ and FVC), vital signs, clinical labs (CBC, urinalysis, electrolytes, CK, cholesterol, glucose, kidney and liver function), pregnancy test (females), inhalation maneuver training, and screens for drug, alcohol, and smoking. At baseline (Day -1) for each treatment, history and physical were updated, screens for drug, alcohol, and smoking were repeated, and inhalation maneuver training was repeated. Vital signs and adverse event monitoring was done frequently during each treatment period, as shown in the table below:

Table 8: Treatment Period Evaluations - Trial AMDC-004-103

Time:	Pre-0	0 s	30 s	1 min	2 min	3 min	5 min	10 min	15 min	30 min	60 min	2 h	4 h	6 h	12 h	24 h
Vital signs	X						X		X	X	X	X	X	X	X	X
Study drug administration		X														
PK sampling	X		X	X	X	X	X	X		X	X	X	X	X	X	X
AE monitoring			X	X	X	X	X	X	X	X	X	X	X	X	X	X

Statistical Analysis

Determination of Sample Size

The planned enrollment of 32 subjects to complete approximately 24 subjects in a 4-way replicate design provides 90% power to show bioequivalence based on AUC_{inf} for a population ratio as high as 1.05. A sample size of greater than 100 subjects would be required to achieve the same power based on C_{max} . The sponsor reasons that given the differences in the variability of C_{max} and AUC_{inf} with *Staccato* Loxapine and other rapid-uptake products, bioequivalence based on AUC_{inf} is the more suitable primary measure of bioequivalence.

Analysis Populations

Three analysis populations were defined:

- Safety Population: Includes all randomized subjects who received any study medication.
- Pharmacokinetic (PK) Population: Includes all subjects who received any study drug and provided measurable loxapine concentration data at 1 or more time points.
- Bioequivalence (BE) Population: Includes all subjects who received any study drug and provided 2 or more C_{max} or AUC_{inf} values.

Note that the Safety and Bioequivalence Populations were pre-defined in the statistical analysis plan (SAP). The Pharmacokinetic Population was defined during the analysis phase of the trial.

The results of the individual subject noncompartmental analysis identified a statistically significant outlier (Subject 008, Sequence CDCD). The data for this subject were excluded from the main presentation of the pharmacokinetic analysis (PK population, without Subject 008) and the Bioequivalence analysis (BE population without Subject 008).

Primary Analysis

By the protocol specified analysis, the commercial version of *Staccato* Loxapine (test) would be established as bioequivalent to the clinical version (reference) if the 90% confidence interval (CI) for the ratio of the geometric least squares means (test/reference) of AUC_{inf} for the parent drug (loxapine) were contained within the acceptance criteria range (80.00%-125.00%).

For the determination of bioequivalence in this trial, the 5-mg and 10-mg doses were combined for the analysis of the primary outcome measures. The sponsor believes that the pooling of data across the 2 doses was justified since each subject received only 1 dose level and all the comparisons were within subject. In addition, prior studies (**AMDC-004-101** and **AMDC-004-102**) indicated that *Staccato* delivery was dose proportional across the dose range of 0.625 to 30 mg.

Based on feedback from the FDA (IND 73,248, Type C Meeting with the Division of Psychiatry Products, 3 December 2008), the analysis of AUC_{0-2h} was included as an additional primary measure of bioequivalence. The primary clinical endpoint in the Phase 3 studies of *Staccato* Loxapine is at 2 hours after administration of the first dose of study drug; therefore AUC_{0-2h} provides an assessment of a relevant period of exposure.

Secondary Analysis

Several parameters were analyzed using the same model as the SAP-specified primary analysis of bioequivalence for loxapine AUC_{inf} . Parameters for supporting analyses included the log transformed dose normalized C_{max} for loxapine, 7-OH-loxapine, and 8-OH-loxapine, as well as the AUC-adjusted C_{max} (ie, C_{max}/AUC_{inf}). Other exploratory analyses included the log transformed dose normalized loxapine AUC_{last} and the log transformed dose normalized loxapine C_{2h} .

Results: Trial AMDC-004-103

Demographics and Baseline Characteristics

Of the 32 randomized subjects, ~60% were female and ~81% were Caucasian. Their mean age was ~26, and ~78% never smoked. The demographic and baseline characteristics of the safety and BE populations and between the different sequences were similar, as shown in the tables below:

Table 9: Baseline Characteristics (Safety Population): Trial AMDC-004-103

Sequence	ABAB (N=8)	BABA (N=8)	CDCD (N=8)	DCDC (N=8)	Overall (N=32)
AGE (years):					
Mean	27.8	25.8	26.4	23.1	25.8
Age Range	21.0-52.0	21.0-43.0	21.0-49.0	20.0-26.0	20.0-52.0
GENDER:					
% Males	50.0%	37.5%	37.5%	37.5%	40.6%
% Females	50.0%	62.5%	62.5%	62.5%	59.4%
RACE					
% Caucasian	100.0%	62.5%	62.5%	100.0%	81.3%
% Asian	0.0%	25.0%	25.0%	0.0%	12.5%
% Hispanic	0.0%	0.0%	12.5%	0.0%	3.1%
% Other	0.0%	12.5%	0.0%	0.0%	3.1%
SMOKING HISTORY					
Never smoked	87.5%	100.0%	75.0%	50.0%	78.1%
Ex-smoker	12.5%	0.0%	25.0%	50.0%	21.9%

A=5-mg *Staccato* Loxapine commercial; B=5-mg *Staccato* Loxapine clinical; C=10-mg *Staccato* Loxapine commercial; D=10-mg *Staccato* Loxapine clinical

Table 10: Baseline Characteristics (BE Population*): Trial AMDC-004-103

Sequence	ABAB (N=7)	BABA (N=8)	CDCD (N=7)	DCDC (N=8)	Overall (N=30)
AGE (years):					
Mean	28.3	25.8	26.9	23.1	25.9
Age Range	21.0-52.0	21.0-43.0	21.0-49.0	20.0-26.0	20.0-52.0
GENDER:					
% Males	57.1%	37.5%	42.9%	37.5%	43.3%
% Females	42.9%	62.5%	57.1%	62.5%	56.7%
RACE					
% Caucasian	100.0%	62.5%	71.4%	100.0%	83.3%
% Asian	0.0%	25.0%	28.6%	0.0%	13.3%
% Hispanic	0.0%	0.0%	0.0%	0.0%	0.0%
% Other	0.0%	12.5%	0.0%	0.0%	3.3%

A=5-mg *Staccato* Loxapine commercial; B=5-mg *Staccato* Loxapine clinical; C=10-mg *Staccato* Loxapine commercial; D=10-mg *Staccato* Loxapine clinical

*excludes Subject 008

Baseline Disease Characteristics

The most frequently reported medical conditions or findings were associated with the Head (non-neurological), Eyes, Ears, Nose (including sinuses), and Throat system (34.4%). Most medical findings were stable or had resolved at the time of the screening visit.

Patient Disposition

A total of 59 subjects were screened for participation in the trial and 32 subjects were randomized into the trial. All subjects completed at least 1 treatment and 27 subjects completed all 4 assigned treatments. The following 5 subjects discontinued the trial prematurely:

- Subject 023 (Sequence ABAB) requested withdrawal from the trial after receiving 2 doses of study medication
- Subject 032 (Sequence ABAB) requested withdrawal from the trial after receiving 1 dose of study medication
- Subject 026 (Sequence BABA) withdrew due to an AE (urticaria) after receiving 3 doses of study medication
- Subject 017 (Sequence DCDC) withdrew due to an AE (upper respiratory tract infection) after receiving 3 doses of study medication
- Subject 025 (DCDC) requested withdrawal from the trial after receiving 2 doses of study medication

Table 11: Reasons for Premature Discontinuation (Safety Population) - Trial AMDC-004-103

Subject Disposition, n (%)	Sequence ABAB (N=8)	Sequence BABA (N=8)	Sequence CDCD (N=8)	Sequence DCDC (N=8)	Total (N=32)
Randomized, n	8	8	8	8	32
Completed trial	6 (75.0%)	7 (87.5%)	8 (100%)	6 (75.0%)	27 (84.4%)
Discontinued prematurely	2 (25.0%)	1 (12.5%)	0	2 (25.0%)	5 (15.6%)
Reason for discontinuation:					
Adverse event	0	1 (12.5%)	0	1 (12.5%)	2 (6.3%)
Subject withdrew consent	2 (25.0%)	0	0	1 (12.5%)	3 (9.4%)

A=5-mg *Staccato* Loxapine commercial; B=5-mg *Staccato* Loxapine clinical; C=10-mg *Staccato* Loxapine commercial; D=10-mg *Staccato* Loxapine clinical

Important Protocol Violations

There were no important protocol deviations in this trial

Reported Device Malfunctions

One clinical *Staccato* Loxapine system was returned via the device complaint system and underwent inspection and testing. It was determined that the subject (006) did indeed actuate the device and receive the drug (*Staccato* Loxapine 5 mg, clinical version). The subject's plasma concentration-time profiles confirmed that drug had been delivered successfully. Thus, this complaint did not represent a device failure, so there were zero device failures among 60 clinical devices and 59 clinical devices used in this trial.

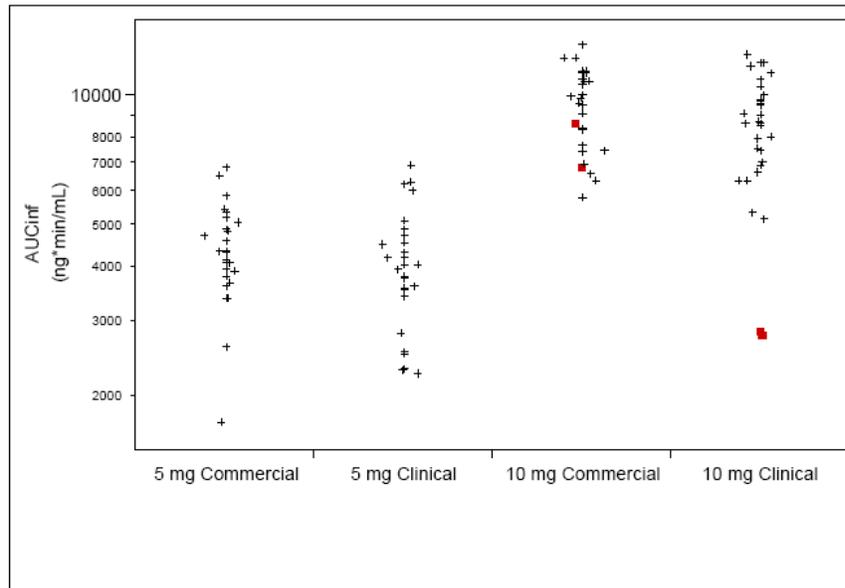
Pharmacokinetic and Bioequivalence Findings: Trial AMDC-004-103

Results of Outlier Testing

The sponsor has identified Subject 008 (Sequence CDCD) as a significant outlier for the parameters of AUC_{inf} , AUC_{last} , AUC_{0-2h} , C_{max} and T_{max} . As shown in the scatter plots below (Subject 008 represented by the red box), the exposure to loxapine for Subject 008 was substantially lower with the clinical version of the device when compared to (1) the commercial version for this subject, and (2) both device versions for all subjects administered the 10 mg dose.

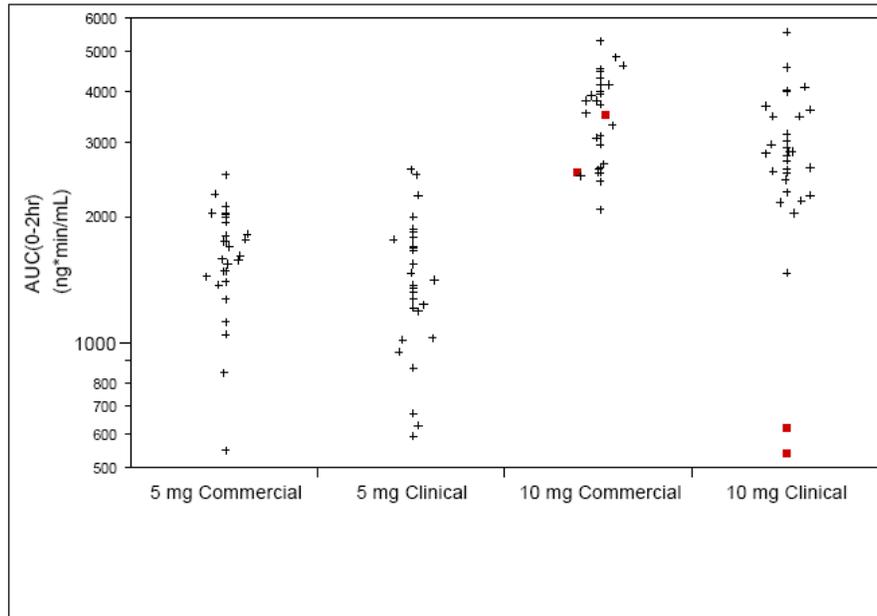
Figure 4: Scatter Plots for AUC_{inf} , AUC_{0-2h} , C_{max} , and T_{max} by Treatment (BE Population, All Subjects) - Trial AMDC-004-103 (electronically copied and reproduced from Sponsor's submission)

a) AUC_{inf}



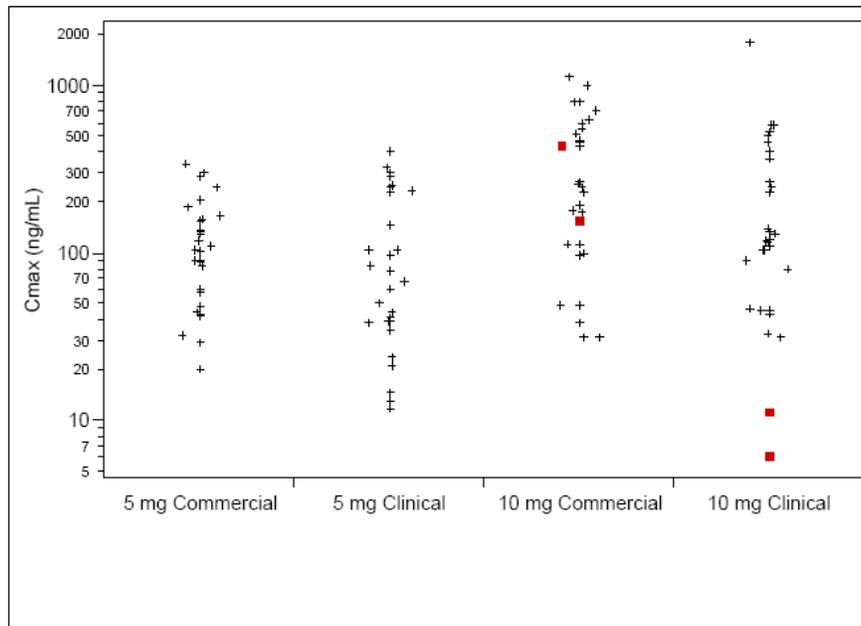
Subject 008 represented by a red box [■]; all other subjects represented by black crosses (+)

b) AUC_{0-2h}



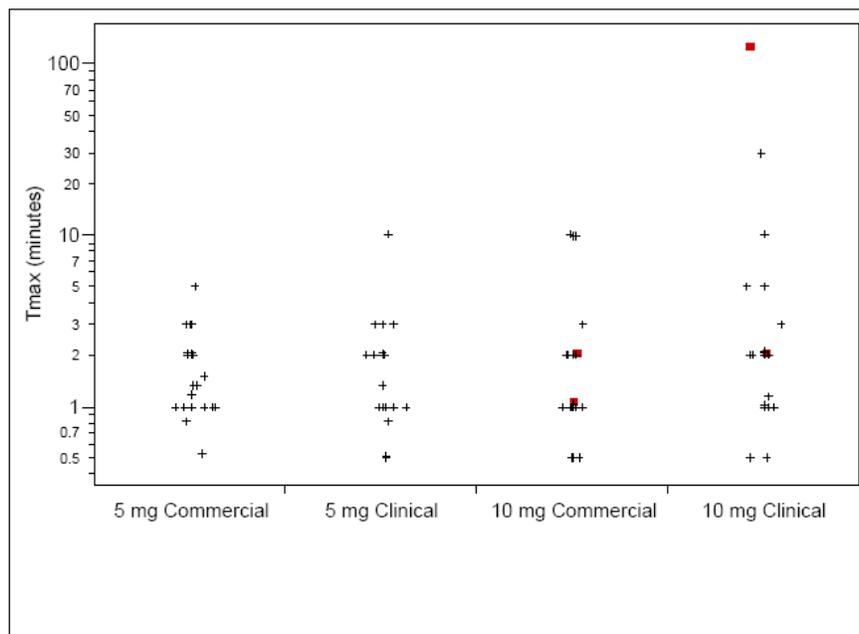
Subject 008 represented by a red box [■]; all other subjects represented by black crosses (+)

c) C_{max}



Subject 008 represented by a red box [■]; all other subjects represented by black crosses (+)

d) T_{max}



Subject 008 represented by a red box [■]; all other subjects represented by black crosses (+)

Examination of the *Staccato* Loxapine devices used by Subject 008 revealed a large amount drug substance (loxapine) remaining on both the clinical version devices but not the commercial version devices. Given these findings, together with the results of the statistical outlier testing, the sponsor did not include data from Subject 008 in the main presentation of the pharmacokinetic and bioequivalence analysis.

In response to FDA query regarding how it was determined that Subject 008 did not receive a full dose of loxapine from the clinical device, the sponsor provided the following additional information on May 1, 2010:

Qualitative evaluation revealed that the 2 clinical version devices used by Subject 008 had excessive drug residual on both the heat package and the interior of the housings in a pattern consistent with drug that had vaporized normally but then only partially emitted from the device, which the sponsor believes could have been related to an atypical inhalation maneuver. In contrast, the commercial version devices used by Subject 008 demonstrated only a small (normal) amount of residual on the heat package and the housing.

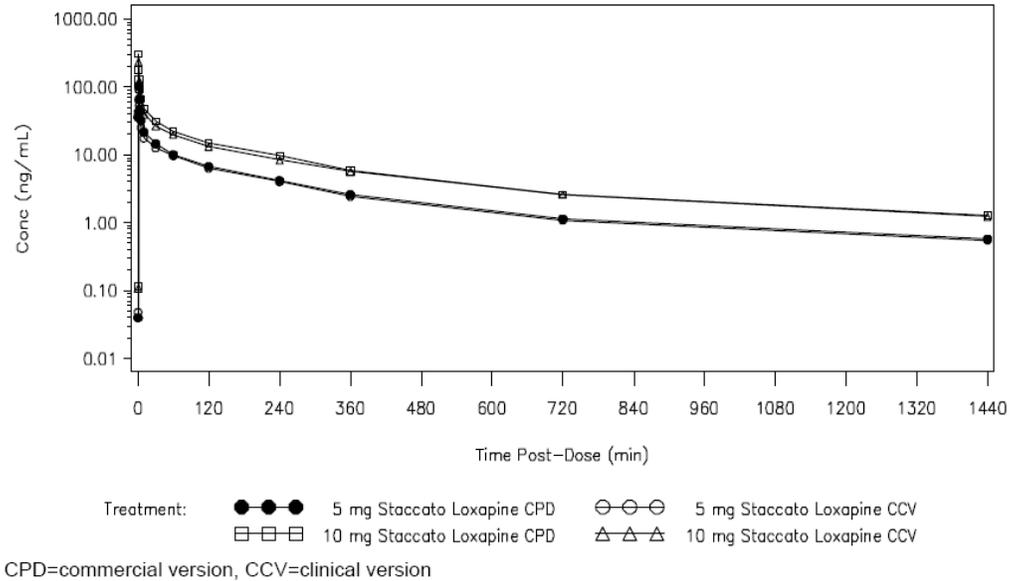
Furthermore, in a quantitative analysis, the estimated emitted dose was calculated by taking the average coated dose and subtracting the drug recovered from the heat package and housing. Based on the product release testing data for the relevant batch, the expected emitted dose was ~9 mg for both the 10 mg clinical and 10 mg commercial devices used in Trial **004-103**. The two commercial devices used by Subject 008 demonstrated an estimated emitted dose of 8.7 mg and 8.4 mg, respectively, which was consistent with the

expected emitted dose. In contrast, the estimated emitted dose for the two clinical devices was 4.8 mg and 4.2 mg, respectively, markedly lower than the expected emitted dose.

Pharmacokinetic Results

The plasma time-concentration profiles by treatment were similar for the commercial and clinical versions of *Staccato* Loxapine and for both the 5- and 10-mg groups, as shown in the figure below (electronically copied and reproduced from sponsor’s submission):

Figure 5: Mean Loxapine Concentration Post-Dose by Treatment (PK Population, Without Subject 008) - Trial AMDC-004-103



The pharmacokinetic parameters for loxapine and loxapine metabolites (7-OH-loxapine and 8-OH-loxapine) are summarized in the table below (electronically copied and reproduced from sponsor’s submission):

Table 12: Pharmacokinetic Parameters for Loxapine and Loxapine Metabolites by Treatment (PK Population, without Subject 008) -Trial AMDC-004-103

Parameter	5 mg Commercial (N=15)	5 mg Clinical (N=15)	10 mg Commercial (N=16)	10 mg Clinical (N=16)
Loxapine				
AUC _{inf} (ng*min/mL), mean ± SD	4332 ± 950	4068 ± 1201	9748 ± 1920	8911 ± 1920
AUC _{0-2h} (ng*min/mL), mean ± SD	1620 ± 386	1450 ± 487	3610 ± 806	3065 ± 792
C _{max} (ng/mL), mean ± SD	116 ± 73.9	115 ± 98.3	363 ± 255	265 ± 256
C _{2h} (ng/mL), mean ± SD	6.75 ± 1.36	6.28 ± 1.59	14.82 ± 3.91	13.07 ± 3.26
T _{max} (min), median (range)	1.25 (0.767, 3.52)	1.50 (0.750, 9.95)	1.50 (0.500, 6.47)	1.52 (0.500, 16.0)
T _{1/2} (min), mean ± SD	452 ± 126	465 ± 144	458 ± 100	492 ± 70.3
k _e (/min), mean ± SD	0.00166 ± 0.000440	0.00162 ± 0.000364	0.00160 ± 0.000328	0.00147 ± 0.000194
CL/F (mL/min), mean ± SD	1.23 ± 0.358	1.34 ± 0.414	1.07 ± 0.249	1.19 ± 0.279
Loxapine Metabolites				
C _{max} 7-OH-loxapine (ng/mL), mean ± SD	0.824 ± 0.263	0.743 ± 0.269	1.44 ± 0.634	1.19 ± 0.312
C _{max} 8-OH-loxapine (ng/mL), mean ± SD	2.68 ± 0.745	2.33 ± 0.683	5.61 ± 2.59	4.71 ± 1.50

Mean=Arithmetic mean of within-subject means

Based on the table above, the mean values for AUC_{inf}, AUC_{0-2h}, C_{max}, and C_{2h} of loxapine, as well as the C_{max} of loxapine metabolites, appear to be consistent within each dose level and to increase with dose. T_{max}, T_{1/2}, k_e, and CL/F were similar across the 4 treatment groups.

Bioequivalence Results

Primary Bioequivalence Measures

The results of the analysis of the primary bioequivalence measures are summarized in the table below (electronically copied and reproduced from sponsor’s submission). The sponsor has presented the results for both the protocol-specified analysis and the supplemental analysis based on the “FDA Guidance for Industry, Statistical Approaches for Establishing Bioequivalence, January 2001.”

Table 13: Primary Bioequivalence Analysis (BE Population, without Subject 008): Trial AMDC-004-103

Analysis Method	Parameter	Commercial (Geometric LS Means)	Clinical (Geometric LS Means)	Ratio Test/Reference ^b	90% CI for Ratio
Protocol-specified analysis (SAP)	Loxapine AUC _{0-2h}	1628	1422	114.44	107.96, 121.32
	Loxapine AUC _{inf}	4432	4114	107.75	103.37, 112.32
FDA Guidance for Statistical Analysis of BE ^a	Loxapine AUC _{0-2h}	1636	1422	114.99	106.62, 124.02
	Loxapine AUC _{inf}	4442	4116	107.91	102.42, 113.70

BE=bioequivalence; SAP=Statistical Analysis Plan

Note: All data are for the BE population without the statistically significant outlier (Subject 008)

Units for AUC measures are ng*min/mL.

a. Appendix E of the FDA Guidance for Industry, Statistical Approaches for Establishing Bioequivalence, January 2001

b. Ratio of commercial/clinical versions of *Staccato* Loxapine.

As shown in the table above, the 90% CIs for the geometric least squares mean ratios (test/reference) for both primary bioequivalence measures (AUC_{inf} and AUC_{0-2h}) were contained within the bounds of 80% and 125% in both the protocol-specified and FDA analysis models. Thus, the bioequivalence of loxapine as delivered by the clinical and commercial versions of *Staccato* Loxapine was demonstrated based on the primary bioequivalence measures of AUC_{inf} and AUC_{0-2h}.

Secondary Bioequivalence Measures

The results of the analysis of the secondary bioequivalence measures are summarized in the table below (electronically copied and reproduced from sponsor's submission):

Table 14: Secondary Bioequivalence Analysis (BE Population, without Subject 008)

Parameter	Commercial (Geometric LS Means)	Clinical (Geometric LS Means)	Ratio Test/Reference ^b	90% CI for ratio
Loxapine AUC _{last}	4038	3717	108.64	104.07, 113.41
Loxapine C _{2h}	6.73	6.17	109.13	103.67, 114.88
Loxapine C _{max}	105	78.4	133.88	110.47, 162.24
Loxapine C _{max} /AUC _{inf}	0.0236 ^a	0.019 ^a	124.10	103.75, 148.44
7-OH-loxapine C _{max}	0.713	0.627	113.62	105.99, 121.79
8-OH-loxapine C _{max}	2.52	2.24	112.88	106.23, 119.94

a. These analyses were carried out without dose adjustment

b. Ratio of commercial/clinical versions of *Staccato* Loxapine.

Units for AUC measures are ng*min/mL; Units for C_{max} measures are ng/mL.

The assessment of bioequivalence based on the secondary measure of AUC_{last} supported the results of the primary analysis. The 90% CI for the geometric least squares mean ratio (test/reference) for AUC_{last} were contained within the bounds of 80% to 125%.

However, the loxapine C_{max} CI did not lie within the bounds of 80% to 125%. The sponsor reports that, since *Staccato* Loxapine mimics IV bolus administration, the pharmacokinetic properties of the drug after this type of administration preclude making a precise determination of C_{max} . In addition, the sponsor cites references in which the use of loxapine metabolites in establishing bioequivalence of other dosage forms containing loxapine has been reported. Following administration of *Staccato* Loxapine, the CIs for the C_{max} ratios for the 7-OH and 8-OH metabolites were within the bounds of 80% to 125%.

Conclusions

Based on the results of the primary and secondary bioequivalence measures, the sponsor has demonstrated bioequivalence between the clinical and commercial versions of *Staccato* loxapine. However, an important factor in the demonstration of bioequivalence was the identification of Subject 008 as an outlier and the decision to exclude data from this subject in the main pharmacokinetic and bioequivalence analyses. Since examination of the clinical versions used by Subject 008 revealed a large amount of drug substance (loxapine) remaining on the clinical versions (but not the commercial versions), this seems reasonable.

The loxapine C_{max} CI did not lie within the bounds of 80% to 125%. However, I agree with the sponsor's assessment that the IV-like pharmacokinetics of *Staccato* Loxapine would make accurate measurement of C_{max} impractical. In addition, I agree that the CIs for the C_{max} ratios for the loxapine metabolites provide additional supportive evidence for bioequivalence.

6 Review of Efficacy

6.1 Efficacy Summary

A. Trials Relevant to the Rapid Treatment of Agitation Associated with Schizophrenia or Bipolar Disorder

Rationale for Selection of Studies for Review

The sponsor has conducted three clinical trials relevant to the efficacy claim of rapid treatment of acute agitation associated with Schizophrenia or Bipolar Disorder. All three trials were conducted in a double-blind, placebo-controlled design, and in all three trials,

the primary efficacy endpoint was the change from baseline in the PANSS Excited Component (PEC) score at 2 hours post-dose. The duration of each trial was 24 hours.

Two of the three trials were Phase 3 pivotal trials, one of which evaluated *Staccato* Loxapine for the treatment of acute agitation associated with Schizophrenia (**AMDC-004-301**), and one of which evaluated *Staccato* Loxapine for the treatment of acute agitation associated with Bipolar Disorder (**AMDC-004-302**). The third trial, **AMDC-004-201**, was a phase 2 proof of concept trial to evaluate *Staccato* Loxapine for the treatment of acute psychotic agitation associated with Schizophrenia, Schizophreniform disorder, or Schizoaffective Disorder. The two pivotal trials (**AMDC-004-301** and **AMDC-004-302**) allowed up to 3 doses of study medication as needed in a 24-hour period, while the proof of concept trial (**AMDC-004-201**) was a single-dose trial.

The proof of concept trial (**AMDC-004-201**) potentially provides data supportive of the two pivotal trials. Therefore, all three trials are selected for review.

6.2 Trial Summaries

6.2.1 Trial AMDC-004-201 (Schizophrenia)

This trial was a Phase 2, 24-hour, inpatient, multi-center, randomized, double-blind, placebo-controlled, fixed-dose, single-dose, parallel group efficacy and safety trial of *Staccato* Loxapine for Inhalation in Schizophrenic patients with acute agitation. The trial was conducted from September 21, 2006 to January 18, 2007 in 19 centers in the United States.

Objectives

The purpose of this trial was to assess the efficacy and safety of *Staccato* Loxapine at 5- and 10-mg fixed, single-dose levels in the treatment of acute agitation in Schizophrenic patients. Efficacy was assessed using the PANSS Excited Component (PEC) of the Positive and Negative Symptoms Scale (PANSS). The primary objective was to assess the change in PEC score from baseline to 2 hours following a single dose of *Staccato* Loxapine (5 or 10 mg), compared with placebo.

Trial Population

Trial patients were male and female, 18 to 65 years of age, inclusive, who met DSM-IV criteria for Schizophrenia, Schizophreniform Disorder, or Schizoaffective Disorder, with acute psychotic agitation. The trial was conducted in patients who were admitted to a hospital setting or a research unit, in inpatients already in a hospital for chronic underlying conditions, and in patients with agitation treated at psychiatric emergency room settings which allowed extended patient stay in a secluded observation room for the period of the trial.

Key Inclusion Criteria

1. DSM-IV criteria for Schizophrenia, Schizophreniform Disorder, or Schizoaffective Disorder
2. Clinically agitated at baseline with total score ≥ 14 on the 5 items (poor impulse control, tension, hostility, uncooperativeness, and excitement) comprising the PANSS Excited Component (PEC)
3. Score ≥ 4 (out of 7) on at least 1 of the 5 items on the PEC
4. Good general health by medical history, physical examination, ECG, clinical laboratory, and in the opinion of the Principal Investigator (PI)
5. If female of child-bearing potential or if male who is sexually active with a partner of child-bearing potential, must use a medically acceptable method of birth control throughout the trial and for one week following the end of the trial.

Key Exclusion Criteria

1. Patients with agitation caused primarily by acute intoxication (investigator's opinion)
2. Patients judged to be at serious risk for suicide
3. History of drug or alcohol dependence within the past 2 months
4. Patients treated with benzodiazepines or other hypnotics or oral or short-acting intramuscular antipsychotics within 4 hours prior to study drug administration were excluded, but could be reassessed subsequently for inclusion.
5. Patients treated with injectable depot neuroleptics within one dose interval prior to study drug administration were excluded, but could be reassessed subsequently for inclusion.
6. History of allergy or intolerance to loxapine or amoxapine
7. If female, positive pregnancy test or breastfeeding
8. Clinically significant laboratory or ECG abnormalities
9. Clinically significant hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrine, neurologic, or hematologic disease
10. Clinically significant acute or chronic pulmonary disease, such as clinically apparent asthma, chronic bronchitis, or emphysema
11. Patients who were considered by the investigator, for any reason, to be an unsuitable candidate for receiving *Staccato* Loxapine, or likely to be unable to use the inhalation device

Trial Design

The trial consisted of two periods: a *Pre-treatment Period* with baseline defined as the period immediately prior to dosing, and a *Treatment/Post-treatment Period*.

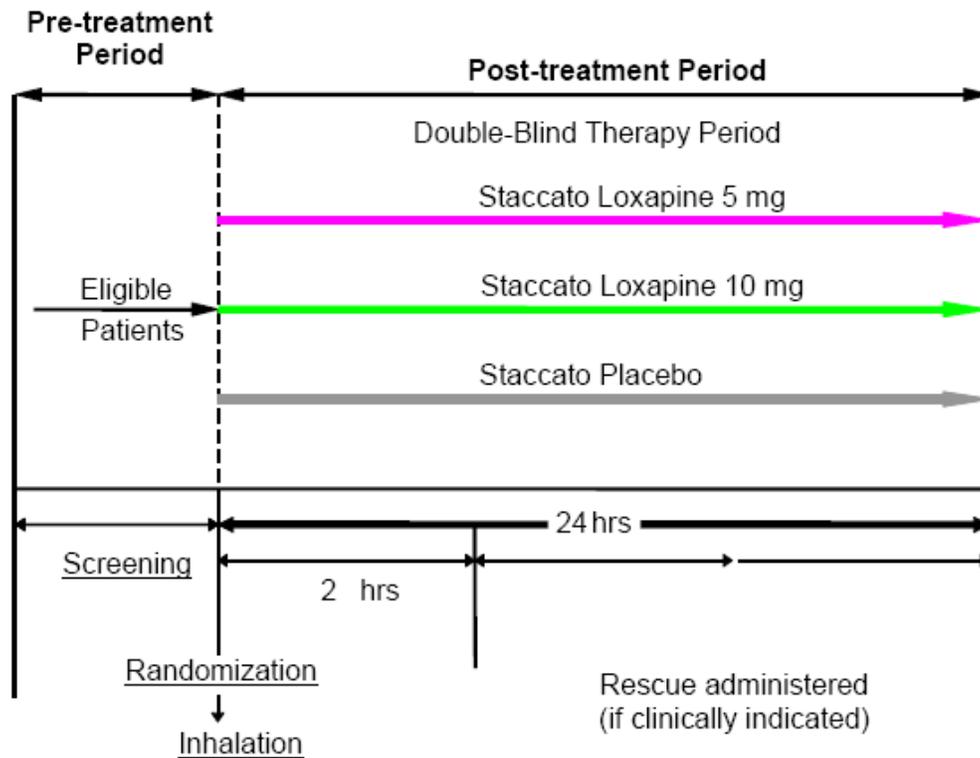
The *Pre-treatment Period* included a screening phase (which may have lasted up to 2 weeks in inpatients) and a baseline assessment phase (done within one hour prior to study

drug administration). The screening phase included initiation of training in the use of the device and evaluating the patient's ability to use the device properly.

Patients who met the screening requirements, satisfied all inclusion and exclusion criteria, and presented with a relevant degree of agitation at baseline were randomized (1:1:1) to receive either a 5 mg dose of *Staccato* Loxapine, a 10 mg dose of *Staccato* Loxapine, or a dose of *Staccato* Placebo. All doses were administered as one inhalation each from a single inhalation device.

The *Treatment/Post-treatment Period* began with study drug administration and lasted 24 hours, with frequent evaluations of agitation during the first 2 hours. Administration of additional agitation treatments (rescue medication) was delayed for 2 hours unless medically necessary.

Figure 6: Design of Trial AMDC-004-201



Concomitant Medication

At 2 hours after treatment, rescue medication for agitation was allowed. Intramuscular lorazepam (0.5 – 2 mg) could be used as a rescue medication and could be repeated as needed during the subsequent 22 hours. Administration of any antipsychotic medication was to be avoided during the 24 hours after *Staccato* treatment.

Patients who developed extrapyramidal signs and symptoms could be treated with anti-Parkinson's or antihistamine agents, as appropriate.

Efficacy Evaluation

Primary Efficacy Endpoint

The primary efficacy endpoint in the trial was the absolute change in PEC score from baseline at 2 hours following *Staccato* administration. The PEC scale had to be administered within 15 to 30 minutes of study drug administration. Subjects not meeting the inclusion criterion for PEC scale at that point were to be either removed from the trial or retested again at a later time-point for eligibility to continue.

Secondary Efficacy Endpoints

Secondary endpoints included: change from baseline in PEC score at 10, 20, 30, 45, 60, and 90 minutes, and 4 hours; total score at 2 hours post-dose in Clinical Global Impression-Improvement (CGI-I) scale; change from baseline at Behavioral Activity Rating Scale (BARS) at 10, 20, 30, 45, 60, and 90 minutes, and 2 and 4 hours; response rate (defined as a 40% decrease in PEC score from baseline); and time to use of rescue medication.

Clinical Global Impression-Severity (CGI-S) scale evaluation was done immediately prior to *Staccato* administration.

Actigraphy

Actigraphy was used to assess efficacy of the study drug as a secondary outcome measure. The actigraphy monitor (Actiwatch), a wrist-worn device, utilizes a motion sensor to monitor and record the occurrence and degree of motion. It has been used to analyze circadian rhythms, automatically collect and store data for sleep parameters, and assess activity in any instance where quantifiable analysis of physical motion is desirable. When attached to a patient's wrist, the Actiwatch accumulates patient activity counts for a specific period of time known as the epoch length.

Actigraphic monitoring (actigraphy) was done on each patient beginning at least 30 minutes pretreatment and continuing for 4 hours post-dose. Data were collected continuously for 2 hours post-dose. A series of 3 custom intervals each 10 minutes long (epoch length) were defined to describe the 30 minutes before each dose, and a series of 12 custom intervals each 10 minutes long were defined to describe the 2 hours after each dose. Thus, data were later scored in 10-minute intervals and assessed at 10, 20, 30, 40, 60, 80, 100, 110, and 120 minutes post-treatment. Actigraphy endpoints included total activity counts, activity counts per epoch, and maximum activity counts. Correlations between actigraphy measurements and other outcomes (especially changes in PEC and BARS) were analyzed.

Safety Assessments

Safety monitoring included:

- Vital signs
- ECG
- Clinical laboratory (complete blood counts, electrolytes, glucose, CK, amylase, uric acid, total cholesterol, kidney and liver function, urinalysis)
- Pregnancy test (if female of childbearing potential)
- Extrapyramidal effects: spontaneously reported extrapyramidal adverse events were recorded
- Adverse events
- Urine drug screen

Table 15: Schedule of Activities - Trial AMDC-004-201

	Pre-Treatment Period		Post-treatment Period									
	Screening	Baseline	Time 0	10 min	20 min	30 min	45 min	60 min	90 min	120 Min	4 hr	24 hr
Inhalation Training	X											
Randomization		X										
<i>Staccato</i> Administration			X									
PEC		X		X	X	X	X	X	X	X	X	X
BARS*		X		X	X	X	X	X	X	X	X	X
Actigraphic Monitoring		X-----X										
CGI-S		X										
CGI-I									X			
Vital signs		X						X		X	X	X
ECG	X											
Clinical labs	X											
Pregnancy Test**	X											
Urine Drug Screen	X											
Physical exam	X											X
Discharge from Trial												X

*BARS= Behavioral Activity Rating Scale

** Pregnancy test: if female of childbearing potential

Statistical Analysis

For the primary efficacy endpoint, the absolute change from baseline in the total PEC score at 2 hours, analysis of covariance (ANCOVA) comparing the changes among the three treatment arms, and Dunnett's t-tests for the 2 active/placebo pair-wise comparisons (adjusted for multiple comparisons) were used for the statistical analysis. Since this was a proof of concept study, the 2 active/placebo comparisons based on Dunnett's t-test were considered the primary analysis. Missing values for applicable outcome variables were

estimated using the last observation carried forward (LOCF) method where post-baseline data would be carried forward for those patients who discontinued early.

Two populations were considered for statistical analysis. The *safety population* was comprised of all randomized patients who took any study medication. The *intent-to-treat (ITT) population* was comprised of all patients who took any study medication and who had both baseline and at least one post-dose efficacy assessment or used rescue medication before 2 hours post-dosing.

Results

Demographics and Baseline Characteristics

The three treatment groups in this trial appeared well matched for demographics and baseline characteristics. Most of the patients were male (81%), Black (44%) or Caucasian (42%), with an overall mean age of 41 years.

Table 16: Baseline Characteristics (Safety Population) - Trial AMDC-004-201

	<i>Staccato</i> Placebo (N=43)	<i>Staccato</i> Loxapine 5 mg (N=45)	<i>Staccato</i> Loxapine 10 mg (N=41)
AGE (years):			
Mean	43.5	40.8	39.3
Age Range	21-57	26-57	23-61
GENDER:			
% Males	77%	84%	83%
% Females	23%	16%	17%
RACE			
% Caucasian	49%	42%	37%
% Black	37%	44%	51%
% Asian	2%	0	2%
% Hispanic	9%	11%	10%
% Other	2%	2%	0

Baseline Disease Characteristics

In this trial, 79% of the patients had a diagnosis of Schizophrenia, and 21% had a diagnosis of Schizoaffective Disorder. The mean \pm SD number of years with the diagnosis was 17.3 ± 10.2 . The mean \pm SD number of previous hospitalizations was 9.7 ± 9.5 , and the mean \pm SD days of current agitation was 7.8 ± 6.6 .

Table 17: Baseline Disease Characteristics (Safety Population) - Trial AMDC-004-201

	<i>Staccato Placebo</i> (N=43)	<i>Staccato Loxapine 5 mg</i> (N=45)	<i>Staccato Loxapine 10 mg</i> (N=41)
<i>Diagnosis</i>			
Schizophrenia	79.1%	77.8%	80.5%
Schizoaffective Disorder	20.9%	22.2%	19.5%
<i>Time since diagnosis (years)</i>			
n	43	45	41
Mean	19.4	17.4	15.0
Range	0-39	2-38	4-42
<i>No. of previous hospitalizations</i>			
n	40	42	39
Mean	11.4	8.5	9.4
Range	0-60	0-25	1-50
<i>Duration of current agitation episode at screening (days)</i>			
n	43	44	41
Mean	8.45	7.23	7.90
Range	0.5-33	1-45	0.7-30

Patient Disposition

Of the 129 patients enrolled, 128 completed the trial. One patient (01-145) in the *Staccato Loxapine 10 mg* treatment group withdrew consent between the 4-hour post-treatment assessment and the end of study assessment.

Table 18: Enumeration of Dropouts by Reason for Dropout -Trial AMDC-004-201

Patient Disposition n (%)	<i>Staccato Placebo</i>	<i>Staccato Loxapine 5 mg</i>	<i>Staccato Loxapine 10 mg</i>	Total
Randomized	43	45	41	129
Trial Completers	43 (100%)	45 (100%)	40 (97.6%)	128 (99.2%)
Dropouts	0	0	1 (2.4%)	1 (0.8%)
Reason for Dropout:				
Patient withdrew consent	0	0	1 (2.4%)	1 (0.8%)

Concomitant Medication Use

The most commonly used medications taken within one week prior to dosing included the antipsychotic drugs (35%), the benzodiazepine and benzodiazepine-related drugs (11%), the antiparkinsonian drugs (9%), and the anticonvulsants (9%).

As shown in the table below, a higher percentage of placebo-treated subjects were taking antipsychotic drugs, benzodiazepine or benzodiazepine-related drugs, and anticonvulsants within one week prior to dosing compared to loxapine-treated patients. It is unlikely that the primary efficacy outcome measure, absolute change in PEC score from baseline at 2 hours following *Staccato* administration, would be affected by these differences, particularly since baseline PEC scores were similar between the 3 treatment groups. Therefore, it is unlikely that efficacy results were confounded.

Table 19: Relevant Medications taken within 1 Week prior to dosing (Safety Population) - Trial AMDC-004-201

	<i>Staccato</i> Placebo (N=43)	<i>Staccato</i> Loxapine 5 mg (N=45)	<i>Staccato</i> Loxapine 10 mg (N=41)
Antipsychotics	18 (42%)	17 (37%)	12 (29%)
Aripiprazole	4 (9%)	1 (2%)	1 (2%)
Haloperidol	0	3 (7%)	1 (2%)
Olanzapine	5 (12%)	2 (4%)	2 (5%)
Quetiapine	5 (12%)	5 (11%)	5 (12%)
Risperidone	3 (7%)	6 (13%)	3 (7%)
Benzodiazepine/related drugs	7 (16%)	4 (9%)	3 (7%)
Zolpidem Tartrate	3 (7%)	1 (2%)	1 (2%)
Lorazepam	4 (9%)	3 (7%)	2 (5%)
Antiparkinsonian drugs			
Benzotropine Mesylate	6 (14%)	3 (7%)	2 (5%)
Anticonvulsants	6 (14%)	4 (9%)	2 (5%)
Valproate Sodium	3 (7%)	2 (4%)	2 (5%)
Valproic Acid	3 (7%)	2 (4%)	0

Important Protocol Violations

Eleven patients (8.5%) had important protocol violations. The most common types were deviations from the study drug/rescue medication regimen and deviations in which a prohibited concomitant medication was administered. None was judged to have affected the findings of the trial.

Five patients had deviations from study drug/rescue medication regimen. Two patients in the placebo group (13-046 and 9-133), two patients in the 5 mg group (15-062 and 17-127), and one patient in the 10 mg group (15-061) were given lorazepam PO rather than the protocol-specified lorazepam IM.

Five patients received a prohibited concomitant medication:

- Patient 9-133 (placebo group) received oxcarbazepine and lithium carbonate 5 minutes prior to study drug.
- Patient 19-037 (5 mg group) received quetiapine 11 hours after study drug.
- Patient 5-019 (5 mg group) received risperidone within 24 hours after study drug.
- Patient 9-012 (5 mg group) received olanzapine and lithium carbonate 13 hours after study drug.
- Patient 2-105 (10 mg group) received quetiapine 12 hours after study drug.

Two patients had deviations related to enrollment criteria:

- Patient 2-104 (placebo group) was inadvertently enrolled with a history of chronic obstructive pulmonary disease. No adverse events were reported.
- Patient 2-106 (5 mg group) was inadvertently enrolled with unstable hypertension. The subject experienced a serious adverse event of worsening hypertension 11 days after dosing that was considered by the investigator as not related to study drug.

Table 20: Patients with Important Protocol Deviations -Trial AMDC-004-201

Patients with Important Protocol Deviations, n (%)	<i>Staccato</i> Placebo (N=43)	<i>Staccato</i> Loxapine 5 mg (N=45)	<i>Staccato</i> Loxapine 10 mg (N=41)	Total (N=129)
Deviation from enrollment criteria	1 (2.3%)	1 (2.2%)	0	2 (1.6%)
Deviation from study drug or rescue drug regimen	2 (4.7%)*	2 (4.4%)	1 (2.4%)	5 (3.9%)
Received prohibited concomitant medication	1 (2.3%)*	3 (6.7%)	1 (2.4%)	5 (3.9%)
<i>Total patients with any important protocol deviation</i>	3 (7.0%)*	6 (13.3%)	2 (4.9%)	11 (8.5%)

*Subject 9-133 had 2 protocol deviations: 1 deviation from study drug or rescue drug regimen and 1 deviation for receiving a prohibited concomitant medication.

Efficacy Findings

Primary Efficacy Endpoint: PEC Scale-Change from Baseline to 2 Hours

For the primary efficacy outcome measure, the absolute change in PEC total score from baseline at 2 hours following *Staccato* administration, a significant overall (both doses) treatment effect of *Staccato* Loxapine compared to placebo was observed, reaching

statistical significance ($p=0.0005$). In addition, PEC score differences were statistically significant ($p=0.0002$) for *Staccato* Loxapine 10 mg group compared to the Placebo group. However, PEC score differences were not statistically significant ($p=0.0880$) for the *Staccato* Loxapine 5 mg group compared to the placebo group.

Table 21: Primary Efficacy Endpoint: Change in PEC Score 2 Hours after Dose (ITT Population with LOCF) - Trial AMDC-004-201

PEC Score	<i>Staccato</i> Placebo (N=105)	<i>Staccato</i> Loxapine 5 mg (N=104)	<i>Staccato</i> Loxapine 10 mg (N=105)
Mean Baseline PEC Score	17.7	17.6	17.3
Mean change in PEC score from baseline to 2 hours after Dose	-5.0	-6.7	-8.6
p-value for overall treatment effect	P=0.0005	----	----
p-value for active/placebo comparisons	----	P=0.0880	P=0.0002

Secondary Endpoints

A statistically significant separation of the 10 mg dose group from placebo in change from baseline in PEC score was found 20 minutes after treatment and remained statistically significant through 24 hours. The 10 mg dose group showed a statistically significant decrease in Behavioral Activity Rating Scale (BARS) score, compared to placebo, beginning at 30 minutes post-dose, and this response was sustained throughout the 24-hour period. For the 5 mg dose group, statistically significant decrease in BARS score, compared to placebo, was reached only at the 45-minute post-dose time point.

At the 2-hour post-dose time point, both the 5 mg ($p=0.0067$) and the 10 mg ($p=0.0003$) *Staccato* Loxapine treatment groups showed statistically significant effects in CGI-I scores compared to placebo. In addition, 21% of patients receiving *Staccato* Placebo were positive CGI-I responders compared to 49% of those receiving *Staccato* Loxapine 5 mg and 63% of those receiving *Staccato* loxapine 10 mg ($p=0.0001$).

No patient in any treatment group used any rescue medication within the first 2 hours post-dose. At 24 hours post-dose, ~15% of patients in the 10 mg dose group and ~11% of patients in the 5 mg dose group had received rescue medication, compared to ~33% of patients in the placebo group. In a survival analysis, *Staccato* Loxapine differed significantly for time to first rescue medication ($p=0.019$). When the survival analysis for time to the first rescue medication is shown for each dose, both the 5 mg ($p=0.014$) and 10 mg ($p=0.046$) treatment groups differ significantly from placebo.

In summary, the results from the secondary endpoints were supportive of the results from the primary outcome measure.

Conclusions

The primary efficacy endpoint (absolute change in PEC score from baseline to 2 hours following *Staccato* Loxapine administration) comparison of *Staccato* Loxapine overall (both doses) to placebo was statistically significant in favor of *Staccato* Loxapine. In addition, PEC score differences were statistically significant for the *Staccato* Loxapine 10 mg group compared to the placebo group. PEC score differences were not statistically significant for the *Staccato* Loxapine 5 mg group compared to the placebo group. The secondary analyses were supportive of the primary efficacy results.

6.2.2 Trial AMDC 004-301 (Schizophrenia)

This trial was a 24-hour, Phase 3, pivotal, in-patient, multicenter, randomized, double-blind, fixed-dose, repeat-dose (as required) placebo-controlled, parallel group, safety, and efficacy trial evaluating *Staccato* Loxapine for Inhalation (*Staccato* Loxapine) for the treatment of agitation in patients with Schizophrenia. The trial, initiated on February 22, 2008 and completed on June 27, 2008, was conducted in twenty-four centers in the United States.

Objectives

The purposes of the trial were to confirm the safety and efficacy of *Staccato* Loxapine at 5- and 10-mg fixed dose levels in the treatment of acute agitation in Schizophrenic patients, and to confirm the tolerability of up to 3 doses administered in a 24-hour period. Efficacy was assessed using the PANSS Excited Component (PEC) of the Positive and Negative Symptoms Scale (PANSS). The primary objective was to assess the change in PEC score from baseline to 2 hours following the first dose of *Staccato* Loxapine (5 or 10 mg), compared with placebo.

Trial Population

Trial patients were adults (18-65 years, inclusive) who met DSM-IV criteria for Schizophrenia and had a baseline total PANSS Excited Component (PEC) score of ≥ 14 . In addition, the patients were to have a score of ≥ 4 on at least 1 of the 5 items on the PEC scale (poor impulse control, tension, hostility, uncooperativeness, and excitement).

The following types of patients could be enrolled:

1. Patients admitted to a hospital setting or research unit for the purpose of the trial
2. Patients already hospitalized for treatment of Schizophrenia who had acute agitation
3. Patients treated at a psychiatric emergency room setting that allowed extended patient stays in a secluded observation room for the period of the trial.

The trial was targeted to enroll approximately 300 patients.

Key Inclusion Criteria

1. Male and female patients between the ages of 18 to 65 years, inclusive.
2. Patients who meet DSM-IV criteria for Schizophrenia.
3. Patients who are judged to be clinically agitated at Baseline with a total score \geq 14 on the 5 items (poor impulse control, tension, hostility, uncooperativeness, and excitement) comprising the PEC scale.
4. Patients who have a value of \geq 4 (out of 7) on at least 1 of the 5 items on the PEC scale.
5. Patients who are in good general health prior to trial participation as determined by medical history, physical examination, and ECG.
6. If female of child-bearing potential or if male who is sexually active with a partner of child-bearing potential, must use a medically acceptable method of birth control throughout the trial and for one week following the end of the trial.

Key Exclusion Criteria

1. Patients with agitation caused primarily by acute intoxication (investigator's opinion)
2. Positive urine drug screen for psychostimulants (e.g., cocaine, PCP)
3. Patients judged to be at serious risk for suicide
4. History of drug or alcohol dependence within the past 2 months
5. Patients treated with benzodiazepines or other hypnotics or oral or short-acting intramuscular antipsychotics within 4 hours prior to study drug administration were excluded, but could be reassessed subsequently for inclusion.
6. Patients treated with injectable depot neuroleptics within one dose interval prior to study drug administration were excluded, but could be reassessed subsequently for inclusion.
7. History of allergy or intolerance to loxapine or amoxapine
8. If female, positive pregnancy test or breastfeeding
9. Clinically significant laboratory or ECG abnormalities
10. Clinically significant hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrine, neurologic, or hematologic disease
11. Clinically significant acute or chronic pulmonary disease, such as clinically apparent asthma, chronic bronchitis, or emphysema
12. Patients who were considered by the investigator, for any reason, to be an unsuitable candidate for receiving *Staccato* Loxapine, or likely to be unable to use the inhalation device

Trial Design

The trial consisted of two periods: a *Pre-treatment Period* including screening, randomization, and baseline assessment phases; and a 24-hour *Treatment/Post-treatment Period*.

Pre-treatment Period (Screening)

During the *Pre-treatment Period*, agitated schizophrenic patients were screened for inclusion in the trial. As part of the screening process, patients were evaluated for their ability to properly perform the inhalation maneuver required to use *Staccato* Loxapine/*Staccato* Placebo. Screening could span up to 2 weeks.

Once all the screening steps were successfully completed, patients satisfying all inclusion and exclusion criteria and presenting with a qualifying degree of agitation were enrolled in the trial and were randomized (1:1:1) to receive 1-3 doses of one of the following treatments: 5 mg *Staccato* Loxapine, 10 mg *Staccato* Loxapine, or *Staccato* Placebo. Following randomization, pre-treatment baseline assessments (rating scales and vital signs) were conducted and were completed within 30 minutes prior to study drug administration. The baseline period also included repeat device training.

Treatment/Post-treatment Period

The *Treatment/Post-treatment Evaluation Period* was defined as beginning with the first administration of study drug (Dose #1) and lasting 24 hours. It included several scheduled evaluations of agitation, most of which took place during the first 2 hours after Dose #1. A maximum of 3 doses of study medication were allowed over the 24-hour evaluation period, with Doses #2 and #3 administered only if needed.

For the purposes of the efficacy analysis, the first 2-hour period after Dose #1 was defined as the *Primary Efficacy Evaluation Period*, and the subsequent period, through 24 hours after Dose #1, was defined as the *Extended Evaluation Period*. Following completion of the efficacy assessment at time = 2 hour (i.e. after the Primary Efficacy Evaluation Period), up to 2 additional doses of study drug (Doses #2 and #3) could be given if agitation did not subside sufficiently or recurred after Dose #1, according to the following rules:

1. Time 0-2 h following Dose #1 (Primary Efficacy Evaluation Period)

- Additional doses of study drug were not allowed until the assessments at time = 2 h were completed.
- Use of rescue medication was not allowed during the first 2 hours following Dose #1 (unless medically necessary) to avoid interference with the primary efficacy measures at time = 2h.

2. Time = 2-24 h following Dose #1 (Extended Evaluation Period)

- Dose #2 may be given > 2 h after Dose #1 (within 24 h of Dose #1)
- Dose #3 may be given \geq 4 h after Dose #2 (within 24 h of Dose #1)

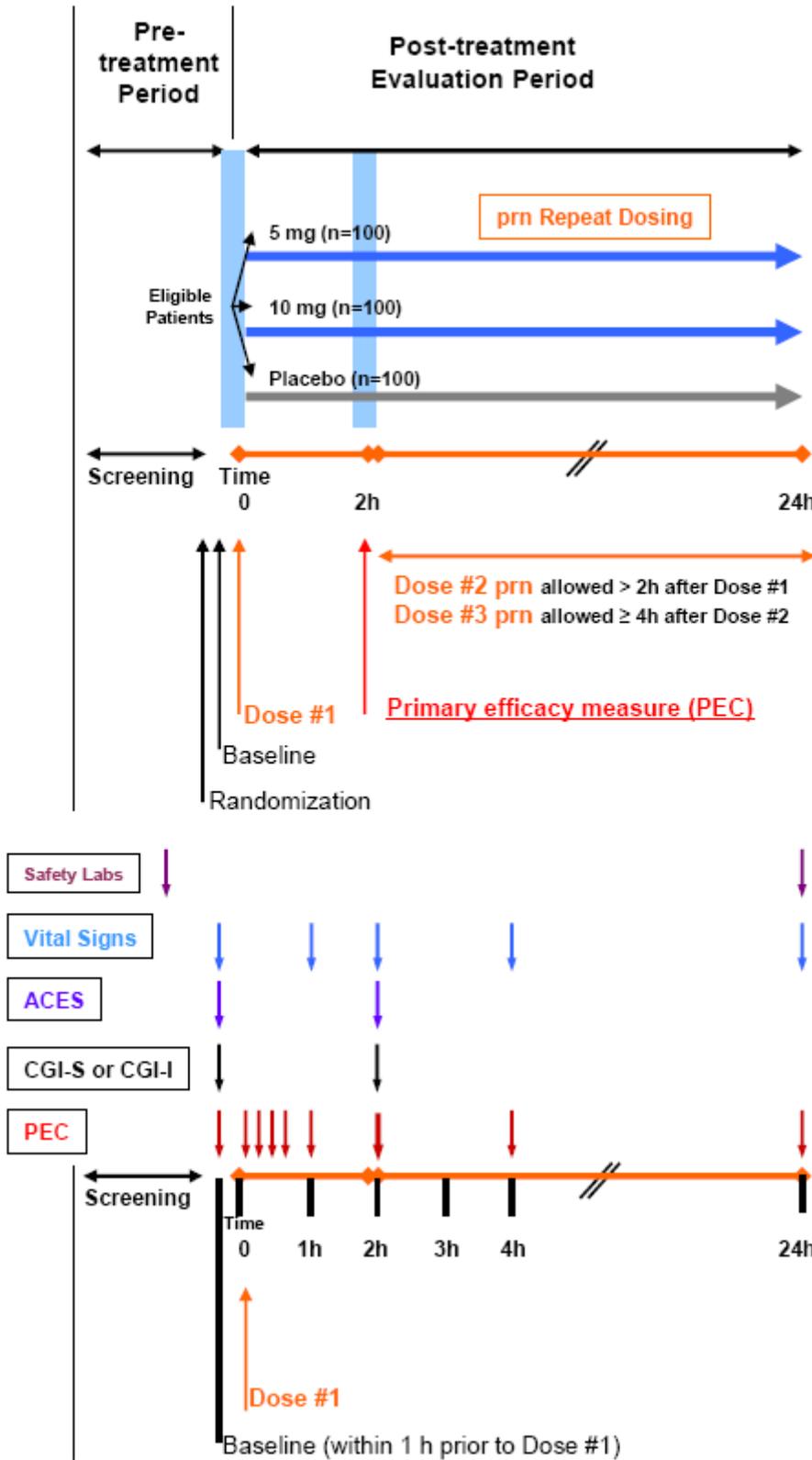
At the end of the 24-h Treatment/Post-treatment Evaluation Period:

- Patients underwent a follow-up evaluation that included: vital signs and physical examination, and repeat chemistry, hematology, and urine evaluations.
- Patients were started on a maintenance therapeutic regimen.
- Patients were discharged from the hospital ≥ 12 h after the last administration of Study Drug or maintained in-hospital depending on their clinical status and the judgment of the investigator.

As detailed in the sections below, efficacy was assessed by PANSS Excited Component (PEC), Clinical Global Impression-Improvement (CGI-I), and Agitation-Calmness Evaluation Scale (ACES) scores; the number of doses of study and rescue medication; the time to Dose 2 of study medication (a prn dose); and the time to use of rescue medication.

Figure 7: Design of Trial AMDC-004-301

(Electronically copied and reproduced from sponsor's submission)



Device Malfunctions

Trial personnel were instructed in the identification and management of suspected device malfunctions as follows:

- If the solid green light does not light when the pull-tab is removed, dispense another device and return the initial device via the device complaint system.
- If the green light does not flash when the patient inhales:
 1. Instruct the patient to inhale through the device 1 more time.
 2. If the green light still does not flash, dispense another device and return the initial device via the device complaint system.

All suspect devices were to be returned to Alexza via the device complaint system.

Rescue Medication

The following are the protocol rules for the use of lorazepam rescue medication:

- If required, intramuscular lorazepam could be used as the rescue medication in this trial and dosed as clinically indicated.
- Rescue medication (IM lorazepam) should only be considered after Dose #2 (and after the efficacy assessments at time =2h have been completed). Patients who received only one dose of study drug (Dose #1) could not be given lorazepam rescue (unless medically required).
- If rescue medication was required after Dose #2 or Dose #3, the rescue medication could not be administered until at least 20 minutes after study drug administration.
- Patients who received lorazepam rescue medication were no longer eligible to receive additional doses of study drug.

Concomitant Medications

In this trial, medications recorded at screening, and which were no longer taken during the trial, were recorded as *prior* medications. *Concomitant* medications included medications taken from the screening phase through discharge. Although there were post-screening concomitant medications, there were restrictions for certain concomitant medications as follows:

1. Antipsychotic drugs and benzodiazepines and other hypnotics were prohibited from at least 4 hours prior to Dose #1 until the end of the 24-hour Post-treatment Evaluation Period.

2. Previously prescribed drugs for extrapyramidal symptoms (EPS) were also to be discontinued during the 24-hour Evaluation Period. Patients who developed EPS could be treated with anti-Parkinson's or antihistamine agents as clinically indicated, but prophylaxis for EPS was not permitted.
3. In general, patients could not receive any psychotropic drug (with the exception of Study Drug or lorazepam rescue medication) from 4 hours prior to Dose #1 until the end of the 24-hour Post-treatment Evaluation Period that, in the opinion of the investigator, would confound the efficacy or safety endpoints of the trial.

Efficacy Evaluation

Primary Efficacy Measure

The primary efficacy measure for this trial was the PANSS Excited Component (PEC), an assessment of agitation, which includes the following 5 items:

- Poor impulse control
- Tension
- Hostility
- Uncooperativeness
- Excitement

The numeric values of the PEC are based on the 1 to 7 scoring system of severity according to:

- 1 = absent
- 2 = minimal
- 3 = mild
- 4 = moderate
- 5 = moderate severe
- 6 = severe
- 7 = extreme

Thus, the total score from the 5 items of the PEC can range from 5 to 35.

Primary Efficacy Endpoint

The primary efficacy endpoint was the absolute change in PEC score from baseline to 2 hours following Dose #1 of *Staccato* Loxapine, compared with placebo.

Key Secondary Endpoint

The key secondary endpoint was the Clinical Global Impression-Improvement (CGI-I) score at 2 hours following Dose #1 of *Staccato* Loxapine, compared with placebo.

Clinical Global Impression-Severity (CGI-S) was done just prior to *Staccato* study drug administration and was used to assess baseline comparability.

Additional Secondary Endpoints

For the 10 mg *Staccato* Loxapine/ *Staccato* Placebo comparison **only**, the changes from baseline in PEC score at 10, 20, 30, and 45 minutes after administration of Dose #1 were considered Secondary Endpoints and were assessed using the downward stepwise procedure outlined in the Statistical Analysis Plan.

Tertiary Endpoints

1. CGI-I Responders at 2 hours after Dose #1: CGI-I responders were defined as patients with a score of 1 or 2 on the CGI-I scale; the CGI-I non-responders were defined as patients with scores from 3 to 7. A value of 0 (“not assessed”) was considered missing.
2. Changes from baseline in PEC score at 60 minutes, 90 minutes, 4 hours, and 24 hours after Dose #1 (10 mg group **only**).
3. Total number of patients per group who received one, two, or three doses of study drug with and without rescue medication by 4 hours and 24 hours after Dose #1.
4. Time to rescue medication during the entire 24 hour Post-treatment Evaluation Period.
5. Time to Dose #2 (PRN) of *Staccato* study drug during the 24 hour evaluation Period.
6. Agitation-Calmness Evaluation Scale (ACES) scores at 2 hours after Dose #1.

Safety Assessments

Safety monitoring included:

- Vital signs
- ECG
- Pregnancy test (if female of child-bearing potential)
- Urine drug screen
- Alcohol screen (urine, saliva, or breathalyzer)
- Clinical laboratory tests (complete blood counts with differential, calcium, CPK, electrolytes, glucose, uric acid, liver and kidney function, urinalysis)
- Adverse event monitoring
- Extrapyrarnidal effects monitoring: spontaneously reported extrapyramidal signs and symptoms were recorded as adverse events

Table 22: Schedule of Activities -Trial AMDC-004-301

Activity	Pretreatment Period		Post-treatment Evaluation Period									
	Screening	Baseline	Time 0	10 min	20 min	30 min	45 min	60 min	90 min	120 min (2h)	4h	24h
Physical Exam	X											X
Inhalation Training	X	X										
Study Drug Given			X	<i>Not allowed through Hour-2 Assessments</i>						<i>PRN after Hour 2</i>		
Adverse events	<i>Recorded when identified by study center staff or volunteered by patient</i>											
PEC		X		X	X	X	X	X	X	X	X	X
CGI-S		X										
CGI-I										X		
ACES		X								X		
Vital signs		X						X		X	X	X
ECG	X											
Clinical labs	X											X
UDS	X											
Alcohol screen	X											
Pregnancy Test	X											
Discharge												X

Statistical Analysis

Determination of Samples Size

The power calculations for this trial were based on the results of the Phase 2A trial of *Staccato* Loxapine (**AMDC-004-201**). Based on the outcome of that trial, 100 patients per treatment arm were estimated to provide 99 % statistical power for the 10 mg *Staccato* Loxapine/ *Staccato* Placebo pairwise comparison and 79 % statistical power for the 5 mg *Staccato* Loxapine/ *Staccato* Placebo pairwise comparison for this primary efficacy endpoint.

Analysis Populations

The *efficacy population* (ITT with LOCF) included all patients who received any study medication and had both baseline and at least one post-dose efficacy assessment or received rescue medication before 2 hours after dosing. Missing values were replaced

using the LOCF algorithm. The *safety population* included all patients who received any study medication.

Primary Efficacy Analysis

For the primary efficacy endpoint (absolute change from baseline in the PEC score at 2 hours), a “gatekeeper” analysis of covariance (ANCOVA) comparing the changes among the three treatment arms using a global F-test, with Dunnett’s t-tests for the 2 follow-up active/placebo pairwise comparisons (adjusted for multiple comparisons) was used for the statistical analysis. The 2 active/placebo comparisons adjusted for multiple comparisons based on Dunnett’s procedure were considered the primary analysis. Testing was 2-sided with a family-wise $\alpha=0.05$.

A main effects ANCOVA model including terms for baseline PEC, treatment, and center (ie, pseudocenter) was used to assess the overall treatment effect. Treatment and pseudocenter effects were considered statistically significant if $p \leq 0.05$. Dunnett’s t-tests were conducted within the framework of the ANCOVA model, which will be based on least squares means (LSMeans) and the pooled standard deviation (SD).

In addition, the treatment-by-pseudocenter interaction term was examined. This interaction term was not significant at $\alpha=0.05$; therefore, no further investigation was undertaken.

Key Secondary Analysis

For the key secondary endpoint (CGI-I score 2 hours after Dose #1), a “gatekeeper” analysis of variance (ANOVA) with terms for pseudocenter and treatment was used to compare the 3 treatment groups, with a global F-test and Dunnett’s t-tests for the 2 follow-up active/placebo pairwise comparisons (adjusted for multiple comparisons). Testing was conducted using the closed-method hierarchical testing strategy based on the outcome of the primary efficacy analysis and Dunnett’s (or Dunn’s for nonparametric approach) multiple-comparisons adjustment for pairwise comparisons.

Analysis of Additional Secondary Efficacy Endpoints

The additional secondary efficacy endpoints were analyzed using ANCOVA models to assess the 10-mg/placebo pairwise comparisons. If both the primary and key secondary efficacy endpoints were statistically significant for the 10-mg/placebo comparison, then testing of the additional secondary endpoints was conducted using a downward stepwise testing rule for the time points. All ANCOVA analyses followed the same structure as used in the primary efficacy analysis.

Analysis of the Tertiary Efficacy Endpoints

The analyses of the tertiary efficacy endpoints were considered exploratory. They were not included in the main efficacy analyses and were not protected within the family-wise error at 0.05. All testing for the tertiary analyses was 2-sided at a nominal $\alpha=0.05$ level.

Results

Demographics and Baseline Characteristics

In this trial, the 3 treatment groups appeared well matched for demographic and baseline characteristics. The mean age of randomized patients was 43.1 years (± 9.84), and the majority of patients were male (73.5%). Most patients were either Black (57.6%) or Caucasian (33.7%) and had a history of smoking.

Table 23: Baseline Characteristics (Safety Population) - Trial AMDC-004-301

	Staccato Placebo (N=115)	Staccato Loxapine 5 mg (N=116)	Staccato Loxapine 10 mg (N=113)
AGE (years):			
Mean	43.9	43.2	42.2
Age Range	23-63	18-65	21-62
GENDER:			
% Males	69.6%	75.0%	76.1%
% Females	30.4%	25.0%	23.9%
RACE			
% Caucasian	27.8%	41.4%	31.9%
% Black	60.9%	52.6%	59.3%
% Asian	3.5%	0.9%	0.9%
% Hispanic	7.8%	5.2%	7.1%
% Other	0	0	0.9%
SMOKING HISTORY			
Never smoked	13.0%	11.2%	7.1%
Current smoker	78.3%	81.0%	85.8%
Ex-smoker	8.7%	7.8%	7.1%

Baseline Disease Characteristics

Across treatment groups, the mean time since diagnosis of Schizophrenia ranged from 16.5 to 18.8 years, and at screening the mean duration of the current episode of agitation ranged from 6.1 to 7.6 days.

The mean baseline PEC score ranged from 17.4 to 17.8, and the mean baseline CGI-I score ranged from 3.9 to 4.1. Thus, baseline agitation was similar in the 3 treatment groups.

Table 24: Baseline Disease Characteristics (Safety Population) - Trial AMDC-004-301

	<i>Staccato Placebo</i> (N=115)	<i>Staccato Loxapine 5 mg</i> (N=116)	<i>Staccato Loxapine 10 mg</i> (N=113)
<i>Diagnosis</i>			
Schizophrenia	100%	100%	100%
<i>PEC score at baseline</i>			
Mean	17.4	17.8	17.6
Range	14-21	14-28	14-27
<i>CGI-S score at baseline</i>			
Mean	3.9	4.0	4.1
Range	2-5	3-6	2-6
<i>Time since diagnosis (years)</i>			
Mean	18.8	16.5	18.2
Range	0-40	0-41	1-49
<i>No. of previous hospitalizations</i>			
Mean	9.6	9.2	9.7
Range	0-50	0-99	0-90
<i>Duration of current agitation episode at screening (days)</i>			
Mean	6.9	6.1	7.6
Range	<1-72	<1-45	<1-90

Patient Disposition

Of the 374 patients who were screened for this trial, 344 (92.0%) were randomized and received at least 1 dose of study medication, and 338 completed the trial. Thirty patients were screened but not enrolled, most commonly because they did not meet enrollment criteria. No patient was reported to have failed screening because of an inability or unwillingness to use the *Staccato* system. The following 6 patients discontinued prematurely:

- Patient 05-313 (10 mg, male, 49 years) was withdrawn because the investigator decided to administer Seroquel (quetiapine fumarate) for insomnia during the trial. This patient received 1 dose of study medication.
- Patient 19-405 (10 mg, female, 59 years) was withdrawn because of an adverse event of moderate bronchospasm after receiving the first dose of study medication.
- Patient 19-408 (5 mg, female, 41 years) was withdrawn before the 45-minute efficacy assessments when it was discovered that she had previously participated in the trial at another center (as patient 18-423, placebo). As Patient 19-408, she received 1 dose of study medication.

- Three patients withdrew consent: Patient 07-160 (10 mg, 2 doses, male, 21 years), Patient 12-386 (5 mg, 2 doses, male, 29 years), and Patient 12-393 (placebo, 2 doses, female, 45 years).

Table 25: Enumeration of Dropouts by Reason for Dropout - Trial AMDC-004-301

Patient Disposition n (%)	<i>Staccato</i> Placebo	<i>Staccato</i> Loxapine 5 mg	<i>Staccato</i> Loxapine 10 mg	Total
Randomized	115	116	113	344
Trial Completers	114 (99.1%)	114 (98.3%)	110 (97.3%)	338 (98.3%)
Dropouts	1 (0.9%)	2 (1.7%)	3 (2.7%)	6 (1.7%)
Reason for Dropout:				
Adverse Event	0	0	1 (0.9%)	1 (0.3%)
Patient withdrew consent	1 (0.9%)	1 (0.9%)	1 (0.9%)	3 (0.9%)
Investigator decision	0	0	1 (0.9%)	1 (0.3%)
Other	0	1 (0.9%)*	0	1 (0.3%)

- “Other” reason: Patient 19-408 was withdrawn when it was discovered that she had completed the trial at another center (as Patient 18-423).

Concomitant Medication Use

Concomitant medications were defined as any medications taken from the screening phase through discharge. Therefore, antipsychotic drugs and benzodiazepines and other hypnotics could be included as concomitant medications, although they were prohibited from at least 4 hours prior to Dose #1 until the end of the 24-hour Post-treatment Evaluation Period. There were a total of 110 reports of concomitant use of antipsychotics during the trial, as shown in the table below:

Table 26: Concomitant Antipsychotic Medications [n (%)] for Safety Population - Trial AMDC-004-301

	<i>Staccato</i> Placebo (N=115)	<i>Staccato</i> Loxapine 5 mg (N=116)	<i>Staccato</i> Loxapine 10 mg (N=113)	Overall (N=344)
Aripiprazole	3 (2.6%)	4 (3.4%)	1 (0.9%)	8 (2.3%)
Fluphenazine	2 (1.8%)	1 (0.9%)	3 (2.7%)	6 (1.8%)
Haloperidol	2 (1.7%)	1 (0.9%)	4 (3.5%)	7 (2.0%)
Loxapine	1 (0.9%)	1 (0.9%)	0 (0.0%)	2 (0.6%)
Olanzapine	2 (1.7%)	4 (3.4%)	11 (9.7%)	17 (4.9%)
Paliperidone	1 (0.9%)	3 (2.6%)	3 (2.7%)	7 (2.0%)
Perphenazine	1 (0.9%)	0 (0.0%)	1 (0.9%)	2 (0.6%)
Quetiapine	9 (7.8%)	17 (14.7%)	13 (11.5%)	39 (11.4%)
Risperidone	7 (6.1%)	6 (5.2%)	4 (3.5%)	17 (4.9%)
Ziprasidone	2 (1.7%)	3 (2.6%)	0 (0.0%)	5 (1.5%)
Total Antipsychotics	30 (26.0%)	40 (34.0%)	40 (35.0%)	110 (32.0%)

In addition, there were 65 reported cases of concomitant use of benzodiazepines or other hypnotics during the trial, and one of concomitant use of buspirone, as shown in the table below:

Table 27: Concomitant Anti-Anxiety Medications [n (%)] for Safety Population - Trial AMDC-004-301

	<i>Staccato</i> Placebo (N=115)	<i>Staccato</i> Loxapine 5 mg (N=116)	<i>Staccato</i> Loxapine 10 mg (N=113)	Overall (N=344)
Alprazolam	0 (0.0%)	1 (0.9%)	1 (0.9%)	2 (0.6%)
Buspirone	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.3%)
Clonazepam	4 (3.5%)	3 (2.6%)	2 (1.8%)	9 (2.6%)
Eszopiclone	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Flurazepam	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.3%)
Lorazepam	6 (5.2%)	13 (11.2%)	6 (5.3%)	25 (7.3%)
Temazepam	1 (0.9%)	1 (0.9%)	1 (0.9%)	3 (0.9%)
Zolpidem	10 (8.6%)	8 (6.9%)	5 (4.4%)	23 (6.7%)
Total	22 (19.1%)	27 (23.4%)	16 (14.2%)	65 (19.0%)

Thus, the distribution of concomitant anti-anxiety medication between the three treatment groups is fairly equal and is unlikely to confound efficacy results. In the case of concomitant antipsychotics, however, it appears that more subjects in the *Staccato* Loxapine treatment groups were on concomitant antipsychotics compared to the placebo group. Since baseline disease characteristics between the three treatment groups, in particular the level of agitation as defined by the PEC score, are quite similar, it is unlikely that the differences in concomitant antipsychotic use could have confounded efficacy measurements.

Important Protocol Violations

Eleven patients (3.2%) had important protocol deviations. The most common type of important protocol deviation related to study and/or rescue medication use. Five patients had such deviations, although all occurred well after completion of the primary and key secondary efficacy assessments. Patient 03-074 (placebo group) and Patients 03-073 and 21-198 (both in 5-mg group) received Dose 3 of study medication earlier than permitted in the protocol, and one of them (Patient 03-074) also received oral (rather than IM) lorazepam as rescue medication. Two patients received rescue medication without first receiving Dose 2 of study medication: Patient 22-139 (5-mg group) received IM lorazepam approximately 17 hours after Dose 1; and Patient 25-208 (10-mg group) received Haldol (haloperidol, a disallowed rescue medication) 12 hours after Dose 1, along with Cogentin (benztropine mesylate).

One patient, 19-408 (5-mg group), had a deviation related to enrollment criteria: As discussed above, this patient had previously completed the trial at a different site and was withdrawn from the trial when this was discovered.

One patient, 14-038 (10-mg group), received disallowed concomitant medication late in the post-treatment evaluation period: Zyprexa (olanzapine) was restarted approximately 20 hours after Dose 1.

Four patients had deviations that were categorized as “other.” Patient 11-279 (placebo) was uncooperative and left the study center without completing the end-of-study safety assessments. The other three deviations related to investigator training in the behavioral assessment scales: For Patient 10-217 (placebo), the CGI-S rating scale was done after the relevant subinvestigator was trained in the use of the test, but before he was notified that he was certified in its use; and for Patients 13-097 (10 mg) and 13-098 (placebo), CGI ratings were done by a subinvestigator who did not have CGI certification in this trial but had been trained for another trial.

Table 28: Patients with Important Protocol Deviations -Trial AMDC-004-301

Patients with Important Protocol Deviations, n (%)	Staccato Placebo (N=115)	Staccato Loxapine 5 mg (N=116)	Staccato Loxapine 10 mg (N=113)	Total (N=344)
Deviation from enrollment criteria	0	1 (0.9%)	0	1 (0.3%)
Patient not managed according to withdrawal criteria	0	0	0	0
Deviation from study drug or rescue drug regimen	1 (0.9%)	3 (2.6%)	1 (0.9%)	5 (1.5%)
Received prohibited concomitant medication	0	0	1 (0.9%)	1 (0.3%)
Other	3 (2.6%)	0	1 (0.9%)	4 (1.2%)
<i>Total patients with any important protocol deviation</i>	4 (3.5%)	4 (3.4%)	3 (2.7%)	11 (3.2%)

Reported Device Malfunctions

Two *Staccato* systems were returned via the device complaint system. The returned devices underwent inspection and testing to determine if there had been a failure, and if so, what the potential causes were.

It was determined that 1 returned device had actuated before it was returned to Alexza and therefore not considered a failure (*Staccato* Placebo device from Patient 20-242). The patient inhaled twice through this device and was not given another device; therefore, there was no duplicate dosing.

The other returned device (*Staccato* Loxapine 5 mg from Patient 24-230) was confirmed to be a device failure; however, the patient was given a second device at the study center and therefore received the planned dose during the study.

Therefore, of the 540 Staccato systems used in the trial, there was 1 (0.2%) confirmed device failure.

Efficacy Findings

Primary Efficacy Endpoint: PEC Scale-Change from Baseline to 2 Hours

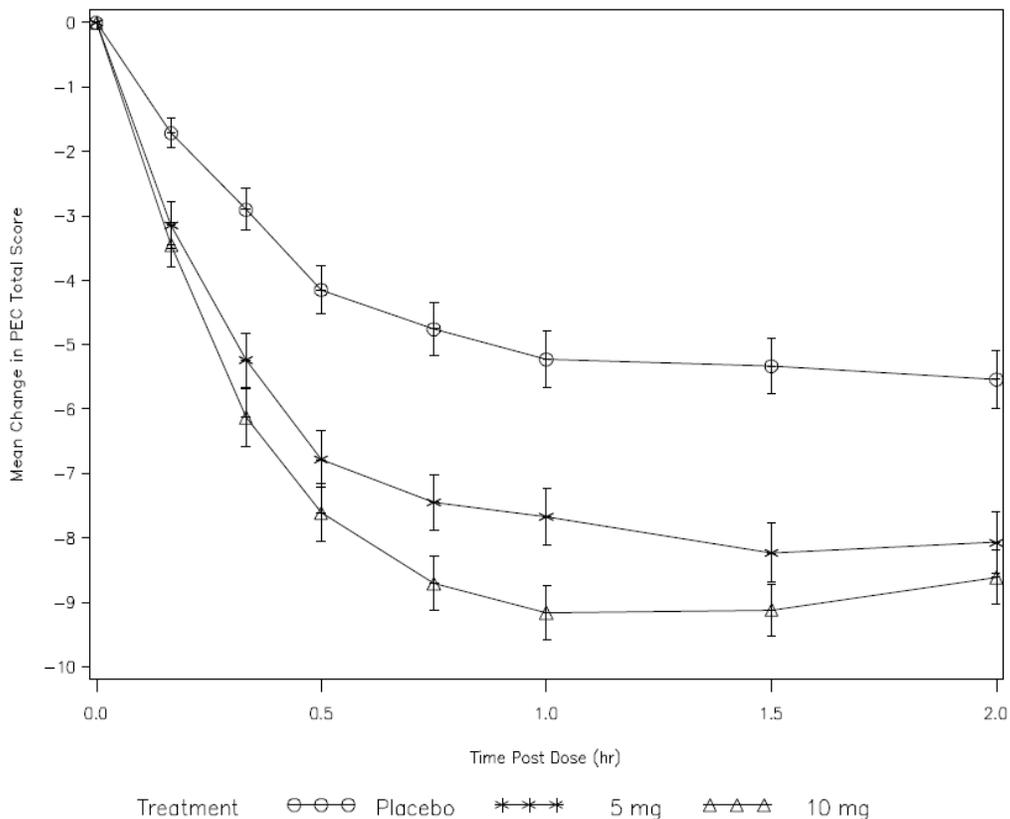
The primary efficacy endpoint was the change in the PEC score from baseline to 2 hours after Dose 1 (active versus placebo). Both the 5- and 10-mg doses met this endpoint, with the tests for overall treatment effect and the 2 follow-up active/placebo comparisons being statistically significant, as shown in the table and figure below:

Table 29: Primary Efficacy Endpoint: Change in PEC Score 2 Hours after Dose 1 (ITT Population with LOCF) -Trial AMDC-004-301

PEC Score	<i>Staccato</i> Placebo (N=115)	<i>Staccato</i> Loxapine 5 mg (N=116)	<i>Staccato</i> Loxapine 10 mg (N=113)
Mean Baseline PEC Score	17.4	17.8	17.6
Mean change* in PEC score from baseline to 2 hours after Dose 1	-5.8	-8.0	-8.7
p-value for overall treatment effect	p<0.0001	----	----
p-value for active/placebo comparisons	----	p=0.0004	p<0.0001

*LS mean (was used in the primary efficacy analysis)

Figure 8: Mean Change from Baseline in PEC Score through 2 Hours after Dose 1 (ITT Population with LOCF) - Trial AMDC-004-301



PEC Scale: Additional Secondary Efficacy Analysis

Changes from baseline to 10, 20, 30, and 45 minutes after Dose 1 for the 10-mg/placebo comparison were analyzed as secondary efficacy endpoints that were included in the main efficacy analysis and therefore protected at a family-wise error rate of 0.05. Changes from baseline to 1, 1.5, 4, and 24 hours after Dose 1 for the 10-mg placebo comparison were analyzed as tertiary efficacy endpoints and not included in the main efficacy analysis. Changes from baseline to 10, 20, 30, and 45 minutes, and 1, 1.5, 4, and 24 hours after Dose 1 for the 5-mg/placebo comparison were not analyzed statistically, per the statistical analysis plan.

Changes from baseline in the PEC score were evident at the first assessment time, 10 minutes after Dose 1, and all subsequent assessments during the 24-hour evaluation period, as shown in the table below. For the 10-mg/placebo comparison, the difference was statistically significant at each assessment time ($p < 0.0001$). Although the 5-mg/placebo comparison was not analyzed statistically (per the statistical analysis plan), a numerical difference between these 2 groups was evident at each assessment time.

The data presented in the table below also provide evidence of a dose-response pattern, since, at each assessment time through 24 hours, the effect was larger in the 10-mg group compared with the 5-mg group.

Table 30: Change in the PEC Score at Assessments through 24 Hours after Dose 1 (ITT Population with LOCF) - Trial AMDC-004-301

PEC Score	<i>Staccato</i> Placebo (N=115)	<i>Staccato</i> Loxapine 5 mg (N=116)	<i>Staccato</i> Loxapine 10 mg (N=112)
Baseline (mean)	17.4	17.8	17.6
+10 min (mean Δ) p-value	-1.7	-3.1 NA	-3.4 p<0.0001
+20 min (mean Δ) p-value	-2.9	-5.2 NA	-6.1 p<0.0001
+30 min (mean Δ) p-value	-4.1	-6.8 NA	-7.6 p<0.0001
+45 min (mean Δ) p-value	-4.8	-7.4 NA	-8.7 p<0.0001
+1 hour (mean Δ) p-value	-5.2	-7.7 NA	-9.2 p<0.0001
+1.5 hours (mean Δ) p-value	-5.3	-8.2 NA	-9.1 p<0.0001
+2 hours; primary endpoint (LS mean Δ) p-value	-5.8	-8.0 P=0.0004	-8.7 p<0.0001
+4 hours (mean Δ) p-value	-6.3	-8.2 NA	-9.5 p<0.0001
+24 hours (mean Δ) p-value	-4.4	-6.2 NA	-6.9 p<0.0001

Key Secondary Endpoint: CGI-I Score at 2 Hours

Both the 5- and 10-mg doses met the key secondary endpoint, CGI-I score 2 hours after the first dose of study medication (active vs. placebo). The overall treatment effect and the 2 follow-up active/placebo comparisons were statistically significant, as shown in the table below. Note that the CGI-S scale was used as an assessment of baseline and is therefore included in this table.

Table 31: Key Secondary Efficacy Endpoint: CGI-I Score 2 Hours after Dose 1 (ITT Population with LOCF) - Trial AMDC-004-301

CGI-S or CGI-I Score	<i>Staccato</i> Placebo (N=115)	<i>Staccato</i> Loxapine 5 mg (N=116)	<i>Staccato</i> Loxapine 10 mg (N=113)
Baseline (mean CGI-S score)	3.9	4.0	4.1
2 hours (mean CGI-I score)	2.8	2.3	2.1
p-value for overall treatment effect	p<0.0001	-----	-----
p-values for active/placebo comparisons	-----	p=0.0015	p<0.0001

Additional Analysis

Tertiary endpoints included the CGI-I responder analysis, ACES score at 2 hours after the first dose of study medication, an analysis of the overall use of additional study medication (beyond Dose 1) and/or rescue medication, time to the use of Dose 2 of study medication (if needed), and time to the first use of rescue medication (if needed). In general, the results of these analyses were supportive of the results of the primary and key secondary endpoints.

CGI-I responders were defined as a CGI-I score of 1 (very much improved) or 2 (much improved) at 2 hours after first dose of study medication. In the CGI-I responder analysis, ~57% of the 5-mg patient and 67.0% of the 10-mg patients were CGI-I responders, compared with 37.5% of placebo patients.

The ACES score at 2 hours after first dose of study drug were consistent with the efficacy demonstrated using the PEC and CGI-I scales, with higher mean scores at 2 hours in each loxapine group compared to placebo, suggesting that the *Staccato* Loxapine groups were calmer than the placebo groups.

An analysis of the overall use of additional study medication (beyond Dose 1) and/or rescue medication by 4 and 24 hours after Dose 1 demonstrated statistically significant differences between 10-mg patients and placebo patients at both time points (4 hours, $p=0.0039$; 24 hours, $p=0.0485$).

When comparing the overall use of additional study medication and/or rescue medication by 4 and 24 hours in the 5-mg and placebo patients, there was a trend at 4 hours ($p=0.0850$) and the difference was not statistically significant at 24 hours. However, a larger percentage of 5-mg patients than placebo patients received only 1 inhaled dose and no rescue medication by both 4 and 24 hours. In addition, a larger percentage of 10-mg patients than placebo patients received only 1 inhaled dose and no rescue medication by both 4 hours (10-mg group, 75%; placebo group, 56%) and 24 hours (10-mg group, 61%; placebo group, 46%) after the first dose.

These data also suggest a dose-response pattern. By 4 hours after Dose 1, 25% of the 10-mg patients required additional medications, compared with ~32% of the 5-mg patients. By 24 hours after Dose 1, ~39% of the 10-mg patients required additional medication, compared to ~46% of the 5-mg patients.

In a time to use of Dose 2 of study medication analysis, placebo-treated patients were found to have taken Dose 2 significantly sooner than loxapine-treated patients ($p=0.0239$). In a pairwise comparison, the difference between the 10-mg group and the placebo group was statistically significant, with placebo-treated patients taking Dose 2 significantly sooner ($p=0.0076$). In the pairwise comparison of the 5-mg and placebo groups, there was a trend favoring earlier use of Dose 2 in the placebo group ($p=0.1155$).

In addition, in an analysis of time to the first use of rescue medication, placebo-treated patients were found to have received rescue medication significantly sooner than loxapine-treated patients ($p=0.0096$). In pairwise comparisons, both the 5-mg group and the 10-mg group were significantly different from the placebo group, with significantly earlier use of rescue medication in placebo-treated patients (5 mg, $p=0.0195$; 10 mg, $p=0.0126$).

Conclusions

Both the 5- and 10-mg doses of *Staccato* Loxapine met the primary efficacy endpoint, the change in PEC score from baseline to 2 hours after Dose 1 (active vs. placebo) and also met the key secondary endpoint, the CGI-I score 2 hours after the first dose of study medication (active vs. placebo), with the tests for overall treatment effect and the 2 follow-up pairwise active/placebo comparisons being statistically significant. Additional analyses were supportive of these findings. At 2 hours, the mean ACES score indicated that patients in the loxapine groups were calmer than those in the placebo group, and loxapine-treated patients were less likely to use multiple doses of study medication and/or use rescue medication compared to placebo-treated patients. In addition, survival analysis showed that placebo-treated patients received Dose 2 of study medication significantly sooner and had a shorter time to first use of rescue medication than loxapine-treated patients. In general, the magnitude of the treatment effect was larger in the 10-mg group than the 5-mg group, demonstrating a dose-response pattern for *Staccato* Loxapine.

6.2.3 Trial AMDC-004-302 (Bipolar I Disorder)

This trial was a 24-hour, Phase 3, pivotal, in-patient, multicenter, randomized, double-blind, fixed-dose, repeat-dose (as required), placebo-controlled, parallel group, safety, and efficacy trial evaluating *Staccato* Loxapine for Inhalation (*Staccato* Loxapine) for the treatment of agitation in patients with Bipolar I Disorder, manic or mixed episodes. The trial, initiated on July 24, 2008 and completed on November 2, 2008, was conducted in seventeen centers in the United States.

The purposes of Trial **AMDC-004-302** were to confirm the safety and efficacy of *Staccato* Loxapine at 5- and 10-mg fixed dose levels in the treatment of acute agitation in patients with a diagnosis of Bipolar I Disorder (manic or mixed episodes), and to confirm the tolerability of up to 3 doses administered in a 24-hour period.

The trial was very similar to Trial **AMDC-004-301**, the Phase 3 pivotal trial of *Staccato* Loxapine for the treatment of agitation in Schizophrenic patients, which was discussed above. The 2 trials had very similar design and had identical safety and efficacy assessments and endpoints, identical statistical analysis plans, and identical doses and dosing regimen. In addition, protocols for suspected device malfunction and for use of rescue medications were identical between the two trials. In both trials, the primary objective was to assess the change in PEC score from baseline to 2 hours following the first dose of *Staccato* Loxapine (5 or 10 mg), compared with placebo.

The 2 trials differed in the type of patients enrolled, and consequently, in some of the inclusion/exclusion criteria and in the rules for prior and concomitant medications.

Trial Population

Trial patients were adults (18-65 years, inclusive) who met DSM-IV criteria for Bipolar I Disorder, manic or mixed episodes, with or without psychotic features and had a baseline total PANSS Excited Component (PEC) score of ≥ 14 . In addition, the patients were to have a score of ≥ 4 on at least 1 of the 5 items on the PEC scale (poor impulse control, tension, hostility, uncooperativeness, and excitement).

The following types of patients could be enrolled:

1. Patients admitted to a hospital setting or research unit for the purpose of the trial
2. Patients already hospitalized for treatment of Bipolar I Disorder who had acute agitation
3. Patients treated at a psychiatric emergency room setting that allowed extended patient stays in a secluded observation room for the period of the trial.

The trial was targeted to enroll approximately 300 patients.

Key Inclusion/Exclusion Criteria

The inclusion/exclusion criteria were essentially identical to the inclusion/exclusion criteria for Trial **AMDC-004-301** except for the addition of the following **Key Exclusion Criteria**:

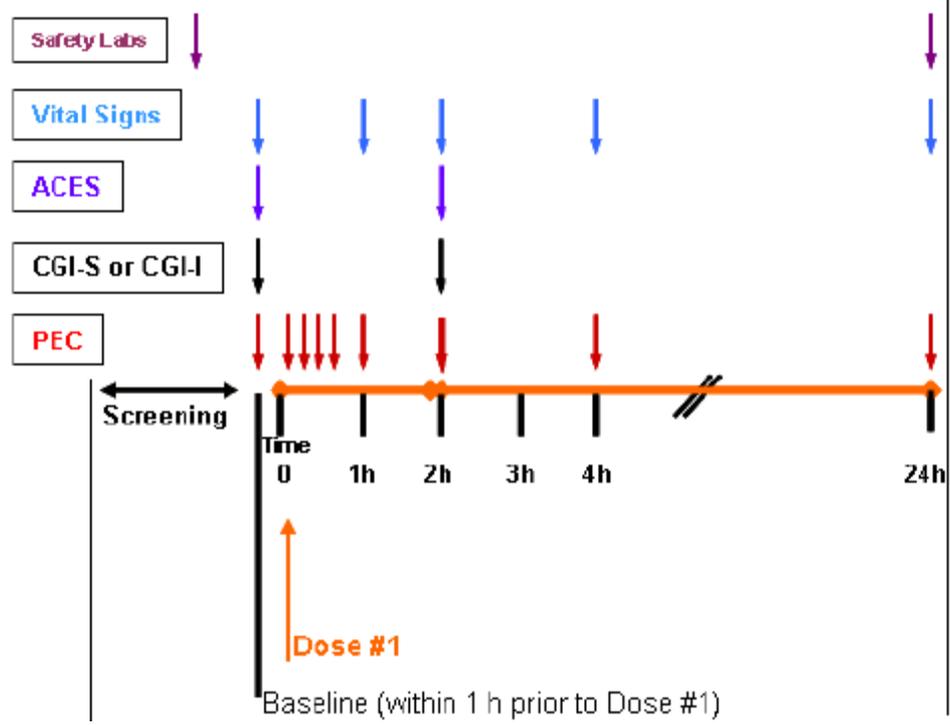
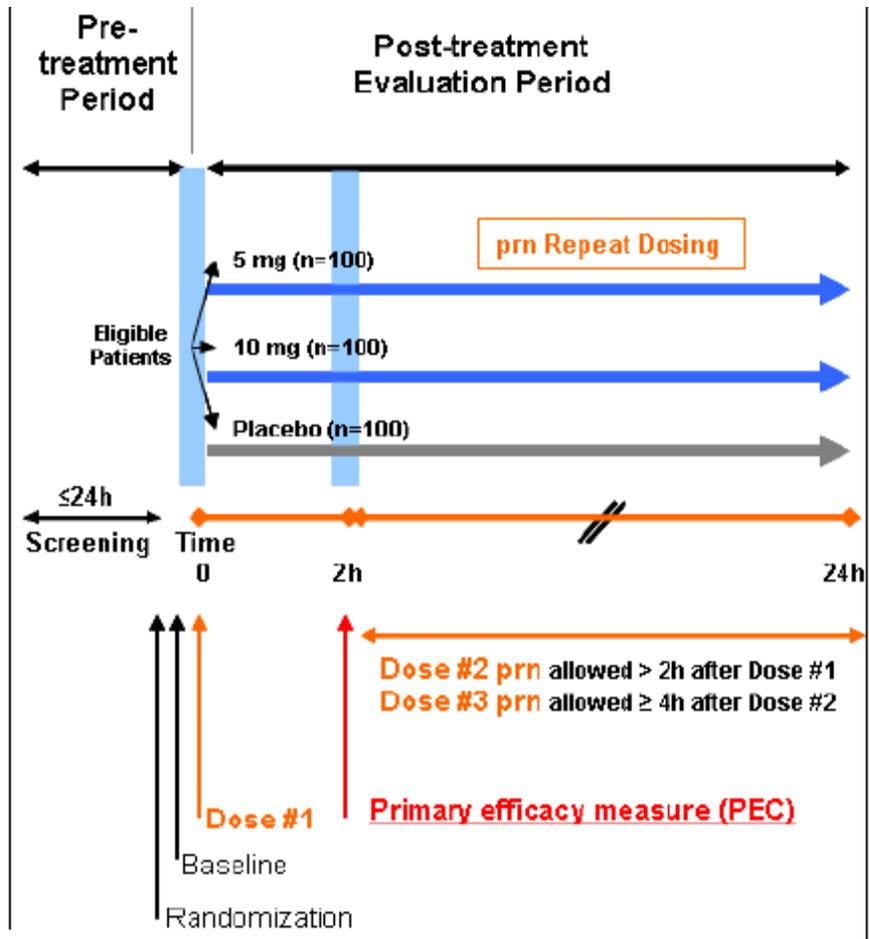
1. Patients who had taken fluoxetine (Prozac) during the 30 days prior to randomization, or other antidepressants during the 7 days prior to randomization
2. Patients who have taken anticonvulsants *with the exception of stable doses of valproate* during the 7 days prior to randomization

Trial Design

As shown in the figure below (electronically copied and reproduced from sponsor's submission), the trial design for Trial **AMDC-004-302** was essentially identical to the trial design for Trial **AMDC-004-301**, consisting of two periods: a *Pre-treatment Period* including screening, randomization, and baseline assessment phases; and a 24-hour *Treatment/Post-treatment Evaluation Period*. The only difference in the two trial designs was in the duration of the screening period: in Trial **AMDC-004-301**, the screening period could span up to 2 weeks, whereas in Trial **AMDC-004-302**, the screening period could only span up to 24 hours.

Figure 9: Design of Trial AMDC-004-302

(See next page)



Concomitant Medication

In this trial, medications recorded at screening, and which were no longer taken during the trial, were recorded as *prior* medications. *Concomitant* medications included medications taken from the screening phase through discharge. Although there were post-screening concomitant medications, there were restrictions for certain concomitant medications as follows:

1. Continuation of ongoing and stable (unchanged for ≥ 7 days) doses of lithium or valproate was allowed, but initiation or dose-adjustment of these agents during the trial was not allowed.
2. Patients who developed extrapyramidal symptoms (EPS) could be treated with anti-Parkinson's or antihistamine agents as clinically indicated. Prophylaxis for EPS during the trial was not allowed.
3. If a sedative-hypnotic drug was required during the screening phase, only short-acting agents such as zolpidem and zaleplon could be used.
4. The following were not allowed at any time during the trial, starting from 7 days prior to randomization:
 - Antidepressant drugs (except fluoxetine, which was not allowed starting 30 days prior to randomization)
 - Anticonvulsant drugs other than valproate
5. CNS-active drugs were not allowed as concomitant therapy from 4 hours prior to Dose #1 until the end of the 24-hour Post-treatment Evaluation Period.

Results

Demographics and Baseline Characteristics

In this trial, the 3 treatment groups appeared well matched for demographic and baseline characteristics except for an imbalance among the treatment groups in race, as shown in the table below. The mean age of randomized patients was 40.8 years. In the total study population, about half of the patients were male (49.7%), most patients were either Black (44.3%) or Caucasian (43.9%), and most patients had a history of smoking.

Table 32: Baseline Characteristics (Safety Population) - Trial AMDC-004-302

	<i>Staccato</i> Placebo (N=105)	<i>Staccato</i> Loxapine 5 mg (N=104)	<i>Staccato</i> Loxapine 10 mg (N=105)
AGE (years):			
Mean	40.6	41.2	40.5
Age Range	19-60	19-62	19-64
GENDER:			
% Males	53.3%	45.2%	50.5%
% Females	46.7%	54.8%	49.5%
RACE			
% Caucasian	31.4%	55.8%	44.8%
% Black	51.4%	36.5%	44.8%
% Asian	0	0	1.0%
% Hispanic	13.3%	7.7%	6.7%
% Native American	1.0%	0	1.0%
% Other	2.9%	0	1.9%
SMOKING HISTORY			
Never smoked	16.2%	19.2%	17.1%
Current smoker	74.3%	76.0%	73.3%
Ex-smoker	9.5%	4.8%	9.5%

Baseline Disease Characteristics

All patients were diagnosed with Bipolar I Disorder (manic in 68.8% of patients, and mixed in the remaining 31.2%), and across treatment groups, the mean time since diagnosis ranged from 11.7 to 12.8 years. The mean duration of the current episode of agitation was shorter in the 10-mg group than the other groups (placebo, 14.2 days; 5-mg, 16 days; 10-mg, 9.7 days), although the median durations were similar (6.2 days in the placebo and 5-mg groups; 5.0 days in the 10-mg group). Agitation at baseline was similar in the three treatment groups: the mean baseline PEC score ranged from 17.3 to 17.7, and the mean baseline CGI-S score ranged from 4.0 to 4.1.

Table 33: Baseline Disease Characteristics (Safety Population) - Trial AMDC-004-302

	<i>Staccato Placebo</i> (N=105)	<i>Staccato Loxapine 5 mg</i> (N=104)	<i>Staccato Loxapine 10 mg</i> (N=105)
<i>Diagnosis</i>			
Bipolar I, manic episodes	68.6%	65.4%	72.4%
Bipolar I, mixed episodes	31.4%	34.6%	27.6%
<i>PEC score at baseline</i>			
Mean	17.2	17.4	17.3
Range	14-31	14-26	14-25
<i>CGI-S score at baseline</i>			
Mean	4.1	4.0	4.0
Range	2-6	3-6	3-5
<i>Time since diagnosis (years)</i>			
Mean	18.8	16.5	18.2
Range	0-45	0-38	0-38
<i>No. of previous hospitalizations</i>			
Mean	5.9	5.5	5.1
Range	0-30	0-30	0-30
<i>Duration of current agitation episode at screening (days)</i>			
Mean	14.2	16.0	9.7
Range	0.25-146	0.25-210	0.25-45

Patient Disposition

Of the 356 patients who were screened for the trial, 314 (88.2%) were randomized and received at least one dose of study medication, and 312 completed the trial. Forty-two patients were screened but not enrolled, although one of these patients was later rescreened and then enrolled (an important protocol violation, discussed below). The most common reason patients failed screening was for not meeting enrollment criteria. No patient was reported to have failed screening because of an inability or unwillingness to use the *Staccato* system. Two patients discontinued prematurely, both because of an adverse event (AE) of moderate anxiety that resolved with medication:

- Patient 03-044 (10 mg, female, 39 years; manic episode) was withdrawn because of a moderate exacerbation of anxiety that was judged to be unrelated to treatment and resolved with medication. The patient entered the trial with a history of intermittent anxiety. Her medications prior to screening were Effexor XR (venlafaxine hydrochloride) 37.5 mg qd, Seroquel (quetiapine fumarate) 100 mg bid, and trazadone 100 mg qd, as well as Vicodin (hydrocodone and acetaminophen) 5 mg/500 mg qd for tooth pain. She received her first dose of *Staccato* Loxapine on 28 August at 10:10 and a second dose at 22:00. The adverse

event started at 23:30, at which time lorazepam, 2 mg IM, was administered. The AE resolved at 01:00 on 29 August.

- Patient 14-280 (10 mg, female, 45 years; mixed episode) was withdrawn because of a moderate exacerbation of anxiety that was judged to be unrelated to treatment and resolved with medication. The patient entered the trial with a history of intermittent anxiety. Her medications prior to screening were Seroquel (quetiapine fumarate) 300 mg tid, lithium 1200 mg qhs, and Ativan (lorazepam) 2 mg qd. During the study, she received one 10-mg dose of *Staccato* Loxapine (10:15 on 11 September), and her lithium dose was withheld on that day (a protocol deviation). The AE started at 12:15, 2 hours after her dose of study medication, and resolved at 21:30. While the AE was ongoing she received Ativan (lorazepam) 1 mg at 17:15, lithium 600 mg at 20:00, and Seroquel (quetiapine fumarate) 200 mg at 20:00.

Table 34: Enumeration of Dropouts by Reason for Dropout - Trial AMDC-004-302

Patient Disposition n (%)	<i>Staccato</i> Placebo	<i>Staccato</i> Loxapine 5 mg	<i>Staccato</i> Loxapine 10 mg	Total
Randomized	105	104	105	314
Trial Completers	105 (100%)	104 (100%)	103 (98.1%)	312 (99.4%)
Dropouts	0	0	2 (1.9%)	2 (0.6%)
Reason for Dropout:				
Adverse Event	0	0	2 (1.9%)	2 (0.6%)

Concomitant Medication Use

The medication classes most commonly used in the 30 days before screening were the diazepines, oxazepines, and thiazepines (i.e., loxapine, olanzapine, quetiapine, and quetiapine fumarate), the fatty acid derivatives (i.e., valproate semisodium and valproic acid), and lithium (i.e., lithium and lithium carbonate). The distribution of diazepines, oxazepines, and thiazepines was fairly equal in the 3 groups. However, more subjects in the active drug groups were taking antidepressants, lithium, sedatives/hypnotics, and/or fatty acid derivatives in the 30 days before screening compared to subjects in the placebo group, as shown in the table below:

Table 35: Relevant Psychotropic Medications taken before Screening (Safety Population - Trial AMDC-004-302)

	<i>Staccato</i> Placebo (N=105)	<i>Staccato</i> Loxapine 5 mg (N=104)	<i>Staccato</i> Loxapine 10 mg (N=105)
Antidepressants			
SSRIs	8 (7.6%)	5 (4.8%)	6 (5.7%)
Bupropion*	1 (1.0%)	4 (3.8%)	6 (5.7%)
Others	4 (3.8%)	9 (8.7%)	12 (11.4%)
Total	13 (12.4%)	18 (17.3%)	24 (22.8%)
Fatty Acid Derivatives			
Valproate semisodium	17 (16.2%)	15 (14.4%)	24 (22.9%)
Valproic acid	1 (1.0%)	1 (1.0%)	1 (1.0%)
Total	18 (17.1%)	16 (15.4%)	24 (22.9%)
Lithium	12 (11.4%)	15 (14.4%)	19 (18.1%)
Sedative/hypnotics			
Benzodiazepine derivatives	11 (10.5%)	15 (14.4%)	10 (9.5%)
Benzodiazepine-related	4 (3.8%)	11 (10.6%)	8 (7.6%)
Others	5 (4.8%)	1 (1.0%)	7 (6.7%)
Total	20 (19.1%)	27 (26.0%)	25 (23.8%)

*Listed by sponsor as “Drugs used in Nicotine Dependence”

During the active treatment period, the percentage of subjects taking antidepressants, lithium or sedative/hypnotics is fairly equal among the 3 groups; however, more subjects in the *Staccato* Loxapine 10-mg group (18/105; 17.1%) were taking fatty acid derivatives compared to the *Staccato* Loxapine 5-mg group (10/104; 9.6%) and the placebo group (9/105; 8.6%). Since the baseline disease characteristics (ie PEC scores) between the three treatment groups were similar, it is unlikely that the differences in use of fatty acid derivatives confounded the results.

A higher percentage (5 mg, ~17%; 10 mg, ~23%) of subjects in the 2 groups treated with active drug were on antidepressants prior to entering the 24-hour screening period compared to the placebo group (~12%). However, since the protocol specified that antidepressants were not allowed for the 7 days prior to randomization (30 days for fluoxetine), it is unlikely that this imbalance confounded efficacy or safety results.

Important Protocol Violations

Twenty-eight patients had a total of 29 important protocol violations.

The most common type of protocol deviation, seen in sixteen patients, was categorized as “other.” Fifteen of these patients had one type of important deviation: the withholding of

either lithium or valproate on the day of study treatment. This deviation was reported for two patients (09-029 and 14-078) in the placebo group, five patients (09-025, 09-030, 09-032, 14-048, and 14-225) in the 5-mg group, and eight patients (09-036, 09-226, 14-081, 14-083, 14-221, 14-224, 14-280, and 14-283) in the 10-mg group. This deviation is considered unlikely to have affected the trial endpoints, given the brief (ie, 24 hour) post-treatment evaluation period.

One additional patient had a deviation categorized as “other”. Patient 14-284 (5-mg group) failed screening the first time and was later rescreened and enrolled.

Three patients had deviations related to enrollment criteria. Two of these patients completed the trial twice, enrolling at different centers each time: Patient 03-037 (10-mg group) later re-enrolled as Patient 17-184 (5-mg group), and Patient 02-098 (5-mg group) later re-enrolled as Patient 17-186 (placebo group). The third subject with a deviation related to enrollment criteria was Patient 11-342 (10-mg group) who took the antidepressant Cymbalta (duloxetine) within 7 days before study treatment (discontinued Cymbalta on 29 September; received *Staccato* Loxapine 10 mg on 01 October).

Six patients had deviations related to study or rescue medication use, although all occurred well after the completion of the primary and key secondary efficacy assessments. Patient 06-291 (placebo) received oral (rather than IM) lorazepam as rescue medication. The other five patients received Dose #3 of study medication earlier than permitted in the protocol: these were patients 07-319, 11-019, and 12-071 in the placebo group; patient 09-234 in the 5-mg group; and patient 09-226 in the 10-mg group.

Four patients received prohibited concomitant medication, although all occurrences were well after completion of the primary and key secondary efficacy assessments. Patients 10-215 (5-mg group), 12-066 (5-mg group), and 13-330 (10-mg group) received Seroquel (quetiapine fumarate) between 6 and 20 hours after administration of Dose #1 of study medication, and patient 18-094 (5-mg group) received Restoril (temazepam) more than 11 hours after Dose #1 of study medication.

Table 36: Patients with Important Protocol Deviations - Trial AMDC-004-302

Patients with Important Protocol Deviations, n (%)	<i>Staccato</i> Placebo (N=105)	<i>Staccato</i> Loxapine 5 mg (N=104)	<i>Staccato</i> Loxapine 10 mg (N=105)	Total (N=314)
Deviation from enrollment criteria	1 (1.0%)	1 (0.9%)	1 (1.0%)	3 (1.0%)
Patient not managed according to withdrawal criteria	0	0	0	0
Deviation from study drug or rescue drug regimen	4 (3.8%)	1 (1.0%)	1 (1.0%)	6 (1.9%)
Received prohibited concomitant medication	0	3 (2.9%)	1 (1.0%)	4 (1.3%)
Other	2 (1.9%)	6 (5.8%)	8 (7.6%)	16 (5.1%)
<i>Total patients with any important protocol deviation</i>	7 (6.7%)	11 (10.6%)	10 (9.5%)	28 (8.9%)

Reported Device Malfunctions

Five *Staccato* systems were returned via the device complaint system and underwent inspection and testing to determine if there had been a failure and, if so, what were the potential causes.

Inspection and testing indicated that all 5 complaints represented device failures. Four of the patients (Subject 02-266 in the *Staccato* Loxapine 10-mg group, and Subjects 07-321, 13-139, 15-119 in the *Staccato* Loxapine 5-mg group) were given another device by the study center and therefore received the intended dose. The fifth subject (16-258 in the *Staccato* Loxapine 5-mg group) was not given another device and therefore did not receive the intended dose (Dose 1). This subject (16-258) was not given Dose 2 or 3 of study medication or any rescue medication. He had no adverse events, and his PEC score generally decreased over time.

Therefore, of the 528 *Staccato* systems (combining *Staccato* Loxapine and *Staccato* Placebo), there were 5 (0.9%) confirmed device failures.

Efficacy Findings**Primary Efficacy Endpoint: PEC Scale-Change from Baseline to 2 Hours**

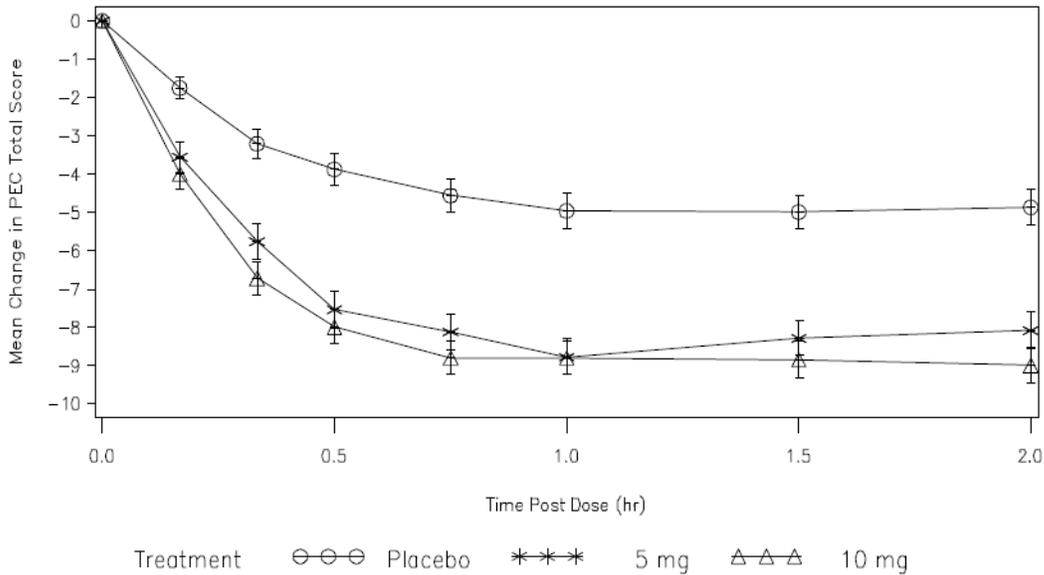
The primary efficacy endpoint was the change in the PEC score from baseline to 2 hours after Dose 1 (active versus placebo). Both the 5- and 10-mg doses met this endpoint, with the tests for overall treatment effect and the 2 follow-up active/placebo comparisons being statistically significant, as shown in the table and figure below:

Table 37: Primary Efficacy Endpoint: Change in PEC Score 2 Hours after Dose 1 (ITT Population with LOCF) - Trial AMDC-004-302

PEC Score	<i>Staccato</i> Placebo (N=105)	<i>Staccato</i> Loxapine 5 mg (N=104)	<i>Staccato</i> Loxapine 10 mg (N=105)
Mean Baseline PEC Score	17.7	17.4	17.3
Mean change* in PEC score from baseline to 2 hours after Dose 1	-4.7	-8.2	-9.2
p-value for overall treatment effect	p<0.0001	----	----
p-value for active/placebo comparisons	----	p<0.0001	p<0.0001

*LS mean (was used in the primary efficacy analysis)

Figure 10: Mean Change from Baseline in PEC Score through 2 Hours after Dose 1 (ITT Population with LOCF) - Trial AMDC-004-302



PEC Scale: Additional Secondary Efficacy Analysis

Changes from baseline to 10, 20, 30, and 45 minutes after Dose 1 for the 10-mg/placebo comparison were analyzed as secondary efficacy endpoints that were included in the main efficacy analysis and therefore protected at a family-wise error rate of 0.05. Changes from baseline to 1, 1.5, 4, and 24 hours after Dose 1 for the 10-mg placebo comparison were analyzed as tertiary efficacy endpoints and not included in the main efficacy analysis. Changes from baseline to 10, 20, 30, and 45 minutes, and 1, 1.5, 4, and 24 hours after Dose 1 for the 5-mg/placebo comparison were not analyzed statistically, per the statistical analysis plan.

Changes from baseline in the PEC score were evident at the first assessment time, 10 minutes after Dose 1, and all subsequent assessments during the 24-hour evaluation period, as shown in the table below. For the 10-mg/placebo comparison, the difference was statistically significant at each assessment time ($p \geq 0.0001$). Although the 5-mg/placebo comparison was not analyzed statistically (per the statistical analysis plan), a numerical difference between these 2 groups was evident at each assessment time.

The data presented in the table below also provide evidence of a dose-response pattern, since, at most assessment times through 24 hours, the effect was larger in the 10-mg group compared with the 5-mg group.

Table 38: Change in the PEC Score at Assessments through 24 Hours after Dose 1 (ITT Population with LOCF) - Trial AMDC-004-302

PEC Score	<i>Staccato</i> Placebo (N=105)	<i>Staccato</i> Loxapine 5 mg (N=104)	<i>Staccato</i> Loxapine 10 mg (N=105)
Baseline (mean)	17.7	17.4	17.3
+10 min (mean Δ) p-value	-1.8	-3.6 NA	-4.0 $p < 0.0001$
+20 min (mean Δ) p-value	-3.2	-5.8 NA	-6.7 $p < 0.0001$
+30 min (mean Δ) p-value	-3.9	-7.5 NA	-8.0 $p < 0.0001$
+45 min (mean Δ) p-value	-4.6	-8.1 NA	-8.8 $p < 0.0001$
+1 hour (mean Δ) p-value	-5.0	-8.8 NA	-8.8 $p < 0.0001$
+1.5 hours (mean Δ) p-value	-5.0	-8.3 NA	-8.8 $p < 0.0001$
+2 hours; primary endpoint (LS mean Δ) p-value	-4.7	-8.2 $p < 0.0001$	-9.2 $p < 0.0001$
+4 hours (mean Δ) p-value	-6.1	-8.3 NA	-9.3 $p < 0.0001$
+24 hours (mean Δ) p-value	-4.5	-6.1 NA	-6.0 $p < 0.0001$

Key Secondary Endpoint: CGI-I Score at 2 Hours

Both the 5- and 10-mg doses met the key secondary endpoint, CGI-I score 2 hours after the first dose of study medication (active vs. placebo). The overall treatment effect and the 2 follow-up active/placebo comparisons were statistically significant, as shown in the table below. Note that the CGI-S scale was used as an assessment of baseline and is therefore included in this table.

Table 39: Key Secondary Efficacy Endpoint: CGI-I Score 2 Hours after Dose 1 (ITT Population with LOCF) - Trial AMDC-004-302

CGI-S or CGI-I Score	<i>Staccato</i> Placebo (N=105)	<i>Staccato</i> Loxapine 5 mg (N=104)	<i>Staccato</i> Loxapine 10 mg (N=105)
Baseline (mean CGI-S score)	4.1	4.0	4.0
2 hours (mean CGI-I score)	3.0	2.1	1.9
p-value for overall treatment effect	p<0.0001	-----	-----
p-values for active/placebo comparisons	-----	p<0.0001	p<0.0001

Sensitivity Analysis for the Primary and Key Secondary Efficacy Endpoints

Because of a baseline imbalance among the treatment groups in race and the duration of the current episode of agitation, sensitivity analyses were conducted by the sponsor for the primary and key secondary efficacy endpoints using race and duration of episode as covariates.

For the primary efficacy endpoint, when race and duration of the episode of agitation were included as covariates in the ANCOVA, both the overall treatment effect and the 2 active/placebo pairwise comparisons remained statistically significant (p<0.0001 for the overall treatment effect and both active/placebo comparisons), and the effects of race and the duration of the current episode were not statistically significant (race, p=0.9281; duration, p=0.7520).

For the key secondary endpoint, when race and duration of the episode of agitation were included as covariates in the ANCOVA, both the overall treatment effect and the 2 active/placebo pairwise comparisons remained statistically significant (p<0.0001 for the overall treatment effect and both active/placebo comparisons), and the effects of race and the duration of the current episode were not statistically significant (race, p=0.6207; duration, p=0.7827).

Thus, it is confirmed that the imbalances in race and duration of the episode of agitation were not confounding factors.

Additional Analysis

Tertiary endpoints included the CGI-I responder analysis, ACES score at 2 hours after the first dose of study medication, an analysis of the overall use of additional study medication (beyond Dose 1) and/or rescue medication, time to the use of Dose 2 of study medication (if needed), and time to the first use of rescue medication (if needed). In general, the results of these analyses were supportive of the results of the primary and key secondary endpoints.

CGI-I responders were defined as having a CGI-I score of 1 (very much improved) or 2 (much improved) at 2 hours after first dose of study medication. In the CGI-I responder

analysis, 66.3% of the 5-mg patient and 74.3% of the 10-mg patients were CGI-I responders, compared with 27.6% of placebo patients.

The ACES score at 2 hours after first dose of study drug were consistent with the efficacy demonstrated using the PEC and CGI-I scales, with higher mean scores at 2 hours in each loxapine group compared to placebo, suggesting that the *Staccato* Loxapine groups were calmer than the placebo groups.

An analysis of the overall use of additional study medication (beyond Dose 1) and/or rescue medication by 4 and 24 hours after Dose 1 demonstrated statistically significant differences between active and placebo patients for both doses by 4 and 24 hours (5-mg/placebo, 4 hours $p=0.0019$, 24 hours $p=0.0280$; 10-mg/placebo, 4 hours $p<0.0001$, 24 hours $p<0.0001$). Also, a larger percentage of loxapine-treated patients than placebo-treated patients received only 1 inhaled dose and no rescue medication by both 4 hours (10-mg group, 76.0%; 5-mg group, 59.6%; placebo group, 36.2%) and 24 hours (10-mg group, 61.5%; 5-mg group, 41.3%; placebo group, 26.7%) after the first dose.

These data also suggest a dose-response pattern. By 4 hours after Dose 1, 24.0% of the 10-mg patients required additional medications, compared with ~40% of the 5-mg patients. By 24 hours after Dose 1, 38.5% of the 10-mg patients required additional medication, compared to ~59% of the 5-mg patients.

In a time to use of Dose 2 of study medication analysis, placebo-treated patients were found to have taken Dose 2 significantly sooner than loxapine-treated patients ($p<0.0001$). In the 2 pairwise comparison, the difference between each loxapine group and the placebo group was statistically significant, with placebo-treated patients taking Dose 2 significantly sooner (5-mg/placebo, $p=0.0048$; 10-mg/placebo, $p<0.0001$). In the pairwise comparison of the 5-mg and placebo groups, there was a trend favoring earlier use of Dose 2 in the placebo group ($p=0.0772$).

In addition, in an analysis of time to the first use of rescue medication, placebo-treated patients were found to have received rescue medication significantly sooner than loxapine-treated patients ($p=0.0067$). In pairwise comparisons, both the 5-mg group and the 10-mg group were significantly different from the placebo group, with significantly earlier use of rescue medication in placebo-treated patients (5 mg, $p=0.0122$; 10 mg, $p=0.0103$).

Conclusions

Both the 5- and 10-mg doses of *Staccato* Loxapine met the primary efficacy endpoint, the change in PEC score from baseline to 2 hours after Dose 1 (active vs. placebo) and also met the key secondary endpoint, the CGI-I score 2 hours after the first dose of study medication (active vs. placebo), with the tests for overall treatment effect and the 2 follow-up pairwise active/placebo comparisons being statistically significant. Additional analyses were supportive of these findings. At 2 hours, the mean ACES score indicated

that patients in the loxapine groups were calmer than those in the placebo group, and loxapine-treated patients were less likely to use multiple doses of study medication and/or rescue medication compared to placebo-treated patients. In addition, survival analysis showed that placebo-treated patients received Dose 2 of study medication significantly sooner and had a shorter time to first use of rescue medication than loxapine-treated patients. In general, the magnitude of the treatment effect was larger in the 10-mg group than the 5-mg group, demonstrating a dose-response pattern for *Staccato* Loxapine.

6.3 FDA Queries Regarding Efficacy Trials, and Sponsor's Response

FDA Query Regarding Concomitant Medications

On April 29, 2010, the Division submitted questions to the sponsor requesting clarification of the screening procedure for concomitant medication use in Trials **AMDC-004-301** and **AMDC-004-302**. The questions and important aspects of the sponsor's response (received May 2, 2010) are as follows:

FDA Question #1: What were the procedures for discontinuing prohibited study medications within the specified time frames before an episode of agitation?

Sponsor's Response:

The exclusion criteria for both studies prohibited patients who had been treated with benzodiazepines or other hypnotics or oral or short-acting intramuscular antipsychotic drugs **within 4 hours prior to first study drug administration**. The determination of whether or not a patient met this criterion occurred at the **baseline assessment** which was conducted within 1 hour of study drug administration in Study 301 (schizophrenia patients) or within 0.5 hour of study drug administration in Study 302 (bipolar disorder patients). In Study 301, if the patient did not satisfy this criterion at baseline, the protocol permitted reassessment for inclusion in the study at a later time if eligibility was maintained and there was at least 4 hours since last treatment (e.g. short acting antipsychotic drug, etc).

The 4-hour window prior to dosing was necessary to avoid any confounding effects of recently administered concomitant medications, particularly on the 2-hour primary and key secondary endpoints. This feature of the study design was consistent with the approach taken previously in the clinical studies which supported the approval of the IM antipsychotic agents for the treatment of agitation in patients with schizophrenia or bipolar disorder (e.g., Zyprexa Phase 3 studies, *NDA 21-253 Medical review*).

It is important to note that the study procedures at the screening assessment (up to 2 weeks before study enrollment in Study 301 and within 24 hours of enrollment in Study 302) did not require discontinuation of psychotropic medications in order for patients to

be eligible for the trial. Therefore, between screening and the first study drug administration, patients were managed according to standard clinical practice.

FDA Question #2: Was the failure to discontinue prohibited medications before study drug administration considered a protocol violation?

Sponsor's Response:

If an enrolled patient had been treated with a benzodiazepine, or other hypnotics or oral or short-acting intramuscular antipsychotic drugs within 4 hours prior to first study drug administration, this would have been considered a protocol deviation. In Studies 301 and 302, no patients deviated from this requirement.

FDA Question #3) Were efficacy data excluded for subjects later found to have been treated with concomitant psychotropic medications during the prohibited time period?

Sponsor's Response:

No data were excluded from the efficacy analyses because of protocol deviations related to concomitant medications.

FDA Query Regarding Subject Enrollment, Screening, and Device Training

On August 9, 2010, the Division submitted a Clinical Information Request to the sponsor regarding Trials **AMDC-004-201**, **AMDC-004-301**, and **AMDC-004-302**. Further information was requested regarding: 1) subgroup analysis of the 3 types of patients that could be enrolled (i.e. patients admitted for the purpose of the trial, patients already hospitalized for treatment of Schizophrenia who had acute agitation, and patients treated at a psychiatric emergency room setting), 2) a description of the screening process including actual duration of time between screening and study drug treatment and how subjects who were already hospitalized for treatment of Schizophrenia in Trial **AMDC-004-301**, where screening could be 2 weeks, were selected, and 3) how were patients evaluated “for their ability to perform the inhalation maneuver” and what was the training process for use of the inhalation device?

On August 13, 2010, in response to this request, the sponsor reported that the setting from which each patient was enrolled was not captured since subgroup analysis was not planned. However, follow-up information from several investigators (14 investigators from phase 3 study sites) indicates that the majority of study patients were enrolled from the community following referral, and much smaller numbers were enrolled from inpatient wards. None of the investigators questioned reported enrollment from a psychiatric emergency room. In addition, although Trials **004-201** and **004-301** both allowed a screening period of up to 2 weeks, most subjects were dosed within 2 days of screening (Trial **004-201**, 82.2%; Trial **004-301**, 82.6%), as a result of which the screening period for Trial **004-302** was narrowed to 24 hours. Only 3.5% of patients in Trial **004-301** were dosed beyond 7 days from screening.

Lastly, device training consisted of simple verbal instructions provided by trained study personnel. In order to “evaluate the patient’s ability to use the device properly,” patients were asked to demonstrate an exhalation (without any device) followed by slow, deep breath and breath hold in accordance with the Instructions for Use. In Trial **004-201**, there was no further training; however, in Trials **004-301** and **004-302**, for the final step prior to dosing, patients used a plastic model (empty shell) of the device, which contained no working parts, to again demonstrate the inhalation maneuver required for dosing.

6.4 Crosscutting Issues

Subgroup Analysis

In the efficacy trials (**AMDC-004-201**, **AMDC-004-301**, and **AMDC-004-302**), subgroup analysis was adequate. For Trial **AMDC-004-302**, this included a sensitivity analysis using race and duration of current episode of acute agitation as covariates due to baseline imbalance in these two factors among the treatment groups. There were no apparent differences in response to treatment between subgroups based on age, sex, race, baseline PEC score, or between Bipolar I patients with manic or mixed episodes.

Subgroup analysis on the setting from which each patient was enrolled (i.e. patients admitted for the purpose of the trial, patients already hospitalized for treatment of Schizophrenia who had acute agitation, and patients treated at a psychiatric emergency room setting) was not done. This is important because patients presenting from these three different settings may have differed significantly in areas such as previous level of medical and psychiatric care, ability to give an accurate history, and ability to undergo device training, that could have had a significant effect on efficacy results.

Dose Response

The sponsor has adequately addressed dose-response for efficacy. Across multiple endpoints (PEC change scores, CGI-I scores, overall use of study and rescue medication, and time to use of Dose 2 of study medication) in the proof-of-concept trial (**AMDC-004-201**) and in both of the pivotal trials (**AMDC-004-301** and **AMDC-004-302**), the magnitude of the treatment effect was larger in the 10-mg group than the 5-mg group, demonstrating a dose-response pattern for *Staccato* Loxapine.

Key Secondary Endpoints

No key secondary endpoints were identified in the proof-of-concept trial (**AMDC-004-201**). However, in both pivotal trials (**AMDC-004-301** and **AMDC-004-302**), the key secondary endpoint (CGI-I score at 2 hours post-dose) was pre-specified in the protocols. The CGI-I provides assessment of domains in agitated patients with Schizophrenia or Bipolar Disorder not assessed by the primary variable (change in PEC from baseline at 2 hours post-dose), and appropriate statistical adjustments were made for multiple

comparisons. In addition, the positive findings were replicated in both pivotal trials. Therefore, including information on the key secondary endpoint in labeling would be justified.

Effect Size

For the primary efficacy endpoint, change from baseline in PEC score at 2 hours, and for the key secondary endpoint, change from baseline in CGI-I score at 2 hours, a significant effect size (defined as study drug endpoint minus placebo endpoint) was demonstrated, as shown in the table below:

Table 40: Effect Size (Study Drug – Placebo) for Primary and Key Secondary Endpoints -Trials AMDC-004-201, AMDC-004-301, and AMDC-004-302

	<i>Staccato</i> Loxapine 5 mg	<i>Staccato</i> Loxapine 10 mg
AMDC-004-201		
PEC	1.7	3.6
CGI-I	N.A.	N.A.
AMDC-004-301		
PEC	2.2	2.9
CGI-I	0.5	0.7
AMDC-004-302		
PEC	3.5	4.5
CGI-I	0.9	1.1

Long-term Efficacy

No maintenance trials of *Staccato* Loxapine were done. Since *Staccato* Loxapine is being developed for acute, intermittent use only (on an as needed basis), this is appropriate.

Pediatric Development

In accordance with the Pediatric Research Equity Act, the sponsor submitted requests for partial waiver (children < 10 years of age) and a deferral of the requirements for pediatric studies for the age group of 10 to 17 years. The partial waiver for children < 10 years was requested because necessary studies would be impossible or highly impractical due to the small number of pediatric patients with a diagnosis of Schizophrenia or Bipolar Disorder in this age group. The deferral for children and adolescents aged 10 to 17 years was requested because: 1) the drug is ready for approval for use in adults before the pediatric studies are complete; and 2) the required lower dose strengths of the *Staccato* Loxapine commercial product have not been optimized for use in children and adolescents.

A Pediatric Plan was provided, describing the sponsor's intention to conduct pediatric studies following approval of *Staccato* Loxapine for patients age 18 years or older. Three studies (1 non-clinical and 2 clinical) are proposed:

1. A single dose inhalation developmental juvenile rat tolerability and toxicokinetic study
2. A double-blind, placebo-controlled, parallel group, single-dose, sequential dose-ascending, pharmacokinetic study in subjects with Bipolar I Disorder (ages 10 to 17, inclusive) and Schizophrenia (age 13 to 17, inclusive). The proposed dose strengths for the 4 dose-ascending cohorts range from 0.625 mg to 5 mg.
3. A single double-blind, placebo-controlled, parallel-group, multi-dose, efficacy and safety study for the treatment of agitation in children and adolescents with Bipolar I Disorder (ages 10 to 17, inclusive) or Schizophrenia (ages 13 to 17, inclusive). The proposed design is similar to Trials **AMDC-004-301** and **AMDC-004-302**, and dose selection will be based on the results of the pharmacokinetic study.

A PeRC PREA subcommittee meeting was held on August 11, 2010 at which time the partial waiver for children < 10 years was granted. In addition, due to pulmonary safety concerns identified in adults (see **Section 7**) that may also pose a risk in pediatric subjects, a waiver was granted for the age group of 10 to 17 as well, with instructions that the absence of pediatric data due to safety concerns be reflected in labeling.

6.5 Efficacy Conclusions Regarding the Rapid Treatment of Agitation Associated with Schizophrenia or Bipolar Disorder

The data provided by the sponsor support the sponsor's claim for efficacy in the rapid treatment of agitation associated with Schizophrenia or Bipolar Disorder. In both the pivotal trials, both the 5- and 10-mg doses of *Staccato* Loxapine met the primary efficacy endpoint, the change in PEC score from baseline to 2 hours after Dose 1 (active vs. placebo) and also met the key secondary endpoint, the CGI-I score 2 hours after the first dose of study medication (active vs. placebo). The findings of the Phase 2 trial (**AMDC-004-201**) were supportive of the results from the pivotal trials in that the primary efficacy endpoint (absolute change in PEC score from baseline to 2 hours following *Staccato* Loxapine administration) comparison of *Staccato* Loxapine overall (both doses) to placebo was statistically significant in favor of *Staccato* Loxapine.

One limitation of the three efficacy trials is the lack of a subgroup analysis regarding the 3 types of patients that could be enrolled (i.e. patients admitted for the purpose of the trial, patients already hospitalized for treatment of Schizophrenia who had acute agitation, and patients treated at a psychiatric emergency room setting). Based on the sponsor's follow-up information from several investigators, the majority of study patients were enrolled from the community following referral, and much smaller numbers were enrolled from inpatient wards. None of the investigators questioned reported enrollment from a psychiatric emergency room. Presumably, patients who were referred from the

community or enrolled from inpatient wards would already be under the care of community health practitioners. Therefore, information regarding past medical and psychiatric history to determine if inclusion and exclusion criteria are met would be accurate and easier to obtain. In addition, a Screening Period of up to 2 days for the majority of patients (and up to 14 days in some patients) in Trials **004-201** and **004-301** would have provided ample time for obtaining this information and for an adequate assessment of ability to perform inhalation maneuver. If patients treated at a psychiatric emergency room had been included, such accurate and time-consuming assessments may not have been possible, and this could have affected the efficacy results. Furthermore, if *Staccato* Loxapine is approved, patients in an emergency room setting would be a significant target population and may represent a more typical use for *Staccato* Loxapine in the “real world.”

7 Review of Safety

Safety Summary

Although *Staccato* Loxapine was reasonably safe and well-tolerated in the overall safety population, significant pulmonary toxicity, particularly in subjects with asthma or COPD, was noted and is a major safety concern. In general, the adverse events associated with *Staccato* Loxapine were either expected from the known adverse event profile of loxapine or related to the method of loxapine administration (inhalation). The types and frequency of safety assessments were appropriate and adequate for detecting potential safety problems.

In a total of 13 clinical trials, 1147 subjects received *Staccato* Loxapine and 578 subjects received placebo. The majority (~73%) of loxapine-treated subjects was exposed to 1 dose of *Staccato* Loxapine, ~20% received 2 doses, ~5% received 3 doses, and ~2% received 4 doses, reflecting the single-dose design of the majority of studies. Doses of *Staccato* Loxapine studied ranged from 0.625 mg up to 10 mg.

There was one death in the trials (a drug overdose in a placebo-treated subject), clearly not related to *Staccato* Loxapine treatment, and there were three non-fatal serious adverse events, none of which appeared to be related to *Staccato* Loxapine treatment. Five subjects in the *Staccato* Loxapine treatment groups were discontinued due to adverse events, and, in two of the five subjects, the adverse event leading to discontinuation (urticaria and bronchospasm) was probably related to *Staccato* Loxapine treatment.

In the pivotal trials (controlled studies in agitated patients population), four adverse events were identified that occurred at a rate of $\geq 2\%$ in either the 5- or 10-mg *Staccato* Loxapine groups and for which the rate exceeds the rate for placebo: dysgeusia, sedation (including sedation combined with somnolence), fatigue, and throat irritation. Dysgeusia was the only adverse event for which a clear dose-response pattern was demonstrated.

The AE profile in the Healthy Volunteer (HV) population was similar to that in agitated patients (CSAP population) with the notable exception that somnolence and dizziness were much more common in the HV population. The most frequently reported AEs for the All *Staccato* Loxapine group were somnolence (~58% vs. ~11% in the placebo group), dizziness (~36% vs. ~8% in the placebo group), and dysgeusia (~27% vs. ~2% in the placebo group).

Based on the known pharmacology and safety profile of oral loxapine, AEs affecting the nervous system and cardiovascular system were identified as areas of particular interest. In addition, given the route of administration of *Staccato* Loxapine, AEs potentially related to airways were also of particular interest. Nervous system disorders were among the most frequently reported adverse events in all of the safety populations. As noted above, sedation and somnolence were the most common nervous system adverse events. In the CSAP population, other nervous system disorder AEs in the *Staccato* Loxapine treatment groups included akathisia (2 patients), tremor (2 patients), and dyskinesia, grimacing, migraine, paraesthesia, balance disorder, dystonia, oculogyration, and restlessness (1 patient each).

The only cardiac disorder reported in the CSAP population was an AE of palpitations experienced by 1 patient in the placebo group. Under vascular disorders, hypertension was reported as an AE in 3 patients (1.2%) in the *Staccato* Loxapine 10 mg group, 2 patients (0.8%) in the *Staccato* Loxapine 5 mg group, and 2 patients (0.8%) in the placebo group. Hypotension was reported for 1 patient (0.4%) in the *Staccato* Loxapine 10 mg group, 2 patients (0.8%) in the *Staccato* Loxapine 5 mg group, and 2 patients (0.8%) in the placebo group.

The most frequently reported respiratory system AEs were throat irritation, pharyngeal hypoesthesia, and wheezing. Bronchospasm was reported for one subject in the *Staccato* Loxapine 10 mg group, which resulted in early discontinuation and required treatment with a bronchodilator. In one trial (**104-202**) of subjects with migraine headaches, 2 cases of dyspnea were reported after *Staccato* Loxapine 1.25 mg.

In the pulmonary safety study in healthy volunteers (Trial **004-104**), maximum FEV₁ decreases of ≥15% or ≥20% were more common after loxapine treatment than placebo treatment, but there were no AEs that suggested effects on airways. In subjects with asthma (Trial **004-105**), there were notable decreases in FEV₁ after *Staccato* Loxapine, and decreases of ≥20% occurred in 12 (46.2%) loxapine-treated subjects compared to 1 (3.8%) placebo-treated subject. Eighteen (69%) loxapine-treated subjects and 3 (12%) placebo-treated subjects had “notable respiratory signs or symptoms” (defined as FEV₁ decrease from baseline of ≥20%, an airway AE, or use of rescue medication). Airway AEs were reported by 14 (~54%) loxapine-treated subjects compared to 3 (11.5%) placebo-treated subjects. Airway AEs that occurred in more than a single loxapine-treated subject were bronchospasm (7 subjects), chest discomfort (6 subjects), wheezing (4 subjects), and dyspnea (3 subjects). In subjects with COPD (Trial **004-108**), decreases of at least 10% from baseline FEV₁ were seen in the majority of subjects in this study (~67% of the placebo group and ~81% of the loxapine group), and airway AEs were

reported for 5 (~19) loxapine-treated subjects compared to 3 (~11%) placebo-treated subjects. Airway AEs that occurred in more than a single loxapine-treated subject were dyspnea (3 subjects), cough (3 subjects), and wheezing (2 subjects).

There were no clinically important changes in any treatment group in clinical laboratory parameters or electrocardiograms. In both the CSAP and HV populations (all treatment groups), there were small reductions in mean systolic and diastolic blood pressures (all < 7 mm Hg) during the 4 hours after dosing that were generally larger in the *Staccato* Loxapine 5 mg and 10 mg groups compared with placebo.

7.1 Methods

For the safety review, I reviewed the Integrated Summary of Safety, Study Reports, figures, and tables, as well as the data sets in the JMP files for all the trials, with focus on the main pooled safety populations (Controlled Studies in Agitated Patients and Healthy Volunteers populations) and the overall safety population. Since *Staccato* Loxapine is proposed to be used in acutely agitated patients with Schizophrenia or Bipolar Disorder, I primarily directed my attention to the Controlled Studies in Agitated Patients (CSAP) population. In addition, due to the method of administration of *Staccato* Loxapine, I focused on the populations from the three pulmonary safety studies (Trials **004-104**, **004-105**, and **004-108**).

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

A total of 13 clinical trials were included in the safety evaluation and are listed in the tables in **Section 5.1**. Eleven of these trials were included in the clinical program to support the use of *Staccato* Loxapine for the treatment of agitation: five Phase 1 clinical pharmacodynamic and pharmacokinetic studies (including a thorough QT/QTc study; Trial **004-107**), one Phase 2 study (Trial **004-201**), two Phase 3 studies (Trials **004-301** and **004-302**), and three clinical safety studies to assess pulmonary safety (Trials **004-104**, **004-105**, and **004-108**). The program included studies that were conducted in healthy volunteers (including smokers; Trial **004-106**), non-agitated subjects with Schizophrenia on stable antipsychotic therapy (Trial **004-102**), agitated patients with Schizophrenia (Trials **004-201** and **004-301**) or Bipolar Disorder (Trial **004-302**), and subjects with compromised lung function due to asthma (Trial **004-105**) or COPD (Trial **004-108**). In addition, *Staccato* Loxapine is being developed for the acute treatment of migraine headache. Two Phase 2 clinical trials (Trials **104-201** and **104-202**), have been completed for this indication and are included in the safety evaluation.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations

Overall exposure was adequate for review at appropriate doses and durations.

Eight safety populations were identified for analysis. The two main pooled populations were based on the controlled studies in agitated (Schizophrenia and Bipolar Disorder) patients (CSAP) and studies in healthy volunteers (HV). Other safety analysis populations were based on individual studies and included stable Schizophrenia patients, patients with asthma, patients with COPD, and patients with migraine headache. As an overview of safety, all of the above patients and subjects are also included in an Overall Safety Population (OSP).

Extent of exposure was summarized for each of the two main pooled safety populations (CSAP and HV populations) and the Overall Safety Population (OSP). The exposure for the remaining safety populations is described in individual study reports.

The doses of *Staccato* Loxapine studied have ranged from 0.625 mg in an early Phase 1 trial (Trial **004-101**) up to 10 mg, the recommended dose for treatment of agitation in Schizophrenia and Bipolar Disorder. In the phase 3 clinical efficacy trials, single doses of 5 and 10 mg were studied, with 2 additional doses permitted over the 24-hour evaluation period if needed to control agitation. In the two clinical trials for acute treatment of migraine headache, the dose range of *Staccato* Loxapine was 1.25 to 5 mg. Therefore, total daily doses have ranged from 0.625 mg to 30 mg.

Table 41: Staccato Loxapine Safety Analysis by Treatment Group

Analysis Population	Study Number	Placebo (N=578)	Staccato Loxapine				Overall (N=1653)
			<5 mg (N=348)	5 mg (N=347)	10 mg (N=452)	All (N=1147)	
<i>CSAP: Controlled Studies in Agitated Patient Population</i>	004-201	43	NA	45	41	86	129
	004-301	115	NA	116	113	229	344
	004-302	105	NA	104	105	209	314
	Total	263	NA	265	259	524	787
<i>HV: Healthy Volunteer Population</i>	004-101	14	21	7	8	36	50
	004-103	NA	NA	16	16	32	32
	004-104*	29	NA	NA	27	27	30
	004-106	NA	NA	NA	35	35	35
	004-107*	47	NA	NA	47	47	48
	Total	90	21	23	133	177	195
<i>Subjects on stable antipsychotic regimens</i>	004-102*	8	NA	16	8	24	32
<i>Subjects with asthma</i>	004-105	26	NA	NA	26	26	52
<i>Subjects with COPD</i>	004-108	27	NA	NA	26	26	52
<i>Patients with migraine headache (in-clinic)</i>	104-201	39	86	43	NA	129	168
<i>Patients with migraine headache (out-patient)</i>	104-202	125	241	NA	NA	241	366
OSP: Overall Safety Population		578	348	347	452	1147	1653

* The total number of subjects is less than the sum of the individual treatments due to the multi-dose design of Study 004-102 (3 doses of 5 mg, 2 doses of 5 mg and 1 dose of 10 mg, or 3 doses of 10 mg) and the crossover design of Studies 004-104 and 004-107.

Overall Safety Population (OSP)

The extent of exposure for the overall safety population is summarized in the table below (electronically copied and reproduced from sponsor's submission). Note that the <5 mg treatment group included doses of 0.625, 1.25, and 2.5 mg. For the multi-dose PK study, (004-102), subjects who received 5+5+5 mg and 10+5+5 mg were included in the Staccato Loxapine 5 mg group and subjects who received 10+10+10 mg were included in the Staccato Loxapine 10 mg group.

Table 42: Summary of Exposure (Overall Safety Population)

Doses of Study Medication, n (%)	Placebo (N=578)	Staccato Loxapine Dose			All Staccato Loxapine (N=1147)
		<5 mg ^a (N=348)	5 mg (N=347)	10 mg (N=452)	
1 dose	351 (60.7%)	348 (100.0%)	203 (58.5%)	283 (62.6%)	834 (72.7%)
2 doses	184 (31.8%)	0 (0.0%)	94 (27.1%)	130 (28.8%)	224 (19.5%)
3 doses	43 (7.4%)	0 (0.0%)	37 (10.7%)	25 (5.5%)	62 (5.4%)
4 doses	0 (0.0%)	0 (0.0%)	13 (3.7%)	14 (3.1%)	27 (2.4%)

Thus, the safety database comprises a total of 1653 subjects (Overall Safety Population) of which 1147 subjects received *Staccato* Loxapine and 578 subjects received placebo (included in these numbers are 72 subjects who received both *Staccato* Loxapine and placebo in crossover studies). Of the 1147 subjects in the OSP who received *Staccato* Loxapine, the majority (~73%) was exposed to 1 dose of *Staccato* Loxapine, ~20% received 2 doses, ~5% received 3 doses, and ~2% received 4 doses, reflecting the single-dose design of the majority of studies.

CSAP and HV Populations

As in the Overall Safety Population (OSP), the majority of subjects in the controlled studies in the agitated patient (CSAP) population (N=524) and in the healthy volunteer population (N=177) received 1 dose of *Staccato* Loxapine, as shown in the tables below (electronically copied and reproduced from sponsor’s submission). In the CSAP population, all exposure data represent exposure within 24 hours of dosing. In the Healthy Volunteer (HV) population, exposure mostly reflected whether the studies were single- or multiple-dose designs.

Table 43: Summary of Exposure (Controlled Studies in Agitated Patient population)

Doses of Study Medication, n (%)	Placebo (N=263)	<i>Staccato</i> Loxapine Dose		All <i>Staccato</i> Loxapine (N=524)
		5 mg (N=265)	10 mg (N=259)	
1 dose	124 (47.1%)	152 (57.4%)	176 (68.0%)	328 (62.6%)
2 doses	104 (39.5%)	93 (35.1%)	67 (25.9%)	160 (30.5%)
3 doses	35 (13.3%)	20 (7.5%)	16 (6.2%)	36 (6.9%)

Table 44: Summary of Exposure (Healthy Volunteer Population)

Doses of Study Medication, n (%)	Placebo (N=90)	<i>Staccato</i> Loxapine Dose			All <i>Staccato</i> Loxapine (N=177)
		<5 mg (N=21)	5 mg (N=23)	10 mg (N=133)	
1 dose	61 (67.8%)	21 (100.0%)	8 (34.8%)	91 (68.4%)	120 (67.8%)
2 doses	29 (32.2%)	0 (0.0%)	1 (4.3%)	27 (20.3%)	28 (15.8%)
3 doses	0 (0.0%)	0 (0.0%)	1 (4.3%)	1 (0.8%)	2 (1.1%)
4 doses	0 (0.0%)	0 (0.0%)	13 (56.5%)	14 (10.5%)	27 (15.3%)

7.2.2 Explorations for Dose Response

The sponsor’s explorations for dose response were acceptable. In general, the incidence of the most frequently reported adverse events did not show important increases in relationship to increases in the daily dose of *Staccato* Loxapine. The possible exception was the adverse event of dysgeusia. In the CSAP population, the incidence of dysgeusia was lower for *Staccato* Loxapine 5 mg (7.2%) compared with those of the higher doses of

Staccato Loxapine 10 mg through 30 mg (ranging from 13.8% to 20.0%), each being greater than that for the placebo group (4.9%).

7.2.4 Routine Clinical Testing

The types and frequency of safety assessments were appropriate for this indication and were adequate for detecting potential safety problems.

7.2.5 Metabolic, Clearance, and Interaction Workup

The sponsor has adequately characterized the metabolism and clearance of *Staccato* Loxapine in four clinical pharmacokinetic studies (**004-101**, **004-102**, **004-106**, and **004-107**) as well as one bioequivalence study (**004-103**). Since loxapine is a known substrate for several cytochrome P450 (CYP) enzymes in addition to flavin-containing monooxygenases (FMO), the risk of metabolic interactions caused by an effect on an individual isoform is minimized; therefore drug interaction studies were not done.

7.3 Major Safety Results

Controlled Studies in Agitated Patients (CSAP) Population

For the agitated patient (CSAP) population, at least one adverse event (AE) was experienced by ~36% of patients in the All *Staccato* Loxapine group and ~37% of patients in the placebo group. A similar incidence was reported for the *Staccato* Loxapine 5 mg (~36%) and 10 mg (~37%) groups. The majority of AEs experienced in the All *Staccato* Loxapine or placebo groups were mild or moderate (184/191, ~96%, and 93/98, ~95%, for the *Staccato* Loxapine and placebo groups, respectively). Severe AEs were experienced by 1.3% and 1.9% of the All *Staccato* Loxapine group and placebo group, respectively. The incidence of severe AEs in the active groups was the same as (10 mg; 1.9%) or less (5 mg; 0.8%) than the incidence in the placebo group (1.9%).

Table 45: Overall Incidence of AEs by Maximum Severity (Controlled Studies in Agitated Patient Population)

MedDRA System Organ Class Preferred Term, n (%)	Placebo (N=263)	<i>Staccato</i> Loxapine 5 mg (N=265)	<i>Staccato</i> Loxapine 10 mg (N=259)	All <i>Staccato</i> Loxapine (N=524)
Patients with at Least One Adverse Event	98 (37.3%)	95 (35.8%)	96 (37.1%)	191 (36.5%)
Mild	72 (27.4%)	69 (26.0%)	66 (25.5%)	135 (25.8%)
Moderate	21 (8.0%)	24 (9.1%)	25 (9.7%)	49 (9.4%)
Severe	5 (1.9%)	2 (0.8%)	5 (1.9%)	7 (1.3%)

The incidence of severe AEs in the CSAP population is listed in the table below. As the table illustrates, most of the severe AEs fell within the nervous system disorders organ class, and sedation was the only severe AE experienced by more than one patient.

Table 46: Overall Incidence of Severe AEs (Controlled Studies in Agitated Patient Population)

MedDRA System Organ Class Preferred Term, n (%)	Placebo (N=263)	Staccato Loxapine 5 mg (N=265)	Staccato Loxapine 10 mg (N=259)	All Staccato Loxapine (N=524)
<i>Nervous System Disorders</i>	<i>1 (0.4%)</i>	<i>1 (0.4%)</i>	<i>3 (1.2%)</i>	<i>4 (0.8%)</i>
Sedation	0 (0.0%)	0 (0.0%)	2 (0.8%)	2 (0.4%)
Headache	1 (0.4%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Somnolence	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%)
<i>Gastrointestinal Disorders</i>	<i>1 (0.4%)</i>	<i>0 (0.0%)</i>	<i>1 (0.4%)</i>	<i>1 (0.2%)</i>
Nausea	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastroenteritis	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
<i>Psychiatric Disorders</i>	<i>2 (0.8%)</i>	<i>0 (0.0%)</i>	<i>1 (0.4%)</i>	<i>1 (0.2%)</i>
Schizophrenia (exacerbation)	1 (0.4%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Agitation	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<i>Vascular Disorders</i>	<i>0 (0.0%)</i>	<i>1 (0.4%)</i>	<i>0 (0.0%)</i>	<i>1 (0.2%)</i>
Hypertension	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)
<i>Skin and Subcutaneous Tissue Disorders</i>	<i>0 (0.0%)</i>	<i>1 (0.4%)</i>	<i>0 (0.0%)</i>	<i>1 (0.2%)</i>
Hyperhidrosis	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)

Healthy Volunteers Population

The AE profile in the Healthy Volunteer (HV) population was similar to that in agitated patients (CSAP population) with the notable exception that somnolence and dizziness were much more common in the HV population. The most frequently reported AEs for the All *Staccato* Loxapine group were somnolence (~58% vs. ~11% in the placebo group), dizziness (~36% vs. ~8% in the placebo group), and dysgeusia (~27% vs. ~2% in the placebo group). Most of the AEs experienced in the All *Staccato* Loxapine group or in the placebo group were mild (~47% and ~28%, respectively) or moderate (~33% and ~8%, respectively).

7.3.1 Deaths

There was one death of a subject in the overall safety population:

- Subject 19-038 in Trial **004-201** died as a result of a severe AE of overdose 6 days after treatment with the study drug (placebo). The patient was a 43-year-old

homeless white male with a history of Schizophrenia and intravenous drug abuse (heroin and cocaine) who was admitted to the hospital (b) (6) for psychosocial problems and remained in the hospital until treatment. He developed agitation, was consented and qualified for the trial, randomized to receive *Staccato* Placebo, treated with the single dose of blinded study medication November 1, 2006, and experienced no adverse effects of treatment. He was followed for the 24 hour observation period and discharged (b) (6) to an independent treatment living home on his regular antipsychotic medications. The patient was found dead on the bathroom floor at the home next to an empty syringe on (b) (6). The presence of the syringe and the patient history suggested that the death was related to intravenous drug overdose. In the sponsor's response to FDA query (5-4-10), it was reported that no further information or records could be obtained, and the investigator was unable to determine whether or not an autopsy was performed.

7.3.2 Nonfatal Serious Adverse Events

Five subjects in the overall safety population (OSP) experienced nonfatal serious adverse events (SAEs) during the studies. This included two subjects in the placebo group, one subject in the *Staccato* Loxapine 5 mg group, and two subjects in the *Staccato* Loxapine 10 mg group. One of the five subjects was in the healthy volunteer (HV) population (Trial **004-001**, Subject 01-004), and the other four subjects were in the Controlled Studied in Agitated Patients (CSAP) population.

Table 47: Treatment-Emergent SAEs (Overall Safety Population)

Study Drug	Subject No.	Trial No.	MedDRA Preferred Term	Outcome	Treatment Required
Placebo	01-004	004-104	Appendicitis perforated	Resolved	Hospitalization Required/ Prolonged
	19-038	004-201	Overdose	Death	None
	17-113	004-301	Schizophrenia	Resolved	Hospitalization Required/ Prolonged
<i>Staccato</i> Loxapine 5 mg	02-106	004-201	Hypertension	Resolved	Hospitalization Required/ Prolonged
<i>Staccato</i> Loxapine 10 mg	12-086	004-201	Schizophrenia	Resolved	Hospitalization Required/ Prolonged
	24-354	004-301	Gastroenteritis	Resolved	Hospitalization Required/ Prolonged

The following narratives describe the nonfatal serious adverse event cases:

1. Subject 01-004 (Trial **004-104**) was a 22-year-old Caucasian female who was randomized to receive *Staccato* Placebo in Period 1 and *Staccato* Loxapine in Period 2. She received both doses of *Staccato* Placebo on (b) (6) and was discharged from the clinic at the end of the treatment period. On (b) (6) the subject presented to a local emergency department with an acute abdomen and was admitted to the hospital. Laparoscopy on (b) (6) identified a perforated appendix and appendectomy was performed. She subsequently received antibiotics and was discharged on (b) (6). As a result of this SAE, the subject was withdrawn from the trial.
2. Subject 17-113 (Trial **004-301**) was a 45-year-old black male diagnosed with Schizophrenia in 1988. The subject was randomized and received *Staccato* Placebo on May 20, 2008. He completed the study and was discharged on (b) (6). No AEs were reported. On (b) (6), he was admitted to the hospital with a severe exacerbation of Schizophrenia. It was reported that he had not been compliant with his medications and experienced increased paranoia and auditory hallucinations. He was discharged on (b) (6) on oral paliperidone.
3. Subject 02-106 (Trial **004-201**) was a 48-year-old white male with Schizophrenia receiving treatment for hypertension. He developed agitation, was consented and qualified for the trial, randomized to receive *Staccato* Loxapine 5 mg, treated with

the single dose of the blinded study medication [REDACTED] (b) (6), and experienced no AEs. He was followed for the 24 hour observation period and was reported as stable when discharged on [REDACTED] (b) (6). During outpatient follow-up, he developed worsening hypertension (BP ~210/130) for which he was hospitalized and treated on [REDACTED] (b) (6), and released on [REDACTED] (b) (6).

4. Subject 12-086 (Trial **004-201**) was a 23-year-old male with Schizophrenia who developed agitation, consented and qualified for the trial, was randomized to receive *Staccato* Loxapine 10 mg, and treated with the single dose of the blinded study medication on [REDACTED] (b) (6). The subject was followed for the 24 hour observation period, and was stable, with no AEs reported, when discharged on [REDACTED] (b) (6). On [REDACTED] (b) (6) the subject was hospitalized for exacerbation of Schizophrenia, agitation, noncompliance with medication taking and response to internal stimuli. The outcome was reported as resolved, but no further information is available.
5. Subject 24-354 (Trial **004-301**) was a 37-year-old Caucasian female, diagnosed with Schizophrenia in 1982, who was randomized and received her first dose of *Staccato* Loxapine 10 mg on May 5, 2008. The subject received Dose 1 at 16:00, Dose 2 at 19:30 and 1 mg of lorazepam IM at 21:00. On May 6, she received 1 mg of lorazepam IM at 10:25. AEs of restlessness, dizziness (lightheadedness), bronchitis, hot and cold flashes, pharyngitis, sedation, and upper respiratory infection were reported, all of which were judged to be mild and unrelated to treatment. The patient completed the trial and was discharged. The SAE of severe gastroenteritis began at 19:00 on May 6 with the development of emesis, abdominal cramping, diarrhea, and chills. The subject was hospitalized on [REDACTED] (b) (6) improved with supportive care, and was discharged on [REDACTED] (b) (6).

None of the SAEs (fatal or nonfatal) were judged to be related to study treatment. Since all of the SAEs occurred several days after study treatment and/or were not consistent with the known adverse event profile of loxapine, this seems reasonable.

7.3.3 Dropouts and/or Discontinuations

A total of six subjects in the overall safety population (OSP) experienced AEs that led to premature discontinuation from the study: 1 subject in the placebo group (Subject 01-004, severe appendicitis, perforated, also a SAE), 1 subject in the *Staccato* Loxapine 5 mg group, and four subjects in the *Staccato* Loxapine 10 mg group. All events resolved, and three of the events were considered remote or possibly related to study drug, as shown in the table below:

Table 48: Adverse Events Leading to Premature Discontinuation of Study Drug (Overall Safety Population)

Study Drug	Subject No.	Trial No.	MedDRA Preferred Term	Outcome	Severity	Relationship to Drug	Treatment Required
Placebo	01-004	004-104	Appendicitis perforated	Resolved	Severe	Unrelated	Hospitalization
<i>Staccato</i> Loxapine 5 mg	01-026	004-103	Urticaria	Resolved	Moderate	Possibly Related	Medication
<i>Staccato</i> Loxapine 10 mg	01-017	004-103	URI*	Resolved	Mild	Unrelated	Medication
	19-405	004-301	Bronchospasm	Resolved	Moderate	Possibly Related	Medication
	03-044	004-302	Anxiety	Resolved	Moderate	Unrelated	Medication
	14-280	004-302	Anxiety	Resolved	Moderate	Remote	Medication

*URI= Upper Respiratory Tract Infection

The following narratives describe the cases of adverse events leading to premature discontinuation:

1. Subject 01-004 (HV Population, Trial **004-104**): see narrative in **Section 7.3.2**.
2. Subject 01-026 (HV population, Trial **004-103**) was a 24 year-old female who was randomized to Sequence BABA and had an AE of moderate urticaria after Treatment 3 (5-mg clinical device) that resulted in her withdrawal from the study and was judged to be possibly related to study treatment. She received Treatment 3 on August 27, 2008 and developed a mild itch on her left leg ~ 11.5 hours later. The itching increased and became generalized, and the subject developed generalized hives over the next 48 hours. She was treated with antihistamines, and the hives gradually resolved. The AE was reported as resolved on September 9.
3. Subject 01-017 (HV population, Trial **004-103**) was a 24 year-old white male who was randomized to Sequence DCDC and developed a mild upper respiratory tract infection that failed to resolve in time to allow his participation in the last treatment period (10-mg commercial).
4. Subject 19-405 (CSAP population, Trial **004-301**) was a 59-year-old black woman who was diagnosed with Schizophrenia and was an active cigarette smoker (25 years, average of 10/day). She was randomized and received *Staccato* Loxapine 10 mg on May 15, 2008. Approximately 5 minutes after her first dose, she developed labored breathing with audible wheezes, although she did not complain of shortness of breath. She was given albuterol (2 puffs, via metered-dose inhaler) and oxygen by nasal cannula, and she was reported to have

responded promptly. She had no other AEs and was reported as stable when discharged.

5. Subject 03-044 (CSAP population, Trial **004-302**) was a 39-year-old Caucasian female diagnosed with Bipolar I Disorder in 2005 who entered the trial during a manic episode and was randomized to *Staccato* Loxapine 10 mg. This subject had a history of intermittent anxiety and insomnia, both of which were judged to be stable, and her medications at screening were venlafaxine hydrochloride 37.5 mg qd, quetiapine fumarate 100 mg bid, trazadone 100 mg qd, and Vicodin 500 mg qd. She received her first dose of *Staccato* Loxapine on August 28, 2008 at 10:10 and a second dose at 22:00. The AE of moderate anxiety started at 23:10, at which time IM lorazepam 2 mg was administered. The AE resolved in 1.5 hours, at 01:00 on August 29. The patient had no other AEs.
6. Subject 14-280 (CSAP population, Trial **004-302**) was a 45-year-old female diagnosed with Bipolar I Disorder in 1996 who entered the trial during a mixed episode and was randomized to *Staccato* Loxapine 10 mg. She had a history of intermittent anxiety, judged to be stable, and a history of extrapyramidal symptoms. Her medications at screening were lorazepam 2 mg qd, lithium 1200 mg qhs, and quetiapine fumarate 300 mg tid. She received 1 dose of *Staccato* Loxapine on September 11, 2008 at 10:15, and her lithium dose was withheld at baseline (an important protocol deviation). The AE, a moderate anxiety attack, started at 12:15, 2 hours after her dose of *Staccato* Loxapine. She received lorazepam 1 mg at 17:15, lithium 600 mg at 20:00, and quetiapine fumarate 200 mg at 20:00. The AE resolved at 21:30. The patient had no other AEs.

It seems a reasonable judgment that the AE of urticaria and the AE of bronchospasm were possibly treatment related. In both cases, the AE developed in an appropriate time period post-dose, suggesting a causal relationship. In the case of the urticaria, the description is consistent with a typical allergic urticaria that could have been induced by the study drug. Induction of bronchospasm after a treatment by inhaler would also seem plausible, particularly given the subject's long history of smoking. Clearly, the AEs of appendicitis perforated and upper respiratory tract infection are not treatment-related. In the two cases of AE of anxiety, one was judged unrelated and one was judged as remote related. This is more difficult to determine. In my opinion, it is possible that the AEs of anxiety were treatment-related, but it is more likely that these AEs represented treatment-failures. Another possibility would be if the episodes of anxiety represented underlying treatment-induced akathisia: however no other AEs were reported for these two subjects, so this seems less likely.

7.3.4 Significant Adverse Events

Based on the known pharmacology and safety profile of oral loxapine, AEs affecting the nervous system and cardiovascular system were identified as areas of particular interest.

In addition, given the route of administration of *Staccato* Loxapine, AEs potentially related to airways were also of particular interest.

Nervous system disorders

Nervous system disorders were among the most frequently reported adverse events in all of the safety populations.

In the CSAP population, sedation AEs were experienced by slightly greater proportions of the All *Staccato* Loxapine patients (~11%) compared to the placebo group (~8%), as shown in the table below (electronically copied and reproduced from sponsor’s submission):

Table 49: Nervous System AEs Experienced by 2 or More Patients by Treatment Group (Controlled studies in Agitated Patient population)

MedDRA system organ class Preferred Term, n (%)	Placebo (N=263)	<i>Staccato</i> Loxapine Dose		All <i>Staccato</i> Loxapine (N=524)
		5 mg (N=265)	10 mg (N=259)	
Patients who experienced at least one AE	98 (37.3%)	95 (35.8%)	96 (37.1%)	191 (36.5%)
Nervous system disorder	58 (22.1%)	55 (20.8%)	51 (19.7%)	106 (20.2%)
Sedation	20 (7.6%)	28 (10.6%)	27 (10.4%)	55 (10.5%)
Dizziness	23 (8.7%)	17 (6.4%)	19 (7.3%)	36 (6.9%)
Headache	26 (9.9%)	9 (3.4%)	8 (3.1%)	17 (3.2%)
Somnolence	5 (1.9%)	4 (1.5%)	4 (1.5%)	8 (1.5%)
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%)

Other nervous system disorder AEs experienced by 1 patient each were: dyskinesia, grimacing, migraine, and paraesthesia for the *Staccato* Loxapine 5 mg group; balance disorder, dystonia, oculogyration, and restlessness for the *Staccato* Loxapine 10 mg group; and paraesthesia and gait disturbance for the placebo group. Severe nervous system AEs in the CSAP population included: sedation (2 patients, 0.8%, in the *Staccato* Loxapine 10 mg group), headache (1 patient in the placebo group), somnolence (1 patient in the *Staccato* Loxapine 5 mg group), oculogyration (1 patient in the *Staccato* Loxapine 10 mg group), and dystonia (1 patient in the *Staccato* Loxapine 10 mg group).

In the subjects on stable antipsychotic regimens (Trial **004-102**), four subjects experienced nervous system disorder AEs: 1 subject (13%) each in the *Staccato* Loxapine 15 mg and 20 mg groups (moderate sedation), and 2 subjects (25%) in the *Staccato* Loxapine 30 mg group (moderate sedation and dizziness) compared to none in the placebo group.

In patients with migraine headaches, somnolence appeared to be dose-related in Trial **104-201** (5% of subjects in the *Staccato* Loxapine 1.25 mg group, 23% each in the

Staccato Loxapine 2.5 mg and 5 mg groups, and 13% in the placebo group), but not in Trial **104-202** (placebo, 3.2%; 1.25 mg, 2.5%; 2.5 mg, 6.7%). Disturbance in attention was reported in Trial **104-201** (5% in *Staccato* Loxapine 1.25 mg and 2% in the *Staccato* Loxapine 5 mg group). No AEs representing extrapyramidal symptoms were reported in either trial.

In the Healthy Volunteer Population, nervous system disorder AEs were experienced by ~73% of subjects in the All *Staccato* Loxapine group and ~27% of subjects in the placebo group, as shown in the table below (electronically copied and reproduced from sponsor's submission):

Table 50: Nervous System AEs Experienced by 2 or More Subjects in Any Treatment Group (Healthy Volunteer Population)

MedDRA System Organ Class Preferred Term, n (%)	Placebo (N=90)	<i>Staccato</i> Loxapine Dose			All <i>Staccato</i> Loxapine (N=177)
		<5 mg (N=21)	5 mg (N=23)	10 mg (N=133)	
Subjects with at least 1 AE	34 (37.8%)	12 (57.1%)	21 (91.3%)	113 (85.0%)	146 (82.5%)
Nervous system disorders	24 (26.7%)	12 (57.1%)	19 (82.6%)	98 (73.7%)	129 (72.9%)
Somnolence	10 (11.1%)	3 (14.3%)	17 (73.9%)	83 (62.4%)	103 (58.2%)
Dizziness	7 (7.8%)	7 (33.3%)	7 (30.4%)	49 (36.8%)	63 (35.6%)
Headache	10 (11.1%)	2 (9.5%)	7 (30.4%)	12 (9.0%)	21 (11.9%)
Lethargy	0 (0.0%)	0 (0.0%)	9 (39.1%)	4 (3.0%)	13 (7.3%)
Akathisia	0 (0.0%)	1 (4.8%)	0 (0.0%)	2 (1.5%)	3 (1.7%)
Disturbance in attention	1 (1.1%)	2 (9.5%)	0 (0.0%)	0 (0.0%)	2 (1.1%)
Presyncope	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.5%)	2 (1.1%)
Tension headache	2 (2.2%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.6%)

Other nervous system disorder AEs in the HV population which were experienced by 1 subject each were: coordination abnormal for *Staccato* Loxapine <5 mg; dizziness postural for *Staccato* Loxapine 5 mg; paraesthesia, burning sensation, dizziness postural, syncope vasovagal, urinary incontinence, migraine, and vision blurred for *Staccato* Loxapine 10 mg; and paraesthesia and sedation for the placebo group.

Cardiovascular System Adverse Events

The only cardiac disorder reported in the CSAP population was an AE of palpitations experienced by 1 patient in the placebo group. Under vascular disorders, hypertension was reported as an AE in 3 patients (1.2%) in the *Staccato* Loxapine 10 mg group, 2 patients (0.8%) in the *Staccato* Loxapine 5 mg group, and 2 patients (0.8%) in the placebo group. Hypotension was reported for 1 patient (0.4%) in the *Staccato* Loxapine 10 mg group, 2 patients (0.8%) in the *Staccato* Loxapine 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 CSAP population.

In Trial **004-102** (subjects on stable antipsychotic regimens), one cardiovascular AE of tachycardia (heart rate 120 bpm) was reported in a 59-year-old man (Subject No. 01-030) with a history of stable moderate hypertension (screening blood pressure 142/98, heart rate 70 bpm) in the *Staccato* Loxapine 30 mg group. The episode of tachycardia was associated with dizziness and hypotension (blood pressure 70/40), occurred 31 hours after the last dose of *Staccato* Loxapine, and was judged by the investigator to be associated with the restarting of the subject's quetiapine (750 mg). The dizziness resolved in an hour and the hypotension and tachycardia resolved the following day. In the sponsor's response to FDA query (5-4-10) regarding whether or not ECGs were done, it was reported that ECG was not obtained to evaluate the tachycardia because of the presumed relationship to the restarting of previous antipsychotic therapy, and ECGs obtained at baseline and 10 minutes after Doses 1, 2, and 3, as well as 40 hours after Dose 3, showed normal sinus rhythm and ventricular rates of 68 to 72 bpm.

In subjects with migraine headaches, AEs of mild hypotension were reported in 4 patients in Trial **104-201** (1 with *Staccato* placebo, 1 with *Staccato* Loxapine 2.5 mg, and 2 with *Staccato* Loxapine 5 mg). None of these events required treatment and all resolved within 4 hours. In addition, 3 patients had changes in machine-read ECGs that were reported as clinically significant AEs but were later read by a cardiologist and judged to be artifacts. In Trial **104-202**, 2 treatment-related cardiovascular AEs (palpitations and tachycardia) were reported. Both resolved spontaneously without medical intervention.

Cardiac disorder AEs in the healthy volunteer population were mild palpitations in one subject (0.5%) and moderate tachycardia (0.8%) in one subject in the *Staccato* Loxapine 10 mg group. Under vascular disorders, hypotension was reported as an AE for 4 subjects (3.0%) in the *Staccato* Loxapine 10 mg group and 1 subject (4.3%) in the *Staccato* Loxapine 5 mg group. There were no reports of orthostatic hypotension in the HV population.

Respiratory System Adverse Events

AEs in the respiratory, thoracic, and mediastinal disorder system order class are summarized for the CSAP population in the table below (electronically copied and reproduced from sponsor's submission):

Table 51: Respiratory System AEs (Controlled Studies in Agitated Patient population)

Preferred Term, n (%)	Placebo (N=263)	Staccato Loxapine Dose		All Staccato Loxapine (N=524)
		5 mg (N=265)	10 mg (N=259)	
Patients with at least One Respiratory, Thoracic, and Mediastinal Disorder AE	3 (1.1%)	6 (2.6%)	13 (5.0%)	19 (3.6%)
Throat irritation	1 (0.4%)	2 (0.8%)	7 (2.7%)	9 (1.7%)
Pharyngeal hypoesthesia	0 (0.0%)	1 (0.4%)	2 (0.8%)	3 (0.6%)
Wheezing	0 (0.0%)	2 (0.8%)	0 (0.0%)	2 (0.4%)
Breath sounds decreased	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)
Bronchitis	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
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%)
Hiccups	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Parosmia	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Pharyngitis	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Rhinitis allergic	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)
Upper respiratory tract infection	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Nasal congestion	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rhinorrhoea	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

The most frequently reported respiratory system AEs were throat irritation, pharyngeal hypoesthesia, and wheezing. The two AEs of wheezing did not require treatment. Bronchospasm was reported for one subject in the *Staccato* Loxapine 10 mg group, and resulted in early discontinuation and required treatment with a bronchodilator. All the respiratory AEs were mild to moderate.

In subjects on stable antipsychotic regimens (Trial **004-102**), cough was experienced by 1 subject (13%) in the *Staccato* Loxapine 20 mg group and 2 subjects (25%) in the *Staccato* Loxapine 30 mg group compared to none in the placebo or *Staccato* Loxapine 15 mg group.

In Trial **104-201** of subjects with migraine headaches, respiratory AEs included throat irritation in 3 patients (7%) in the *Staccato* Loxapine 1.25 mg group, and pharyngeal hypoesthesia in 3 patients (7%) in the *Staccato* Loxapine 5 mg group. Moderate cough was reported by 2 patients, 1 following administration of *Staccato* Placebo and 1 following administration of *Staccato* Loxapine 1.25 mg. These events resolved without treatment, and there were no reports of dyspnea, wheezing, or bronchospasm.

However, in Trial **104-202** of subjects with migraine headaches, 2 cases of dyspnea were reported after *Staccato* Loxapine 1.25 mg. Patient 10-216 experienced mild dyspnea and patient 23-308 experienced moderate dyspnea. Moderate cough was reported after

Staccato Loxapine 1.25 mg, and mild cough was reported after *Staccato* Placebo. All four cases resolved spontaneously without medical intervention. There were no reports of wheezing or bronchospasm in any patient during the study.

AEs for respiratory effects are summarized for the HV population in the table below (electronically copied and reproduced from sponsor’s submission) and show that cough was the most frequently reported respiratory system AE:

Table 52: Respiratory System AEs Experienced by $\geq 2\%$ of subjects in Any Treatment Group (Healthy Volunteer Population)

MedDRA System Organ Class Preferred Term, n (%)	Placebo (N=90)	<i>Staccato</i> Loxapine Dose			All <i>Staccato</i> Loxapine (N=177)
		<5 mg (N=21)	5 mg (N=23)	10 mg (N=133)	
Respiratory, thoracic and mediastinal disorders	5 (5.6%)	0 (0.0%)	1 (2.3%)	24 (18.0%)	25 (14.1%)
Cough	2 (2.2%)	0 (0.0%)	0 (0.0%)	13 (9.8%)	13 (7.3%)
Pharyngeal hypoesthesia	0 (0.0%)	0 (0.0%)	1 (4.3%)	2 (1.5%)	3 (1.7%)
Pharyngitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.3%)	3 (1.7%)
Pharyngolaryngeal pain	2 (2.2%)	0 (0.0%)	0 (0.0%)	3 (2.3%)	3 (1.7%)

Other respiratory, thoracic and mediastinal disorder AEs included: nasal congestion by 2 subjects (1.5%) in the *Staccato* Loxapine 10 mg group, rhinitis allergic, sinus headache, throat irritation, and upper respiratory tract infection by 1 subject each in the *Staccato* Loxapine 10 mg group, and sinus headache by 1 subject (1.1%) in the placebo group. All these respiratory AEs were mild to moderate.

7.3.5 Spirometry Assessments and Pulmonary Safety Studies

Spirometry Assessments

Spirometry was assessed as a measure of pulmonary safety in the healthy volunteer population of Trial **004-104**, in the asthma population of Trial **004-105**, and in the COPD population of Trial **004-108**.

The early Phase 1 safety and pharmacokinetic trial (**004-101**) also included spirometry assessments, but only at 2 and 6 hours after dosing. In this trial, no observable trends were identified for any of the pulmonary function tests assessed.

7.3.5.1 Healthy Volunteers (Trial 004-104)

In the pulmonary safety study in healthy volunteers (Trial **004-104**), thirty healthy nonsmokers were randomized to receive *Staccato* Loxapine 10 mg or *Staccato* Placebo (a functioning device with no excipients or loxapine) in a double-blind, 2-period, crossover design. In each of 2 treatment periods, subjects received 2 doses of the same treatment within 24 hours (doses separated by 8 hours).

There were no systematic changes from same-period baseline in LSmean FEV₁ with either treatment (*Staccato* Loxapine or *Staccato* Placebo). The largest change in FEV₁ following loxapine treatment was -0.104 L.

The LSmean FVC decreased from same-period baseline at all assessment times after loxapine treatment and at 15 of the 16 assessment times after placebo treatment. Although these decreases were larger after loxapine treatment than placebo treatment, particularly after Dose 2, the magnitude of the treatment-group difference in the change from same-period baseline FVC (loxapine – placebo) was small.

In addition, the LSmean FEV₁/FVC increased from same-period baseline at 12 of the 16 assessment times after placebo treatment and at 15 of the 16 assessment times after loxapine treatment. Although these increases were larger after loxapine treatment than placebo treatment, particularly after Dose 2, the magnitude of the mean treatment-group difference in the change from same-period baseline FEV₁/FVC (loxapine – placebo) was small.

The sponsor notes that this pattern of decreases in FVC without corresponding decreases in FEV₁ is inconsistent with drug-induced bronchospasm. However, it is consistent with a sedative effect of loxapine on expiratory effort. Sedation was evaluated immediately before each spirometry assessment, using a visual analog scale (VAS) anchored by the terms “sleepy” and “awake”. In this trial, sedation was apparent after each dose of loxapine, with maximum mean sedation occurring 30 minutes to 1 hour after each dose of loxapine (greater sedation after the second dose). The figures below (electronically copied and reproduced from sponsor’s submission) demonstrate the similarity of the time course of the FVC and FEV₁/FVC findings to the time course of sedation:

Figure 11: Sedation Change from Same-Period Baseline, Treatment Difference (Loxapine – Placebo) (Spirometry Population) - Trial 004-104

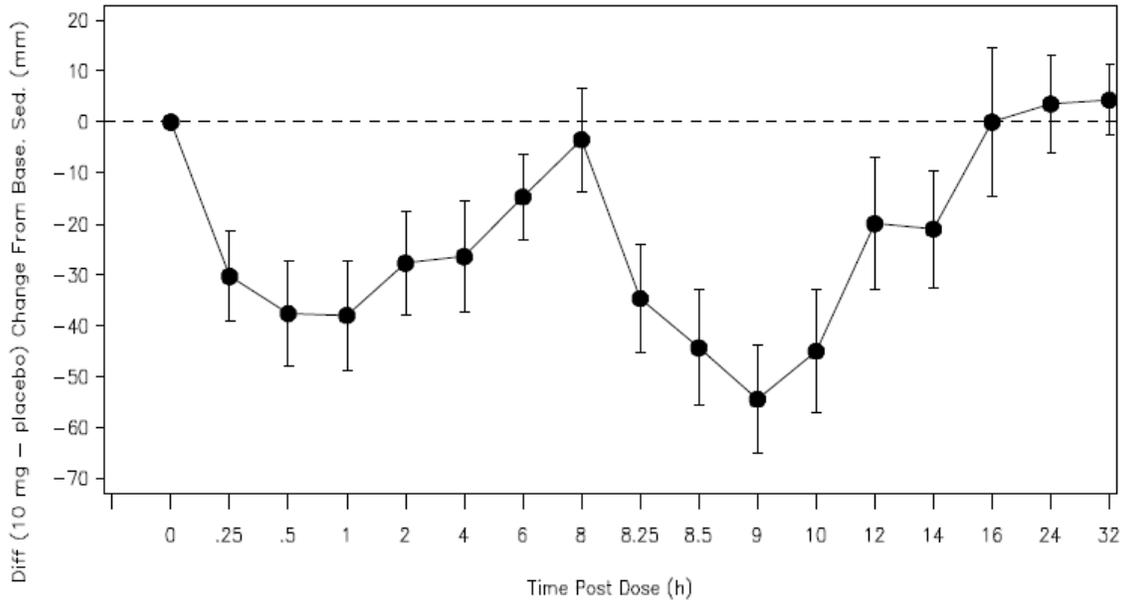


Figure 12: FVC Change from Same-Period Baseline, Treatment Difference (Loxapine – Placebo) (Spirometry Population) - Trial 004-104

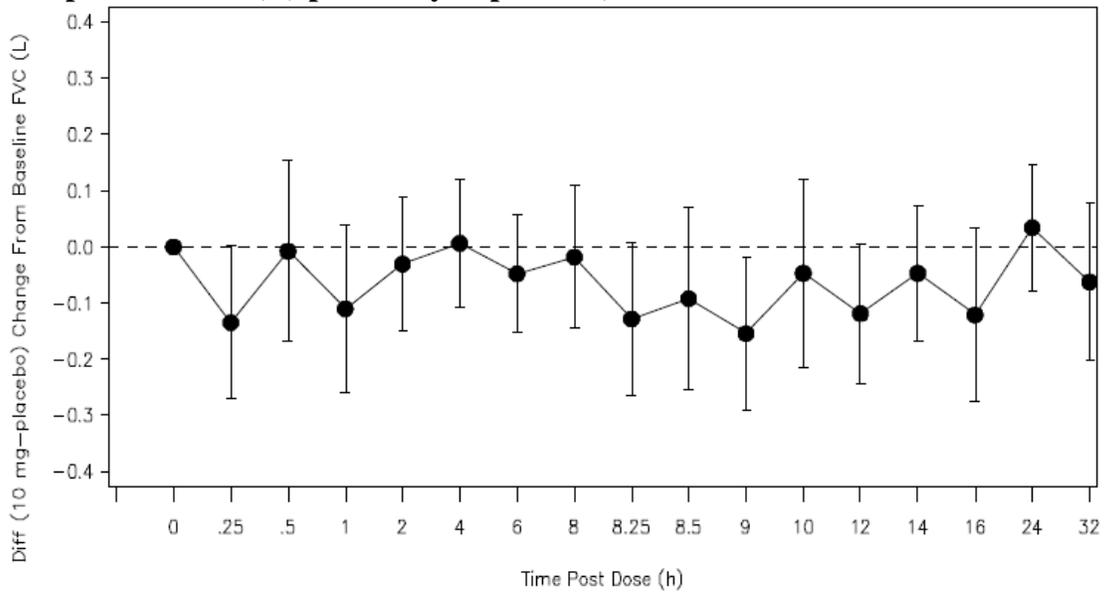
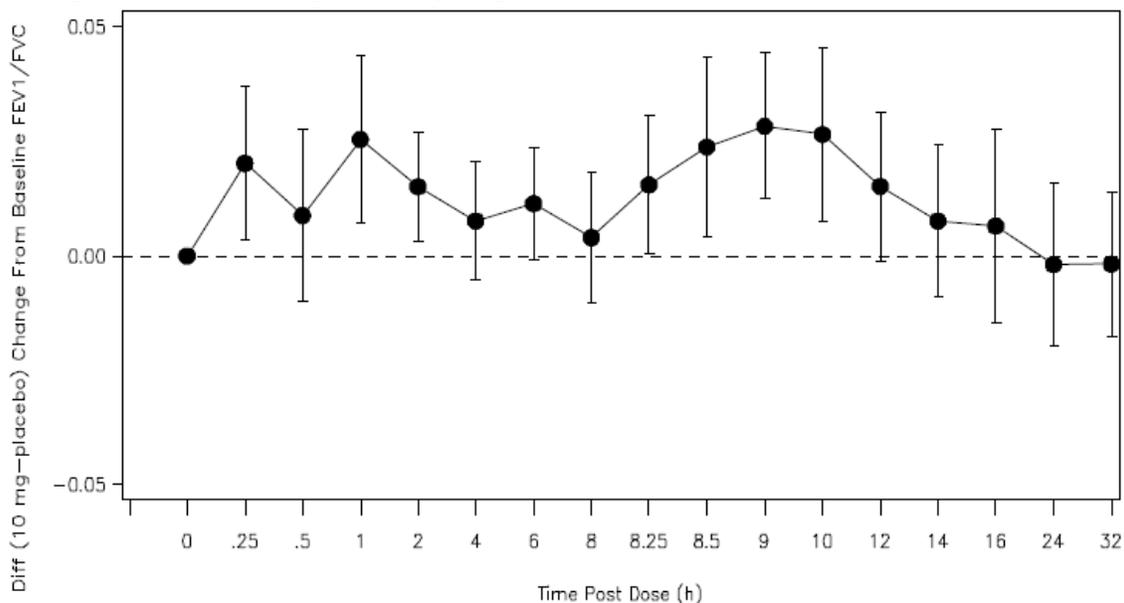


Figure 13: FEV₁/FVC Change from Same-Period Baseline, Treatment Difference (Loxapine – Placebo) (Spirometry Population) - Trial 004-104



There was no difference between placebo and loxapine in the percentage of subjects with a maximum FEV₁ decrease of $\geq 10\%$. However, maximum FEV₁ decreases of $\geq 15\%$ or $\geq 20\%$ were more common after loxapine treatment than placebo treatment and were more common after Dose 2 of loxapine than after Dose 1 of loxapine. After loxapine treatment, 6 subjects had maximum FEV₁ decrease of $\geq 15\%$, with 2 of them having a maximum decrease of $\geq 20\%$. One of the subjects who had a decrease of $\geq 15\%$ after loxapine treatment also had a $\geq 15\%$ FEV₁ decrease after placebo treatment (Subject 01-022); this was the only decrease of $\geq 15\%$ after placebo treatment. No subject had a maximum decrease of $\geq 25\%$ with either treatment.

According to the sponsor, when the 7 instances of decreased FEV₁ $\geq 15\%$ were evaluated, each had one or more features that were either inconsistent with an etiology of drug-induced bronchospasm or suggested an alternative explanation. Data that indicate that drug-induced bronchospasm was an unlikely cause of these decreases in FEV₁ are as follows:

- In 3 subjects (01-011, 01-014, and 01-016), the flow-volume loop of the spirometry tracing showed specific evidence of an incomplete effort.
- In 2 subjects (01-014 and 01-022), the FEV₁ decrease appeared at approximately Hour 16 (i.e., ~8 hours after Dose 2), a time course that indicates that it was unlikely to be drug-induced bronchospasm.
- In 3 subjects (01-011, 01-016, and 01-029), the FEV₁ recovered to within 10% of baseline within 30 minutes of the lowest FEV₁ value, a recovery time that is inconsistent with bronchospasm.

- In 4 subjects (01-008, 01-011, 01-014, and 01-029), the maximum decrease in FEV₁ occurred at a time of notable sedation (as measured by VAS).
- In 1 subject (01-022), there was an 18% decrease in FEV₁ after both placebo and loxapine treatment.

Furthermore, in all 7 instances:

- There was no specific evidence for development of a new obstructive effect, based on the contour of the spirometry flow-volume loop.
- There were no AEs that suggested an effect on airways (e.g., wheezing, dyspnea, or cough).
- No data suggested respiratory distress (e.g., changes in SpO₂, respiratory rate, or heart rate).

7.3.5.2 Subjects with Asthma (Trial 004-105)

This phase 1, multicenter, double-blind, placebo-controlled, parallel-group study assessed the pulmonary safety of two 10-mg doses of *Staccato* Loxapine administered 10 hours apart (at Hours 0 and 10 of each 34-hour study period) in 52 male and female subjects with a history of mild to moderate persistent asthma.

All subjects were 18 to 65 years old (inclusive), with no other clinically significant medical illnesses, and, at screening, met the following key inclusion/exclusion criteria:

Key Inclusion Criteria:

1. FEV₁ ≥60% of predicted.
2. History of FEV₁ reversibility of ≥10% after administration of a short-acting bronchodilator.
3. On asthma drug regimen stable for ≥2 weeks prior to study drug administration.
4. No use of tobacco products within 12 months prior to screening.

Key Exclusion Criteria:

1. ≥10 pack-year smoking history.
2. Diagnosis of another pulmonary disease (COPD, cystic fibrosis, bronchopulmonary dysplasia, lung tumor, pulmonary hypertension, cor pulmonale, bronchiectasis, tuberculosis, sarcoidosis, lung fibrosis, or interstitial lung disease).
3. Lung resection or other thoracic operation within 12 months prior to screening.
4. Received treatment in an emergency room or hospital admission for asthma exacerbation within 3 months prior to randomization.
5. History of ventilator support for respiratory failure secondary to asthma.
6. Experienced acute worsening of asthma requiring systemic corticosteroids or antibiotics within 6 weeks prior to screening.

7. Received any other treatment with a systemic corticosteroid within 30 days prior to screening.
8. Had used short-acting β -2 agonists or short-acting anticholinergic agents within 6 hours prior to study drug administration.

Trial Design

There were 3 study visits. At Visit 1, subjects were screened for eligibility. At Visit 2, continued eligibility was confirmed, randomization occurred, baseline measurements were obtained, treatment was administered (*Staccato* Loxapine 10 mg or *Staccato* Placebo; 2 doses, 10 hours apart), and post-treatment assessments were performed. Visit 2 occurred ≤ 28 days after Visit 1. At Visit 3, the end-of-study assessments were performed; Visit 3 occurred 7 ± 3 working days after Visit 2.

Safety was assessed by serial spirometry testing (15 post-treatment assessment times over 34 hours), and each spirometry test was accompanied by assessment of AEs, SpO₂, respiratory rate, heart rate, and sedation (measured by VAS). Before randomization to treatment, subjects were stratified based on their pre-bronchodilator FEV₁ of $\geq 80\%$ (*well controlled*) or $< 80\%$ (*not well controlled*) of predicted. Subjects who met the screening and baseline requirements were randomized to treatment within *Staccato* Loxapine or *Staccato* Placebo. Randomization was 1:1 within each stratum.

The 10-mg dose of *Staccato* Loxapine was selected for evaluation in this study because it was the highest dose evaluated in clinical studies of *Staccato* Loxapine for the treatment of agitation. The 10-hour interval between doses was selected to allow sedation from Dose 1 to subside before Dose 2 was administered, given the effort-dependence of spirometry testing. It was extended from the 8-hour interval used in the prior lung safety study of normal healthy volunteers (Trial **004-104**) based on the sedation profiles seen in this study.

Albuterol via metered-dose inhaler or nebulizer could be used as clinically indicated if a subject's FEV₁ decreased $\geq 20\%$ from baseline after any dose of study medication, or a subject had an AE of wheezing, dyspnea, or bronchospasm. Such subjects were not eligible to receive Dose 2.

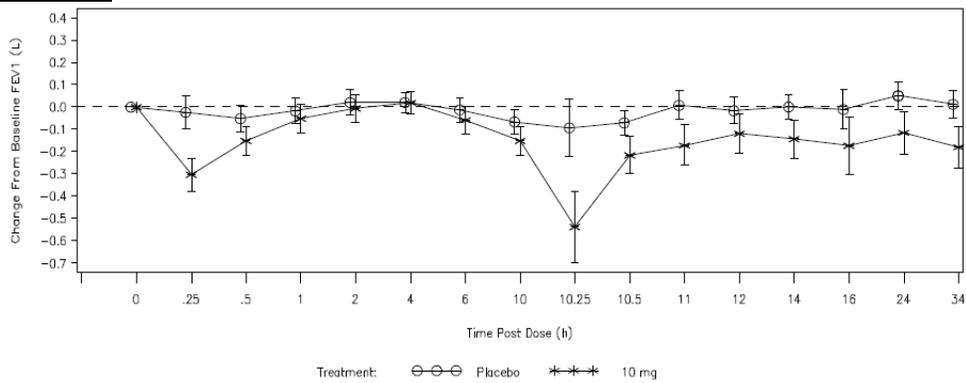
The majority of subjects were using controller medications at home prior to enrollment. While these were allowed to continue during the treatment period, quick-relief agents were withheld until the 34-hour time point, with the exception of albuterol used as rescue therapy. This was done to maximize the probability of detecting any acute effect of the administration of *Staccato* Loxapine. Withholding these agents was expected to increase asthma symptoms in at least some study subjects, which could mimic any airways effects of orally inhaled study medication.

Spirometry Findings

There were notable decreases in FEV₁ after loxapine, especially at the 0.25- and 10.25-hour time points (i.e., 15 minutes after Dose 1 and Dose 2, respectively). The largest changes in the loxapine group were -0.303 L (LSmean) at 0.25 hours and -0.537 L (LSmean) at 10.25 hours after Dose 1 (i.e., 0.25 hours after Dose 2). These decreases were short-lived and returned quickly toward baseline. There were no systematic changes from baseline in FEV₁ after placebo treatment.

The treatment-group differences in FEV₁ change from baseline are illustrated in the figure below (electronically copied and reproduced from sponsor's submission). After the 0.25- and 10.25-hour time points, the treatment-group difference decreased quickly. However, beyond the 10.25 time point, there was a small (~200 ml) sustained difference between the treatments groups. Note that subjects who used rescue medication or did not receive Dose 2 at Hour 10 were subsequently excluded from the spirometry population at all subsequent time points. Therefore, the population size represented on the figures to follow greatly decreases over time.

Figure 14: FEV₁ Change from Baseline, by Treatment (Spirometry Population) - Trial 004-105

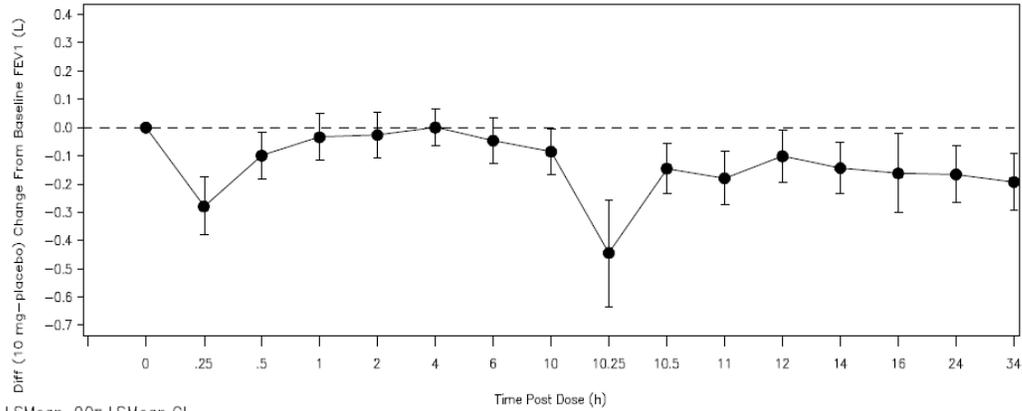


LSMean, 90% LSmear CI
 Program Name:f-3-3-fev.sas Date:02OCT2009: 6:29:54 Source Data:Table 3.15.1

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. Active:	26	26	22	22	22	21	20	20	17	12	12	12	12	12	11	10

LSmean and 90% LSmear CI
 Note: Placebo=Staccato Placebo, 10 mg=Staccato Loxapine 10 mg.
 Note: As shown in the time chart above, the number of subjects represented in this figure is decreasing 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; and, as such, the population size represented on the figure decreases over time.

Figure 15: FEV₁ Change from Baseline, Treatment Difference (Loxapine – Placebo) (Spirometry Population) - Trial 004-105



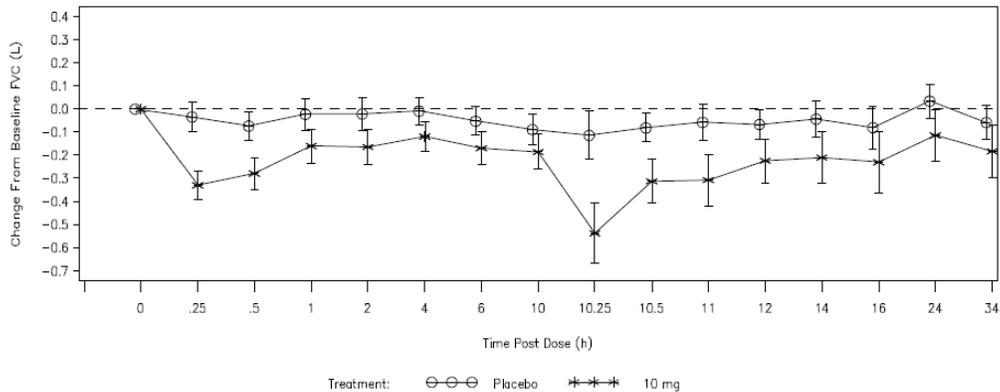
LSMean, 90% LSMean CI
 Program Name:f-3-4-fevd.sas Date:02OCT2009: 6:29:57 Source Data:Table 3.15.1

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. Active:	26	26	22	22	22	21	20	20	17	12	12	12	12	12	11	10

LSmean and 90% LSmean CI of treatment difference

The LSmean FVC showed a small decrease from most assessment times after placebo, which the sponsor believes reflected a modest reduction in effort accompanying repeat testing. There were larger decreases from baseline after loxapine at all time points. The largest change from baseline FVC in the loxapine group was -0.537 L (LSmean), which occurred at 10.25 hours after Dose 1, and the treatment-group difference (loxapine – placebo) was most notable at the 0.25 hour and 10.25 hour time points, as illustrated in the figures below (electronically copied and reproduced from sponsor’s submission):

Figure 16: FVC Change from Baseline, by Treatment (Spirometry Population) - Trial 004-105

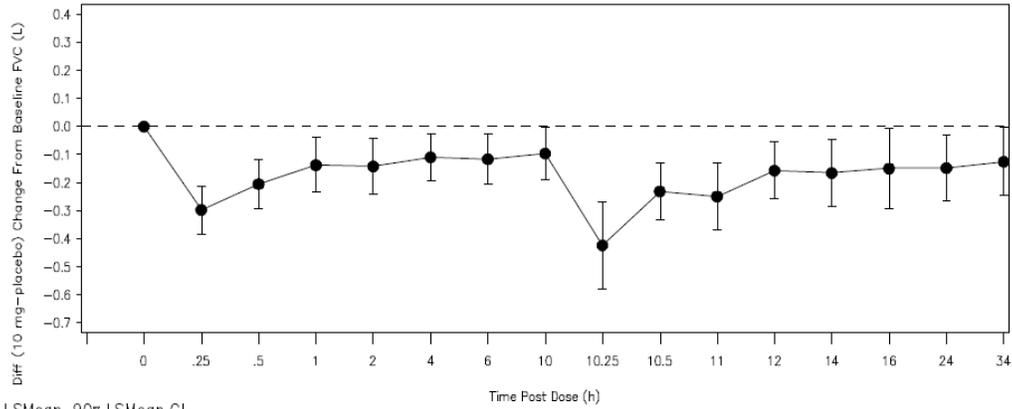


LSMean, 90% LSMean CI
 Program Name:f-3-5-fvc.sas Date:02OCT2009: 6:29:59 Source Data:Table 3.16.1

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. Active:	26	26	22	22	22	21	20	20	17	12	12	12	12	12	11	10

Note: Placebo=Staccato Placebo, 10 mg=Staccato Loxapine 10 mg.
 Note: As shown in the time chart above, the number of subjects represented in this figure is decreasing 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; and, as such, the population size represented on the figure decreases over time.

Figure 17: FVC Change from Baseline, Treatment Difference (Loxapine – Placebo) (Spirometry Population) - Trial 004-105



LSMean, 90% LSmean CI
 Program Name: f-3-6-fvcd.sas Date: 02OCT2009: 6:30:02 Source Data: Table 3.16.1

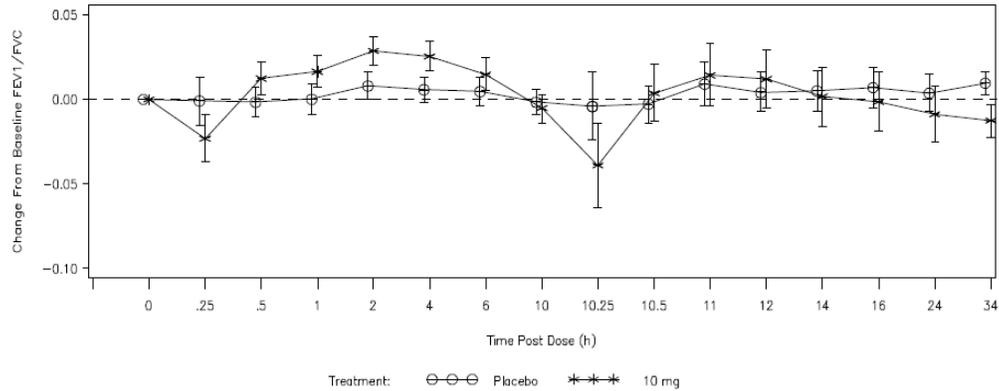
LSmean and 90% LSmean CI of treatment difference

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. Active:	26	26	22	22	22	21	20	20	17	12	12	12	12	12	11	10

LSmean and 90% LSmean CI of treatment difference

There was no systematic difference in FEV₁/FVC after placebo treatment compared to baseline values. After loxapine treatment, FEV₁/FVC decreased to below baseline at 0.25 hour and 10.25 hours, consistent with a new obstructive defect. After loxapine treatment, FEV₁/FVC was above baseline at several time points, which the sponsor believes is consistent with incomplete testing effort, particularly at end-exhalation. The treatment-group differences show a net decrease in FEV₁/FVC at the 0.25-hour and 10.25-hour time points, consistent with a new obstructive defect, and a net increase after Dose 1, consistent with incomplete testing effort. Please see figures below (electronically copied and reproduced from sponsor’s submission):

Figure 18: FEV1/FVC Change from Baseline, by Treatment (Spirometry Population) - Trial 004-105



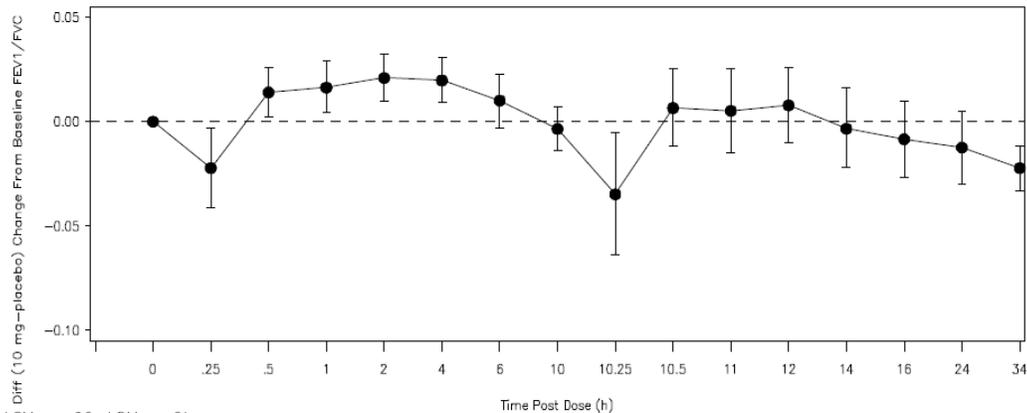
LSMean, 90% LSmean CI
 Program Name:f-3-7-fevfc.sas Date:02OCT2009: 6:30:04 Source Data:Table 3.17.1

LSmean and 90% LSmean CI

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. Active:	26	26	22	22	22	21	20	20	17	12	12	12	12	12	11	10

Note: Placebo=Staccato Placebo, 10 mg=Staccato Loxapine 10 mg.
 Note: As shown in the time chart above, the number of subjects represented in this figure is decreasing 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; and, as such, the population size represented on the figure decreases over time.

Figure 19: FEV1/FVC Change from Baseline, Treatment Difference (Loxapine – Placebo) (Spirometry Population) - Trial 004-105



LSMean, 90% LSmean CI
 Program Name:f-3-8-fevfc.d.sas Date:02OCT2009: 6:30:06 Source Data:Table 3.17.1

LSmean and 90% LSmean CI of treatment difference

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. Active:	26	26	22	22	22	21	20	20	17	12	12	12	12	12	11	10

LSmean and 90% LSmean CI of treatment difference

Notable Respiratory Signs or Symptoms

Eighteen (69%) loxapine-treated subjects and 3 (12%) placebo-treated subjects had “notable respiratory signs or symptoms” (defined as FEV₁ decrease from baseline of ≥20%, an airway AE, or use of rescue medication). Of these 18 loxapine-treated subjects, all but one (who withdrew for personal reasons) completed the intensive spirometry testing regimen and were eligible for discharge as the scheduled time (based on

spirometry testing, AE assessment, SpO2, heart rate, respiratory rate, blood pressure and sedation).

When these loxapine-treated subjects were compared across strata (i.e., the FEV₁ strata of <80% or ≥80%, notable respiratory signs or symptoms occurred in a larger percentage of subjects in the FEV₁ <80% stratum: 9 (~53%) of 17 subjects in the FEV₁ ≥80% stratum, and 8 (80%) of the 10 subjects in the FEV₁ <80% stratum.

Decreases of ≥20% occurred in 12 (~46%) loxapine-treated subjects and 1 (3.8%) placebo-treated subject. Eight of these loxapine-treated subjects had an FEV₁ ≥20% below baseline just before rescue with albuterol. Of these, 6 subjects showed an FEV₁ returned to within 10% of baseline between 0.25 and 0.67 hours, 1 at 1.33 hours, and 1 at 3.65 hours (both of these last 2 subjects steadily improved with each subsequent spirometry measurement).

As shown in the table below (electronically copied and reproduced from sponsor's submission), airway AEs were reported by 14 (~54%) loxapine-treated subjects and 3 (11.5%) placebo-treated subjects. Airway AEs that occurred in more than a single loxapine-treated subject were bronchospasm (7 subjects), chest discomfort (6 subjects), wheezing (4 subjects), and dyspnea (3 subjects). Airway AEs were also reported for 3 (11.5%) placebo-treated subjects (chest discomfort in 2 subjects; bronchospasm in one subject).

Table 53: Adverse Events Related to Airways (Safety Population) - Trial 004-105

Adverse Event, n (%)	<i>Staccato</i> Placebo (N=26)	<i>Staccato</i> Loxapine (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.

All Airway AEs were mild to moderate. In the loxapine group, airway AEs resolved without treatment in 1 of the 14 subjects. In the remaining 13 loxapine-treated subjects and in the 3 placebo-treated subjects, the AEs were treated with albuterol by metered-dose inhaler or nebulizer. None of the airway AEs led to withdrawal from the study,

prevented a subject from completing the spirometry testing regimen, or delayed discharge at the end of the treatment day.

A larger percentage of loxapine-treated subjects (~54%) received rescue medication compared to placebo-treated subjects (11.5%), as shown in the table below (electronically copied and reproduced from sponsor’s submission). In the placebo group, rescue medication was more often used after Dose 2 of study medication than after Dose 1. In the loxapine group, rescue medication was used with the same frequency after Dose 1 as after Dose 2.

Table 54: Number of Subjects Receiving Rescue Medication (Safety Population) - Trial 004-105

	<i>Staccato</i> Placebo (N=26)	<i>Staccato</i> Loxapine (N=26)
Number of subjects receiving rescue at any time	3 (11.5%)	14 (53.8%)
Number of subjects receiving only Dose 1 ^a of study drug:	1	9
Number receiving rescue	1	7
Number of subjects receiving Doses 1 ^a and 2 ^b of study drug:	25	17
Number receiving rescue after Dose 2 ^b of study drug	2	7

a. “After Dose 1” captures time points from 0.25 through 10 hours after Dose 1

b. “After Dose 2” captures time points from 10.25 through 24 hours after Dose 1. Data obtained at 34 hours were not included.

Overall, a larger percentage of loxapine-treated subjects had at least 1 AE (~92%) compared with placebo-treated subjects (61.5%). Sedation was the most common AE in loxapine-treated subjects (~69%). Other AEs reported by more than 10% of loxapine-treated subjects were dysgeusia (~31%); bronchospasm (~27%); chest discomfort (~23%); dizziness, headache, wheezing (~15% each); and dyspnea (11.5%). Most AEs were mild to moderate; there were no deaths, SAEs, or AEs that led to withdrawal from the study.

7.3.5.3 Subjects with COPD (Trial 004-108)

This phase 1, multicenter, double-blind, placebo-controlled, parallel-group study assessed the pulmonary safety of two 10-mg doses of *Staccato* Loxapine administered 10 hours apart (at Hours 0 and 10 of each 34-hour study period) in 53 subjects with an established history of COPD and a screening FEV₁ of ≥40% of predicted. The trial was very similar in design to Trial **004-105** (subjects with asthma), differing in the type of patients enrolled (subjects with COPD), and consequently, in some of the inclusion/exclusion criteria and in the rules for prior and concomitant medications.

All subjects were 40 to 70 years old (inclusive), with no other clinically significant medical illnesses, and, at screening, met the following key inclusion/exclusion criteria:

Key Inclusion Criteria:

1. FEV₁/FVC <0.70
2. >15 pack-year history of smoking
3. Willing to abstain from smoking within 2 hours before baseline and within 2 hours of each post dose pulmonary function tests
4. COPD drug regimen stable for at least 2 weeks prior to study drug administration.

Key Exclusion Criteria

1. Diagnosis of another pulmonary disease (asthma, cystic fibrosis, bronchopulmonary dysplasia, lung tumor, pulmonary hypertension, cor pulmonale, bronchiectasis, tuberculosis, sarcoidosis, lung fibrosis, or interstitial lung disease).
2. Lung resection or other thoracic operation within 12 months prior to screening.
3. Received treatment in an emergency room or hospital admission for COPD exacerbation within 3 months prior to randomization.
4. History of ventilator support for respiratory failure secondary to COPD.
5. Experienced acute worsening of COPD requiring systemic corticosteroids or antibiotics within 6 weeks prior to screening.
6. Received any other treatment with a systemic corticosteroid within 30 days prior to screening.
7. Had used short-acting β -2 agonists or short-acting anticholinergic agents within 6 hours prior to study drug administration.
8. History of sleep apnea with daytime hypersomnolence within 12 months prior to screening.
9. Current use or history of chronic use of supplemental oxygen

Trial Design

There were 3 study visits. At Visit 1, subjects were screened for eligibility. At Visit 2, continued eligibility was confirmed, randomization occurred, baseline measurements were obtained, treatment was administered (*Staccato* Loxapine 10 mg or *Staccato* Placebo; 2 doses, 10 hours apart), and post-treatment assessments were performed. Visit 2 occurred ≤ 28 days after Visit 1. At Visit 3, the end-of-study assessments were performed. Visit 3 occurred 7 ± 3 working days after Visit 2.

Safety was assessed by serial spirometry testing (15 post-treatment assessment times over 34 hours), and each spirometry test was accompanied by assessment of AEs, SpO₂, respiratory rate, heart rate, and sedation (measured by VAS). Before randomization to treatment, subjects were stratified based on their post-bronchodilator FEV₁ at screening (<50% or $\geq 50\%$ of predicted). Subjects who met the screening and baseline requirements

were randomized to treatment within *Staccato* Loxapine or *Staccato* Placebo. Randomization was 1:1 within each stratum.

The 10-mg dose of *Staccato* Loxapine was selected for evaluation in this study because it was the highest dose evaluated in clinical studies of *Staccato* Loxapine for the treatment of agitation. The 10-hour interval between doses was selected to allow sedation from Dose 1 to subside before Dose 2 was administered, given the effort-dependence of spirometry testing. It was extended from the 8-hour interval used in the prior lung safety study of normal healthy volunteers (Trial **004-104**) based on the sedation profiles seen in this study.

Albuterol via metered-dose inhaler or nebulizer could be used as clinically indicated if a subject's FEV₁ decreased $\geq 20\%$ from baseline after any dose of study medication, or a subject had an AE of wheezing, dyspnea, or bronchospasm. Such subjects were not eligible to receive Dose 2.

Subjects were allowed to remain on their usual controller respiratory medications, including long-acting β_2 agonists, methylxanthines, Spiriva (tiotropium), and inhaled corticosteroids. COPD medications were to be given ≥ 2 hours before Dose 1 of study medication. Short-acting β_2 agonists or short-acting anticholinergic agents were not allowed, unless medically required, from 8 hours before Dose 1 through 24 hours after Dose 2.

Spirometry Findings

As shown in the figures below (electronically copied and reproduced from sponsor's submission), there were differences from baseline in the LSmean FEV₁ at most assessment times after placebo or loxapine treatment, with a slightly larger decrease after loxapine treatment. The difference was most noticeable in the hour after each dose. The largest change following placebo treatment was -0.077 L, which occurred 16 hours after Dose 1 (ie, 6 hours after Dose 2). The largest change from baseline FEV₁ following loxapine treatment was -0.125 L, which occurred 10.25 hours after Dose 1 (ie, 0.25 hours after Dose 2). The largest treatment difference (loxapine – placebo) in the FEV₁ in the 4 hours following each dose was -0.084 L, which occurred 0.25 hours after Dose 1.

Figure 20: FEV₁ Change from Baseline, by Treatment (Spirometry Population) - Trial 004-108

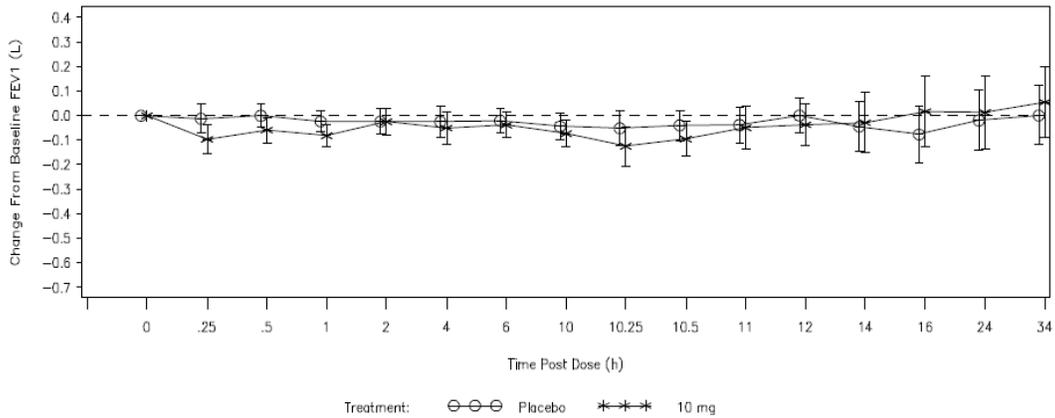
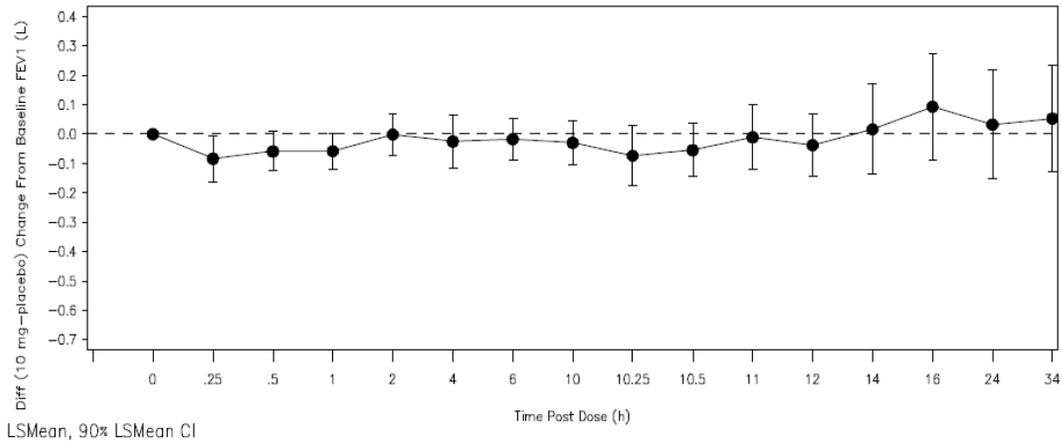


Figure 21: FEV₁ Change from Baseline, Treatment Difference (Loxapine – Placebo) (Spirometry Population) - Trial 004-108



There were small decreases from baseline in LSmean FVC at all assessment times after placebo treatment and at most assessment times after loxapine treatment, as shown in the figures below (electronically copied and reproduced from sponsor's submission). The decreases were larger after loxapine treatment than after placebo treatment.

Figure 22: FVC Change from Baseline, by Treatment (Spirometry Population) - Trial 004-108

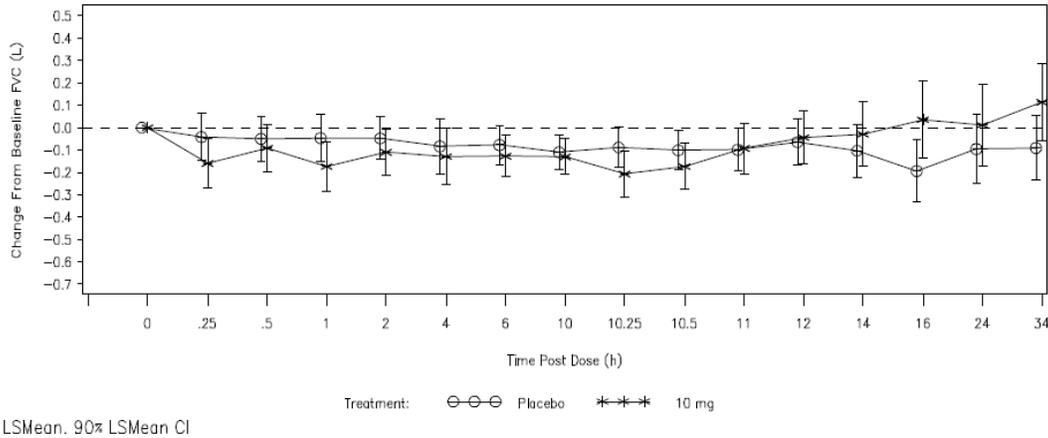
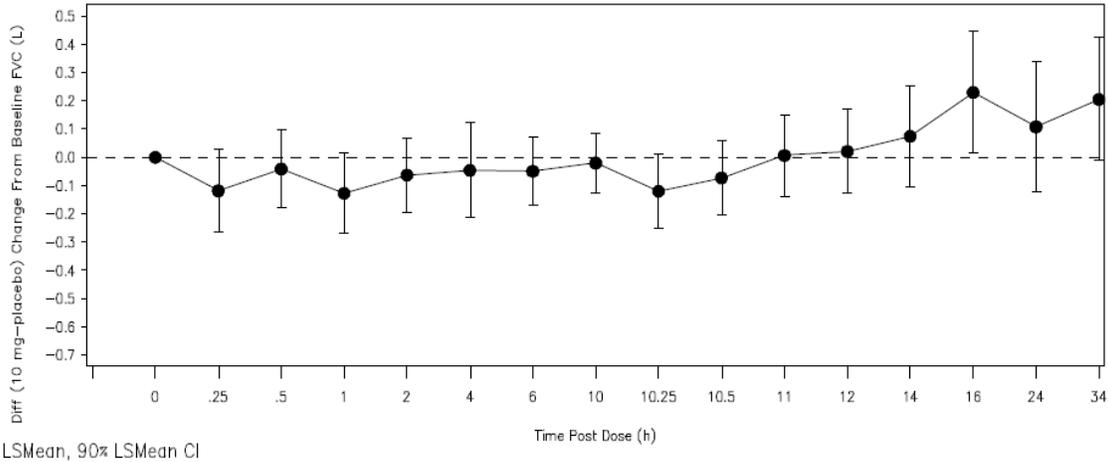


Figure 23: FVC Change from Baseline, by Treatment Difference (Loxapine – Placebo) (Spirometry Population) - Trial 004-108



There was no systematic pattern of change in FEV₁/FVC in either the *Staccato* Placebo or *Staccato* Loxapine group after dosing, as shown in the figures below (electronically copied and reproduced from sponsor’s submission). The treatment-group difference (loxapine – placebo) in the change from baseline FEV₁/FVC was negative at most of the assessment times.

Figure 24: FEV₁/FVC Change from Baseline, by Treatment (Spirometry Population) - Trial 004-108

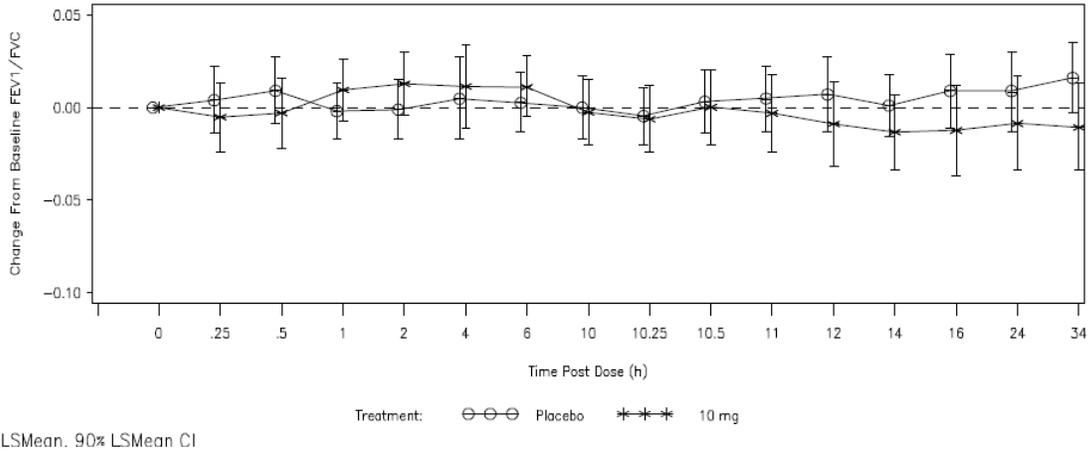
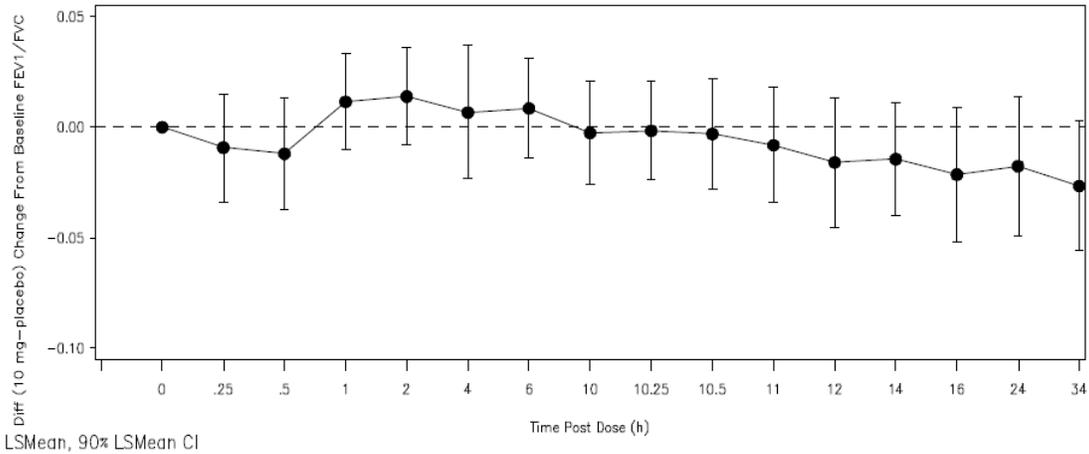


Figure 25: FEV₁/FVC Change from Baseline, by Treatment Difference (Loxapine – Placebo) (Spirometry Population) - Trial 004-108



Notable Respiratory Signs or Symptoms

Fifteen (~58%) loxapine-treated subjects had notable respiratory signs and/or symptoms (defined as subjects who had a maximum FEV₁ decrease from baseline of ≥20%, had a respiratory AE that could suggest an effect on airways, and/or received rescue medication). In almost two-thirds of these subjects (9 of 15) there was no intervention, while the remaining 6 subjects received 1 dose of albuterol per episode.

Decreases of at least 10% from baseline FEV₁ were seen in the majority of subjects in this study (~67% of the placebo group and ~81% of the loxapine group). The sponsor theorizes that this may reflect the effects of underlying airway disease, and possibly the withholding of quick relief agents, testing fatigue, and/or variable testing efforts. However, decreases of ≥10%, 15%, or ≥20% were more common in loxapine-treated subjects than placebo-treated subjects, as shown in the table below (electronically copied and reproduced from sponsor’s submission):

Table 55: Maximum FEV₁ Decrease from Baseline at Any Assessment – Decreases of at Least 10%, 15%, or 20% (Safety Population) - Trial 004-108

Maximum FEV ₁ Decrease ^a	<i>Staccato</i> Placebo ^b (N=27)	<i>Staccato</i> Loxapine ^b (N=26)
≥10%	18 (66.7%)	21 (80.8%)
≥15%	9 (33.3%)	15 (57.7%)
≥20%	3 (11.1%)	10 (38.5%)

Table presents the number of subjects.

- a. FEV₁ categories are cumulative (eg, a subject with a maximum decrease of 21% would be included in the ≥10%, ≥15%, and ≥20% categories).

The FEV₁ data was summarized by screening FEV₁ stratum (<50% or ≥50%), although the ability to generalize from these data were severely limited by small numbers. In loxapine-treated subjects, a decrease of ≥20% occurred in 7 of 18 subjects (~39%) in the ≥50% stratum and in 3 of 8 subjects (37.5%) in the <50% stratum. In the placebo-treated subjects, a ≥20% decrease occurred in 1 of 19 subjects (~5%) in the ≥50% stratum and in 2 of 8 subjects (25%) in the <50% stratum.

Airway AEs were reported for 5 (~19%) loxapine-treated subjects compared to 3 (~11%) placebo-treated subjects. Airway AEs that occurred in more than a single loxapine-treated subject were dyspnea (3 subjects, 11.5%), cough (3 subjects, 11.5%), and wheezing (2 subjects, 7.7%). No airway AEs occurred in more than a single placebo-treated subject. All of the airway AEs were judged to be mild or moderate, and none led to withdrawal, prevented completion of the spirometry testing, or delayed discharge.

A larger percentage of loxapine-treated subjects (6 subjects, ~23%) received rescue medication compared to placebo-treated subjects (4 subjects, ~15%). Of the 6 loxapine-treated subjects who received rescue medication, 5 received albuterol by metered-dose inhaler; the remaining subject (Subject 03-112) received 2.5 mg of albuterol by nebulizer for an FEV₁ decrease from baseline of ~28%. All 6 loxapine-treated subjects received only a single dose of rescue medication per episode. Of the 4 placebo-treated subjects who received rescue medication, all received albuterol by metered-dose inhaler. Three of the subjects received a single dose per episode. The remaining subject (Subject 02-008) received 2 doses for an AE of bronchospasm and later received another dose for an FEV₁ decrease.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Controlled Studies in Agitated Patient Population (Trials 004-201, 004-301, and 004-302)

In the agitated patient population (CSAP population), adverse events were reported for a similar percentage of *Staccato* Loxapine- and placebo-treated patients. The most frequently reported system organ classes were nervous system disorders (~20% of all subjects who received *Staccato* Loxapine compared to ~22% who received placebo) and gastrointestinal disorders (~17% of all *Staccato* Loxapine and ~13% of placebo; mainly dysgeusia). As shown in the table below (electronically copied and reproduced from sponsor's submission), the most frequently reported AEs in patients treated with *Staccato* Loxapine were dysgeusia (All *Staccato* loxapine ~13%) and sedation (All *Staccato* Loxapine 10.5%).

Table 56: Incidence of AEs Experienced by ≥2% of Patients in Any Treatment Group (Controlled Studies in Agitated Patients Population)

MedDRA system organ class Preferred Term n (%)	Placebo (N=263)	Staccato Loxapine Dose		All Staccato Loxapine (N=524)
		5 mg (N=265)	10 mg (N=259)	
Patients who experienced at least one AE	98 (37.3%)	95 (35.8%)	96 (37.1%)	191 (36.5%)
Nervous System Disorders	58 (22.1%)	55 (20.8%)	51 (19.7%)	106 (20.2%)
Sedation	20 (7.6%)	28 (10.6%)	27 (10.4%)	55 (10.5%)
(Sedation/Somnolence) ^a	25 (9.5%)	32 (12.1%)	31 (12.0%)	63 (12%)
Dizziness	23 (8.7%)	17 (6.4%)	19 (7.3%)	36 (6.9%)
Headache	26 (9.9%)	9 (3.4%)	8 (3.1%)	17 (3.2%)
Gastrointestinal Disorders	35 (13.3%)	44 (16.6%)	46 (17.8%)	90 (17.2%)
Dysgeusia	13 (4.9%)	30 (11.3%)	37 (14.3%)	67 (12.8%)
Nausea	8 (3.0%)	1 (0.4%)	3 (1.2%)	4 (0.8%)
Respiratory, Thoracic and Mediastinal Disorders	3 (1.1%)	6 (2.3%)	13 (5.0%)	19 (3.6%)
Throat irritation	1 (0.4%)	2 (0.8%)	7 (2.7%)	9 (1.7%)
General Disorders and Administration Site Conditions	6 (2.3%)	6 (2.3%)	4 (1.5%)	10 (1.9%)
Fatigue	5 (1.9%)	6 (2.3%)	3 (1.2%)	9 (1.7%)

The nervous system disorder AE with the highest incidence for the All *Staccato* Loxapine group was sedation (10.5%), which was numerically greater than that for the placebo

group (7.6%). In addition, somnolence was experienced by 1.5% of patients (8 patients) in the All *Staccato* Loxapine group and by 1.9% of patients (5 patients) in the placebo group. Thus, the combined incidence of sedation and somnolence was 12.0% in the All *Staccato* Loxapine group and 9.5% in the placebo group. There was no difference in the combined incidence of sedation and somnolence between the 5-mg and 10-mg *Staccato* Loxapine dose groups.

The incidence of dysgeusia for patients in the All *Staccato* Loxapine group (~13%) was higher than in the placebo group (~5%). The incidence of dizziness, headache, and nausea in the placebo group (~9%, ~10%, and 3%, respectively) was greater than in the All *Staccato* Loxapine group (~7%, ~3%, and ~1%, respectively).

Only four adverse events were identified that occurred at a rate of $\geq 2\%$ in either the 5- or 10-mg *Staccato* Loxapine groups and for which the rate exceeds the rate for placebo: dysgeusia, sedation (including sedation combined with somnolence), fatigue, and throat irritation. These adverse events are listed in the table below:

Table 57: *Staccato* Loxapine Adverse Events with an Incidence of at Least 2% and Greater than Placebo (Controlled Studies in Agitated Patient Population)

MedDRA Preferred Term n (%)	Placebo (N=263)	<i>Staccato</i> Loxapine 5 mg (N=265)	<i>Staccato</i> Loxapine 10 mg (N=259)
Dysgeusia	13 (4.9%)	30 (11.3%)	37 (14.3%)
p-value		0.0102	0.0003
Sedation/Somnolence	25 (9.5%)	32 (12.1%)	31 (12.0%)
p-value		0.4005	0.3978
Sedation	20(7.6%)	28 (10.6%)	27 (10.4%)
p-value		0.2894	0.2866
Fatigue	5 (1.9%)	6 (2.3%)	3 (1.2%)
p-value		1.000	0.7245
Throat Irritation	1 (0.4%)	2 (0.8%)	7 (2.7%)
p-value		1.000	0.0364

It is noteworthy that 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 and 10-mg *Staccato* Loxapine dose groups compared to the placebo group. In addition, the incidence of sedation and the combination of sedation and somnolence were numerically higher for both *Staccato* Loxapine dose groups compared with placebo, but the differences were not statistically significant. Furthermore, throat irritation was significantly higher in the 10-mg *Staccato* Loxapine dose group compared to placebo, but there was no significant difference in the incidence of throat irritation between the 5-mg *Staccato* Loxapine dose group and the placebo group.

Subjects on Stable Antipsychotic Regimens (Trial 004-102)

In the stable Schizophrenia population (Trial **004-102**), 31% of subjects (10/32) reported AEs: 42% (10/24) of subjects in the *Staccato* Loxapine groups and none of the subjects in the placebo group. Three subjects (38%) each in the *Staccato* Loxapine 15 mg and 20 mg groups and 4 subjects (50%) in the *Staccato* Loxapine 30 mg group reported AEs. The most frequently reported AEs by primary system organ class (≥ 3 subjects) were nervous system disorders (4 subjects), gastrointestinal disorders (4 subjects), and respiratory, thoracic, and mediastinal disorders (3 subjects). The most frequently reported AEs were cough (3 subjects), sedation (3 subjects), and dysgeusia (2 subjects). None of the AEs were serious; none led to discontinuation, and all resolved without sequelae except for elevated blood glucose in one subject.

Patients with Migraine Headache (Trials 104-201 and 104-202)

In the two trials, none of the AEs were serious, there were no deaths, and no patient discontinued because of an AE. In Trial **104-201**, the AEs most frequently reported for *Staccato* Loxapine 1.25, 2.5, and 5 mg vs. placebo were dysgeusia (19%, 23%, 37% vs. 13% respectively), somnolence (5%, 23%, and 23% vs. 13%, respectively), and fatigue (0%, 7%, and 14% vs. 8%, respectively). These AEs appeared to be dose related. In Trial **104-202**, the most common AEs were dysgeusia (placebo, 4.8%; 1.25 mg, 13.2%; 2.5 mg, 8.3%) and dizziness (placebo, 9.6%; 1.25 mg, 6.6%; 2.5 mg, 5.0%), and appeared unrelated to dose level. Five patients in Trial **104-202** reported severe AEs: nausea (2 patients), diarrhea, fatigue, migraine, and nightmare (1 patient each).

One pregnancy occurred during the course of Trial **104-202**. A 26-year-old patient received *Staccato* Loxapine 2.5 mg. No AEs were reported throughout the trial. After 5 months, during Visit 3, pregnancy was reported and confirmed by her gynecologist.

Healthy Volunteer Population (Trials 004-101, 004-103, 004-104, 004-106, and 004-107)

For the most frequently reported AEs in the HV population, the incidence of somnolence was greater for the *Staccato* Loxapine 5 mg and 10 mg groups (~74% and ~62%, respectively), compared with the <5 mg group (~14%) or placebo (~11%). Dysgeusia was greater for the *Staccato* Loxapine 10 mg group (~30%) compared with the *Staccato* Loxapine <5 mg group (~9%) or the placebo group (~2%), and dizziness was greater for the *Staccato* Loxapine <5 mg, 5 mg and 10 mg daily doses (~33%, ~30% and ~37%, respectively) compared to that for the placebo group (~8%). In addition, the incidence of cough for the *Staccato* Loxapine 10 mg group (~10%) was higher than for the *Staccato* Loxapine <5 or 5 mg groups (0%) or the placebo group (~2%).

Table 58: Incidence of AEs Experienced by $\geq 2\%$ of Subjects in the All *Staccato* Loxapine Group and with Greater Incidence than placebo (Healthy Volunteer Population)

MedDRA System Organ Class Preferred Term, n (%)	Placebo (N=90)	<i>Staccato</i> Loxapine Dose			All <i>Staccato</i> Loxapine (N=177)
		<5 mg (N=21)	5 mg (N=23)	10 mg (N=133)	
<i>Nervous system disorders</i>	21 (23.3%)	12 (57.1%)	19 (82.6%)	98 (73.7%)	129 (72.9%)
Somnolence	10 (11.1%)	3 (14.3%)	17 (73.9%)	83 (62.4%)	103 (58.2%)
Dizziness	7 (7.8%)	7 (33.3%)	7 (30.4%)	49 (36.8%)	63 (35.6%)
Headache	8 (8.9%)	2 (9.5%)	5 (21.7%)	10 (7.5%)	17 (9.6%)
Lethargy	0 (0.0%)	0 (0.0%)	8 (34.8%)	4 (3.0%)	12 (6.8%)
<i>Gastrointestinal disorders</i>	3 (3.3%)	7 (33.3%)	3 (13.0%)	43 (32.3%)	53 (29.9%)
Dysgeusia	2 (2.2%)	5 (23.8%)	2 (8.7%)	40 (30.1%)	47 (26.6%)
Nausea	0 (0.0%)	5 (23.8%)	1 (4.3%)	2 (1.5%)	8 (4.5%)
<i>Respiratory, Thoracic, & Mediastinal disorders</i>	3 (3.3%)	0 (0.0%)	1 (4.3%)	19 (14.3%)	13 (7.3%)
Cough	1 (1.1%)	0 (0.0%)	0 (0.0%)	13 (9.8%)	13 (7.3%)
<i>General disorders & Administrative site conditions</i>	1 (1.1%)	3 (14.3%)	5 (21.7%)	5 (3.8%)	13 (7.3%)
Fatigue	1 (1.1%)	1 (4.8%)	1 (4.3%)	2 (1.5%)	4 (2.3%)
Feeling of relaxation	0 (0.0%)	2 (9.5%)	1 (4.3%)	1 (0.8%)	4 (2.3%)
<i>Vascular disorders</i>	0 (0.0%)	0 (0.0%)	1 (4.3%)	7 (5.3%)	8 (4.5%)
Hypotension	0 (0.0%)	0 (0.0%)	1 (4.3%)	4 (3.0%)	5 (2.8%)

Severe AEs were experienced by four subjects in the *Staccato* Loxapine 10 mg group and by 1 subject in the placebo group. The severe AEs in the *Staccato* Loxapine 10 mg group were pallor (2 subjects), dizziness, migraine, fatigue, and feeling of relaxation by 1 subject each, and severe appendicitis perforated was experienced by 1 subject in the placebo group.

7.4.2 Laboratory Findings

Across the clinical program, laboratory data were collected at different time points according to the study protocols. In two trials (Trials **004-101** and **004-102**), laboratory data were collected at screening, baseline, and post-dose, whereas in another three trials, laboratory data were collected at screening and then only post-dose (Trials **004-103**, **004-301**, and **004-302**). In the other 8 trials, laboratory data were collected at screening only. Trial **004-201** did not include post-baseline laboratory assessments. Therefore modified CSAP population (Trials **004-301** and **004-302**) were used to assess laboratory data.

The main findings for clinical laboratory evaluations were as follows:

- There were no clinically important mean changes in any treatment group in hemoglobin concentration, hematocrit, platelet count, white blood cell (WBC) count, or other hematology parameters. The incidence of marked hematology abnormalities in the modified CSAP population was similar for the *Staccato* Loxapine 5 mg and 10 mg treatment groups and the placebo treatment group.
- There were no clinically important mean changes in any treatment group in blood chemistry parameters. The incidence of marked blood chemistry abnormalities in the modified CSAP population was similar for the *Staccato* Loxapine 5 mg and 10 mg treatment groups and the placebo treatment group.
- There were no important changes in urinalysis parameters in the modified CSAP population based on mean changes or shift tables.
- There were no clinically important differences of laboratory findings by demographic categories (age, sex, race, and weight), nor were there important differences in these safety evaluations by smoking status.

7.4.3 Vital Signs

In both the CSAP and HV populations (all treatment groups), there were small reductions in mean systolic and diastolic blood pressures (all < 7 mm Hg) during the 4 hours after dosing that were generally larger in the *Staccato* Loxapine 5 mg and 10 mg groups compared with placebo. There were small decreases in heart rate in the CSAP population (all < 3 bpm) that were numerically larger in the *Staccato* Loxapine 5 mg and 10 mg groups. By contrast, in the HV population, there were small increases in heart rate, most notably at 1 hour after dosing (placebo, 2.0 bpm; 5 mg, 6 bpm; 10 mg, 5.1 bpm).

Marked abnormalities in vital signs were defined by the sponsor as shown in the table below (electronically copied and reproduced from sponsor’s submission):

Table 59: Vital Signs - Criteria for Marked Abnormalities

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

In the CSAP population, there were relatively few marked abnormalities in vital signs in the *Staccato* Loxapine 5 mg and 10 mg and placebo groups. As shown in the table below, the most frequently reported abnormalities in vital signs in the All *Staccato* Loxapine group compared to placebo were: systolic blood pressure ≤ 90 mm Hg & decrease ≥ 20 mm Hg; and diastolic blood pressure ≤ 50 mm Hg & decrease ≥15 mm Hg The marked

decreases in diastolic blood pressure in the CSAP population were primarily isolated abnormalities (without other abnormalities in systolic blood pressure or heart rate at the same time: only 1 subject in the *Staccato* Loxapine 5 mg group had a single time point with both low diastolic and low systolic measurements. This subject, Subject 13-298 in Trial **004-302**, had a baseline blood pressure of 126/75, followed by blood pressures of 110/66, 86/50, 123/76, and 117/71 at 60 minutes post-dose 1, 120 minutes post-dose 1, 4 hours post-dose 1, and 24 hour post-dose 1, respectively.

Table 60: Marked Abnormalities by Treatment Group (CSAP Population)

	Placebo (N=263)	<i>Staccato</i> Loxapine 5 mg (N=265)	<i>Staccato</i> Loxapine 10 mg (N=259)	All <i>Staccato</i> Loxapine (N=524)
Heart rate (beats/minute) \leq 50 & decrease \geq 20	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Heart rate (beats/minute) \geq 120 & increase \geq 20	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Systolic Blood Pressure (mm Hg) \leq 90 & decrease \geq 20	2 (0.8%)	3 (1.1%)	4 (1.5%)	7 (1.3%)
Systolic Blood Pressure (mm Hg) \geq 180 & increase \geq 20	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diastolic Blood Pressure (mm Hg) \leq 50 & decrease \geq 15	1 (0.4%)	1 (0.4%)	2 (0.8%)	3 (0.6%)
Diastolic Blood Pressure (mm Hg) \geq 105 & increase \geq 15	2 (0.8%)	2 (0.8%)	0 (0.0%)	2 (0.4%)
Respiratory Rate (breaths/minute) \leq 6 & decrease \geq 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory Rate (breaths/minute) \geq 30 & increase \geq 5	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

In the HV population, the most frequently reported abnormalities in vital signs in the All *Staccato* Loxapine group compared to placebo were: systolic blood pressure \leq 90 mm Hg & decrease \geq 20 mm Hg; and diastolic blood pressure \leq 50 mm Hg & decrease \geq 15 mm Hg, as shown in the table below. Of the 19 subjects that showed at least one marked abnormality of low diastolic blood pressure, 13 subjects had isolated low diastolic blood pressure and 6 subjects (1 *Staccato* Loxapine 5 mg patient and 5 *Staccato* Loxapine 10 mg patients) had a single time point with both low diastolic and low systolic measurements.

Table 61: Marked Abnormalities by Treatment Group (HV Population)

	Placebo (N=90)	<i>Staccato</i> Loxapine <5 mg (N=21)	<i>Staccato</i> Loxapine 5 mg (N=23)	<i>Staccato</i> Loxapine 10 mg (N=133)	All <i>Staccato</i> Loxapine (N=177)
Heart rate (beats/minute) ≤ 50 & decrease ≥ 20	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Heart rate (beats/minute) ≥ 120 & increase ≥ 20	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Systolic Blood Pressure (mm Hg) ≤ 90 & decrease ≥ 20	1 (1.1%)	0 (0.0%)	2 (8.7%)	7 (5.3%)	9 (5.1%)
Systolic Blood Pressure (mm Hg) ≥ 180 & increase ≥ 20	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diastolic Blood Pressure (mm Hg) ≤ 50 & decrease ≥ 15	3 (3.3%)	0 (0.0%)	6 (26.1%)	10 (7.5%)	16 (9.0%)
Diastolic Blood Pressure (mm Hg) ≥ 105 & increase ≥ 15	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory Rate (breaths/minute) ≤ 6 & decrease ≥ 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory Rate (breaths/minute) ≥ 30 & increase ≥ 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

There were no clinically significant changes in vital signs in subjects on stable antipsychotic regimens (Trial **004-102**) or in patients with migraine headache (Trials **104-201** and **104-202**).

The sponsor reports that there were no important changes in vital signs observed with repeat dosing. In Trial **004-102**, a double-blind, placebo-controlled, clinical pharmacology study in non-agitated patients with Schizophrenia (N=32) in which safety and tolerability of 3 doses of *Staccato* Loxapine administered 4 hours apart were evaluated, no significant change in mean or individual vital signs were observed. In patients receiving the maximal dosing regimen (i.e., three 10 mg doses), mean changes from baseline in systolic BP were -1.75, -3.13, and -4.38 mm Hg. 10 minutes after the first, second, and third doses, respectively.

None of the marked abnormalities in vital signs showed a clear dose-response in any group.

7.4.4 Electrocardiograms

Electrocardiograms were recorded in Trials **004-107** (Thorough QT/QTc study) and **004-102** (clinical pharmacology study in non-agitated patients with Schizophrenia). Trial **004-107** was a negative Thorough QT/QTc study as defined in the ICH E14 guideline, 2005 (see **Section 4.4.2**)

ECG abnormalities in Trial **004-107** were observed in 2 subjects at 135 minutes and in 2 subjects at 5 hours after *Staccato* Loxapine treatment; in 3 subjects after 135 minutes and in 3 subjects at 5 hours after placebo treatment; and in 2 subjects after moxifloxacin treatment. The observed abnormalities were sinus bradycardia, first degree AV block, nonspecific T wave abnormality, sinus bradycardia, and right axis deviation. All of the observed abnormalities were judged as not clinically significant.

In Trial **004-102**, 12-lead ECGs were performed at screening, at baseline (before dosing), at 10 minutes after each dose, and at the end of the study. No clinically relevant abnormalities in ECG findings were reported. Most of the QTc outliers occurred in the placebo and 15 mg dose groups, and no clinically relevant dose-response patterns were observed in the QTc outlier counts (based on > 450 ms for males and > 480 ms for females). No patterns or dose-related trends were apparent in QTc changes from screening in the time-averaged analysis.

Table 62: QTc Outlier Frequencies in Post-Baseline ECGs (Safety Population): Trial 004-102 (electronically copied and reproduced from sponsor's submission)

Dose	Number (%) of ECGs with QTc Finding [number of subjects]					
	Number of		QTc (absolute)		QTc (change from baseline)	
	ECGs	Subjects	> 450/480 ms ^a	> 500 ms	> 30 ms	> 60 ms
Bazett's Correction						
Placebo	32	8	0	0	2 (6.3%) [2]	1 (3.1%) [1]
15 mg	32	8	3 (9.4%) [1]	2 (6.3%) [1]	3 (9.4%) [3]	1 (3.1%) [1]
20 mg	32	8	0	0	0	0
30 mg	32	8	1 (3.1%) [1]	0	0	0
TOTAL	128	32				
Fridericia's Correction						
Placebo	32	8	0	0	1 (3.1%) [1]	1 (3.1%) [1]
15 mg	32	8	2 (6.3%) [1]	1 (3.1%) [1]	1 (3.1%) [1]	1 (3.1%) [1]
20 mg	32	8	0	0	0	0
30 mg	32	8	0	0	0	0
TOTAL	128	32				

a. 450 ms for male subjects, 480 ms for female subjects.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Due to the small number of patients in some of the daily dose groups (i.e., 15 mg, n=20; 30 mg, n=16) in the agitated patient population (CSAP population), AEs with incidence $\geq 2\%$ often included only 1 patient for these dose groups and therefore are not an adequate or reliable basis for comparisons.

In general, the incidence of the most frequently reported AEs in the gastrointestinal, nervous system, respiratory, thoracic-and-mediastinal, and general-disorders-and-administrative-site disorders categories did not show significant increases in relationship to increases in the daily dose of *Staccato* Loxapine.

Dysgeusia, however, was the exception, demonstrating a lower incidence for the *Staccato* Loxapine 5 mg group compared to the higher doses of *Staccato* Loxapine 10 mg through 30 mg, each being greater than that for placebo. Overall and taking into consideration the number of subjects in each dose group, there appears to be reasonable evidence for a dose-dependent incidence of dysgeusia, as shown in the table below:

Table 63: Incidence of Dysgeusia by Daily Dose (Controlled Studies in Agitated Patient Population)

Adverse Event n (%)	Placebo (N=263)	<i>Staccato</i> Loxapine Total Daily Dose				
		5 mg (N=152)	10 mg (N=269)	15 mg (N=20)	20 mg (N=67)	30 mg (N=16)
Dysgeusia	13 (4.9%)	11 (7.2%)	37 (13.8%)	4 (20.0%)	12 (17.9%)	3 (18.8%)

7.5.3 Drug-Demographic Interactions

In the agitated patient population (CSAP population), there were no clinically important differences in the incidence of AEs based on demographic characteristics (age, sex, race, and weight), nor were there important differences in these safety evaluations by smoking status.

7.5.4 Drug-Disease Interactions

The overall incidence of adverse events experienced by Schizophrenia and Bipolar Disorder patients in the CSAP population was similar for the All *Staccato* Loxapine group (35.4% and 35.9%, respectively) and the placebo group (39.6% and 36.2%). Sedation was experienced at a greater incidence in the Schizophrenia patients (All *Staccato* Loxapine ~13% vs. placebo ~11%) than Bipolar Disorder patients (All *Staccato*

Loxapine ~6% vs. placebo ~3%). Conversely, dysgeusia was experienced at a greater incidence in the Bipolar Disorder patients (All *Staccato* Loxapine ~17% vs. placebo ~6%) than in the Schizophrenia patients (All *Staccato* Loxapine ~9% vs. placebo ~5%). For all other adverse events represented by $\geq 2\%$ of patients, there appeared to be little or no differences in incidence between Schizophrenia and Bipolar Disorder patients.

The AE profile in healthy volunteers was similar to that in patients in the CSAP population except that somnolence and dizziness were much more common in healthy volunteers (see **Sections 7.3** and **7.4.1**). This probably reflects the known increased sensitivity of healthy subjects to antipsychotics compared to subjects with Schizophrenia and Bipolar Disorder.

Subjects with asthma had a high incidence of bronchospasm (*Staccato* Loxapine ~27% vs. placebo ~4%), chest discomfort (*Staccato* Loxapine ~23% vs. placebo ~8%), wheezing (*Staccato* Loxapine ~15% vs. placebo 0.0%), and dyspnea (*Staccato* Loxapine 11.5% vs. placebo 0.0%). Subjects with COPD had a similar incidence of dyspnea (*Staccato* Loxapine 11.5% vs. placebo ~4%), and a slightly lower incidence of wheezing (*Staccato* loxapine ~8% vs. placebo 0.0%). Cough was a much more frequent airway AE for subjects with COPD (*Staccato* Loxapine 11.5% vs. placebo 0.0%) compared to subjects with asthma (*Staccato* Loxapine ~4% vs. placebo 0.0%).

In contrast, the most frequently reported respiratory system AEs in the CSAP population were throat irritation (All *Staccato* Loxapine 1.7% vs. placebo 0.4%), pharyngeal hypoesthesia (All *Staccato* Loxapine 0.6% vs. placebo 0.0%), and wheezing (All *Staccato* Loxapine 0.4% vs. placebo 0.0%). For healthy volunteers, cough was the most frequent respiratory system AE (All *Staccato* Loxapine ~7% vs. placebo ~2%).

The differences in incidence of airway adverse events may be at least partially explained by the underlying pathophysiology. Subjects with asthma by definition have reactive airway disease and therefore are more likely to manifest bronchospasm and wheezing. Subjects with COPD by definition have less reversible airway disease and would therefore be less likely to develop auditory wheezing, but instead may develop decreased air movement manifest as dyspnea (or decrease in FEV₁). One known cause of cough is acute bronchospasm which may be present without signs of wheezing. This is one possible explanation for the high incidence of cough in healthy volunteers, which would imply a significant respiratory effect of *Staccato* Loxapine in this group.

7.5.5 Drug-Drug Interactions

Since loxapine is a substrate for several cytochrome P450 (CYP) enzymes in addition to flavin-containing monooxygenases (FMO), the risk of metabolic interactions caused by an effect on an individual isoform is minimized. The primary metabolites in humans are amoxapine, 7-OH-loxapine, 8-OH-loxapine, and loxapine N-oxide. In vitro studies demonstrate that 7-OH-loxapine is formed mainly by CYPs 3A4 and 2D6, 8-OH-

loxapine is formed mainly by CYP1A2, amoxapine is formed mainly by CYP3A4 and 2C19, and loxapine N-oxide is formed by FMOs.

The potential for loxapine and its metabolites to inhibit CYP P450-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.

During chronic oral administration of loxapine, there have been rare reports in the literature of significant respiratory depression, stupor, and/or hypotension with the concomitant use of loxapine and lorazepam. Since intramuscular lorazepam was allowed as a rescue medication in the *Staccato* Loxapine controlled studies in agitated patients (CSAP) once the 2-hour efficacy measurements had been completed, an analysis of adverse events by co-administration of lorazepam was conducted. The AE profiles were similar in patients who received lorazepam and those who did not. Of note, the combined incidence of sedation/somnolence for subjects in the All *Staccato* Loxapine group who used lorazepam (8.6% vs. placebo 9.2%) was less than those who did not use lorazepam (7.1% vs. placebo 4.6%). There were no apparent effects of lorazepam use on the incidence of hypotension.

Table 64: Incidence of AEs by Preferred Term in $\geq 2\%$ of *Staccato* Loxapine Group by Use of Lorazepam (Controlled Studies in Agitated Patient population)

MedDRA Preferred Term	<i>Used lorazepam</i>		<i>Did not use lorazepam</i>	
	Placebo N=65	<i>Staccato</i> Loxapine N=70	Placebo N=198	<i>Staccato</i> loxapine N=454
Dysgeusia	3 (4.6%)	9 (12.9%)	10 (5.1%)	58 (12.8%)
Dizziness	3 (4.6%)	5 (7.1%)	20 (10.1%)	31 (6.8%)
Sedation/Somnolence	6 (9.2%)	6 (8.6%)	19 (9.6%)	57 (12.5%)
Headache	4 (6.2%)	2 (2.9%)	22 (11.1%)	15 (3.3%)
Stomach Discomfort Or Dyspepsia	0 (0.0%)	4 (5.7%)	4 (2.0%)	2 (0.4%)
Anxiety	0 (0.0%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
Euphoric Mood	0 (0.0%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
Fatigue	1 (1.5%)	0 (0.0%)	4 (2.0%)	9 (2.0%)

7.6 Additional Safety Evaluations

7.6.2 Human Reproduction and Pregnancy Data

There was one pregnancy reported during the clinical studies of *Staccato* Loxapine. The pregnancy was reported during Trial **104-202** (migraine out-patient study). On May 7,

2009, a 26-year-old patient (012-202) received *Staccato* Loxapine 2.5 mg. After 5 months, during Visit 3 (October 6, 2009), pregnancy was reported with estimated conception May 15, 2009 (confirmed by her gynecologist). The sponsor has submitted a 120-day Safety Update Summary on April 6, 2010, in which it is reported that the subject delivered a healthy baby on January 19, 2010.

For use in pregnancy, the Prescribing information for Loxapine Capsules provides the following guidance:

“Safe use of loxapine during pregnancy or lactation has not been established; therefore, its use in pregnancy, in nursing mothers, or in women of childbearing potential requires that the benefits of treatment be weighed against the possible risks to mother and child”.

For use in nursing mothers, the Prescribing information for Loxapine Capsules provides the following guidance:

“The extent of the excretion of loxapine or its metabolites in human milk is not known. However, loxapine and its metabolites have been shown to be transported into the milk of lactating dogs. Loxapine administration to nursing women should be avoided if clinically possible.”

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Prescribing Information for Loxapine Capsules states the following:

“Signs and symptoms of overdosage will depend on the amount ingested and individual patient tolerance. As would be expected from the pharmacologic actions of the drug, the clinical findings may range from mild depression of the CNS and cardiovascular systems to profound hypotension, respiratory depression, and unconsciousness. The possibility of occurrence of extrapyramidal symptoms and/or convulsive seizures should be kept in mind. Renal failure following loxapine overdosage has also been reported.”

In the sponsor’s literature search, several reports of overdose related to loxapine administration were found (see **Section 9**). Seizures were a common manifestation.

Staccato Loxapine is intended for acute administration and has not been studied in humans for its potential for abuse, tolerance, or physical dependence. There is no mention of abuse potential in the Prescribing Information for Loxapine Capsules, and the antipsychotics as a class are not associated with abuse liability. A single report in the literature describes 3 patients seeking prescriptions for loxapine.

7.7 Additional Submissions/Safety Issues

7.7.1 Effect on Ability to Drive or Operate Machinery

The Prescribing Information for Loxapine Capsules includes the following guidance:

“Loxapine, like other antipsychotics, may impair mental and/or physical abilities, especially during the first few days of therapy. Therefore, ambulatory patients should be warned about activities requiring alertness (e.g., operating vehicles or machinery) and about concomitant use of alcohol and other CNS depressants”.

Since the combined incidence of sedation and somnolence in the CSAP population was increased in the *Staccato* Loxapine groups compared to placebo, the sponsor advises that patients should be cautioned about operating hazardous machinery, including automobiles, following treatment with *Staccato* Loxapine.

7.8 Clinical Safety Conclusions

Staccato Loxapine was reasonably safe and well-tolerated in the overall safety population but not in the pulmonary safety population (subjects with asthma or COPD). In general, the adverse events associated with *Staccato* Loxapine were either expected from the known adverse event profile of loxapine or related to the method of loxapine administration (inhalation). Throughout the clinical program, only 6 SAEs were reported, none of which were considered related to *Staccato* Loxapine. One SAE (a reported drug overdose in a placebo-treated patient with a history of heroin and cocaine abuse) resulted in death. There was a very low incidence of AEs that led to premature discontinuation (for the overall safety population 6/1653, 0.4%). Two of these events were considered related to *Staccato* Loxapine: urticaria in a healthy subject who received *Staccato* Loxapine 5 mg; and bronchospasm in a patient with agitation treated with *Staccato* Loxapine 10 mg.

In the agitated patient population, the most frequently reported AEs in patients treated with *Staccato* Loxapine were dysgeusia (All *Staccato* Loxapine 12.8%) and sedation (All *Staccato* Loxapine 10.5%). Most AEs (96.3%) were mild to moderate. Dysgeusia, sedation (including sedation combined with somnolence), fatigue, and throat irritation were identified as potential adverse reactions associated with *Staccato* Loxapine (incidence rate $\geq 2\%$ and greater than placebo in either the 5-mg or 10-mg *Staccato* Loxapine groups). Akathisia and tremor were observed rarely, each occurring in 2 patients (0.4%), and there was one report of neck dystonia combined with oculogyration. There were a few reports of hypotension, but no clinically important effects on mean clinical laboratory values, mean vital signs, or ECGs.

Both asthma and COPD patients had more respiratory symptoms (wheezing, bronchospasm, and dyspnea) and/or changes in flow parameters (eg, FEV₁) after *Staccato*

Loxapine treatment than after placebo treatment. Eighteen (69%) loxapine-treated subjects with asthma and fifteen (~58%) loxapine-treated subjects with COPD had notable respiratory signs or symptoms (defined as FEV₁ decrease from baseline of $\geq 20\%$, an airway AE, or use of rescue medication). Although a high incidence of respiratory adverse events was not found in the CSAP population, it is noteworthy that subjects with clinically significant acute or chronic pulmonary disease, such as clinically apparent asthma, chronic bronchitis, or emphysema, were excluded. In addition, although there were no incidences of wheezing or bronchospasm in the healthy volunteer population, a high incidence of cough (~7%) was noted, which may be suggestive of underlying airway disease. Furthermore, in the pulmonary safety study in healthy adults (Trail **004-104**), maximum FEV₁ decreases of $\geq 15\%$ or $\geq 20\%$ were more common after *Staccato* Loxapine treatment than placebo treatment. Thus, respiratory adverse events in the target population are a relevant clinical concern.

8 Post Market Experience

There is no postmarket experience with *Staccato* Loxapine for Inhalation. However, the sponsor has reviewed and summarized safety data from individual studies and/or review articles of oral and intramuscular loxapine (see **Section 9.1**).

9 Appendices

9.1 Literature Review/References

9.1.1 Sponsor's Methodology

The sponsor conducted a comprehensive review of the literature through a search of Ovid MEDLINE, Cambridge Scientific Abstracts (CSA) PsycINFO, and EMBASE. The final literature citation list comprised 3461 citations.

9.1.2 Safety Findings

CNS Adverse Effects

Most adverse effects of oral loxapine reported in the literature are CNS-related, including sedation and extrapyramidal symptoms (akathisia, dystonia, rigidity, and tremors). Loxapine appears to be more sedating than other typical antipsychotics. In general, sedation (or similar adverse event e.g. drowsiness, sleepiness, lethargy, fatigue, and somnolence) is the most common reported adverse event, noted in 73 publications. Sedation is dose-dependent and occurs following initial loxapine administration in

advance of improvement of psychotic status and in advance of extrapyramidal symptoms (EPS). The incidence of EPS following loxapine administration for the treatment of Schizophrenia in early studies was ~39%. In general, the incidence of EPS is dose-dependent and appears to disappear several hours after acute administration of loxapine in most cases. As with other antipsychotics, chronic loxapine administration may lead to tardive dyskinesia. Neuroleptic malignant syndrome (NMS) has rarely been associated with loxapine administration and resulted in death in one instance. Seizures have been reported following administration of loxapine.

Cardiovascular Effects

Cardiovascular AEs were reported in 43 of the safety reports reviewed. Most commonly reported were hypotension in 20 (including orthostatic hypotension in 9) publications and tachycardia in 18 reports. Hypotension is rare or absent with lower loxapine doses, but occurs in a significant portion of patients at oral doses >150 mg/day. Tachycardia may be present in up to 82% of subjects after therapeutic doses, but pulse rates typically return to normal values after several days of treatment, and in no instance was tachycardia associated with ventricular arrhythmias. Although loxapine blocks the hERG channel, it does so at a much higher concentration compared to other antipsychotics known to produce QTc prolongation, indicating a relatively low risk for QTc prolongation after loxapine at therapeutic doses. QT prolongation was reported in 3 out of 10 patients who overdosed loxapine in one study, but ventricular arrhythmias were not reported.

Other Adverse Effects

Other reported adverse effects reported with loxapine administration have include anticholinergic effects (dry mouth due to decreased salivation, nasal congestion, constipation, blurred vision, urinary retention, and paralytic ileus), drug-induced rashes, and isolated cases of transient liver enzyme elevation. As with other antipsychotics, case reports of hematologic abnormalities, including agranulocytosis, following loxapine administration exist, but such events are rare after loxapine administration compared to its structural analog, clozapine. Reports of metabolic abnormalities including hyperglycemia have also been described. Loxapine elevates serum prolactin, which, when administered chronically, may lead to impotence, galactorrhea, gynecomastia, and amenorrhea.

Mortality

There were 15 deaths identified in the loxapine literature. These were attributable to suicide and/or overdose (n=8), death-NOS (n=2), myocardial infarction/heart disease (n=2), neuroleptic malignant syndrome (n=1), head injury during altercation (n=1), and opioid-neurotoxicity (n=1). In comparison to risperidone, loxapine was found to have the lowest increase in mortality ratio of the conventional antipsychotics.

Safety of Loxapine after Parental Administration

The effects of IM loxapine administration were evaluated in ~20 published studies of doses ranging from 10 to 200 mg. The adverse effects of loxapine following parenteral delivery appear to be similar to those reported after its oral administration. Thus, increasing the rate of delivery of loxapine and bypassing hepatic metabolism does not appear to be associated with increased incidence of adverse effects.

Safety in Pregnancy and Lactation

Antipsychotics readily cross the fetal-placental barrier. In the literature, French reports of possible teratological effects of loxapine have been described, but no epidemiological studies of congenital anomalies in infants born to women treated with loxapine during pregnancy have been reported.

Overdose

Four literature reports deal specifically with loxapine overdose. The first was a report of 2 adult suicides: a 22 year old female who ingested 50 x 50mg capsules, developed seizures during transport to the hospital, and never regained consciousness, and a 32 year old female who was found dead after taking loxapine and possibly other drugs. In addition, a 20 month old female ingested an unknown number of 50 mg capsules and exhibited oculogyric movements and involuntary movements of the lower extremities, and an 8 year old male was administered 375 mg (instead of the intended 15 mg) of loxapine and received activated charcoal 45 minutes after ingestion. Both children recovered without sequelae. In the other reports, sedation and seizures were common, and one patient who ingested 790 mg of loxapine and 56 mg of benztropine experienced a seizure and died of cardiac arrest.

Abuse, Tolerance, or Physical Dependence

Although antipsychotics as a class, including loxapine, are not associated with abuse liability, one report was identified in the literature search of 3 patients who presented to their emergency department requesting prescriptions for loxapine succinate. The patients reported that loxapine provided a warm, relaxed feeling. All three patients were in their early thirties, gave histories of sleep and mood disturbances as well as brief hallucinatory episodes and had long histories of outpatient psychiatric care for antisocial or borderline personality disorders and polypharmacy.

9.2 Labeling Recommendations

In view of the numerous and profound issues that would need to be addressed prior to approval and my recommendation for Complete Response action, no labeling recommendations will be made at this time.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting is planned for this application.

Francis E. Becker, M.D., F.A.C.P.
Medical Officer,
FDA CDER ODE1 DPP HFD 130

cc: NDA 22549
HFD 130
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/s/

FRANCIS E BECKER
09/17/2010

ROBERT L LEVIN
09/17/2010

DIVISION OF PULMONARY, ALLERGY, and RHEUMATOLOGY PRODUCTS
MEDICAL OFFICER CONSULTATION

1. General Information

Date: August 25, 2010
To: Thomas Laughren, M.D., Director, Division of Psychiatry Products
From: Anya Harry, M.D., Ph.D., Medical Reviewer
Through: Theresa Michele, M.D., Medical Team Leader
Through: Sally Seymour, M.D., Deputy Division Director, Safety
Through: Badrul Chowdhury, M.D., Ph.D., Division Director
Subject: Pulmonary Toxicity Review for Inhaled Loxapine

NDA/IND#: NDA 22-549
Applicant: Alexza Pharmaceuticals, Inc.
Drug Product: Loxapine
Request From: Kimberly Updegraff
Date of Request: December 23, 2009
Date Received: December 23, 2009
Date Due: September 13, 2010
Materials Reviewed: Sections of NDA 22-549 related to pulmonary toxicity of drug product, including eCTD Module 1, including proposed labeling; eCTD Module 2, including Summary of Clinical Safety; eCTD Module 5, including Integrated Safety Summary; as well as prior DPARP consults for this drug product (dated 8/28/07, 11/14/08, 3/29/09, and 6/29/09).

2. Executive Summary

This is a Medical Officer Consultation intended to respond to a request for consultation by the Division of Psychiatry Products (DPP) to evaluate the pulmonary safety of NDA 22,549 for Staccato® Loxapine submitted by Alexza Pharmaceuticals. Staccato® Loxapine for Inhalation (Staccato Loxapine) is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery by inhalation of a thermally generated aerosol of loxapine. Oral inhalation through the Staccato device triggers the controlled rapid heating of a thin film of excipient-free loxapine to form a drug vapor which is then inhaled. This represents a new formulation delivered by a new device for loxapine, which is a member of the subclass of tricyclic antipsychotic/anti-anxiety agents available in the United States since 1975 [NDA 17-525].

The exact therapeutic action of loxapine is unknown, but it is thought to be mediated by the binding of loxapine with high affinity to dopamine D₂ receptors as an antagonist as well as binding with high affinity to serotonin 5-HT_{2A} receptors. Loxapine is marketed in oral and parenteral formulations under the name Loxitane. The intramuscular form (not currently marketed in the United States) has been shown to be effective in treatment of acute agitation and is approved for prompt symptomatic control in acutely agitated schizophrenia patients [NDA 18-039, 1979]. Alexza Pharmaceuticals has undertaken the development of an inhaled formulation of loxapine to provide a rapid onset alternative to the slow acting oral formulation and to eliminate the potential risk of needle stick injury to caregivers with the parenteral formulation in the immediate treatment of acute agitation in patients with schizophrenia and mania of bipolar disease.

DPARP has provided four prior consultations to DPP during the Staccato Loxapine development program. At the onset, DPARP advised that the Sponsor did not have adequate assessment for the possibility of Staccato Loxapine causing acute bronchospasm. Incorporating many of the recommendations provided by the Division during the IND development, the NDA now includes three Phase 1 studies assessing the pulmonary safety of Staccato Loxapine. These include one study in healthy subjects, one in patients with asthma, and one in patients with chronic obstructive pulmonary disease (COPD) who may be included in the target population intended to receive the drug product. DPARP has been asked to review and comment on the safety data related to pulmonary toxicity submitted to NDA 22-549 for this single use inhaled product. This consultation includes review of the 3 pulmonary safety studies in addition to review of pulmonary-related adverse events in the safety and efficacy studies.

Across the three pulmonary safety trials, FEV1 measures were decreased in Staccato Loxapine-treated subjects compared to placebo. These decreases were particularly marked and clinically significant in patients with asthma. Further, greater decreases, which did not quickly return to baseline, were found following the second dose of medication compared to the first. Of note, Staccato placebo-treatment also resulted in a modest decrease in lung function, suggesting that the Staccato device may play a role in causing the bronchospasm. The Sponsor used the term Airway related adverse events (AE) throughout the study to relate to a subset of preferred terms under the respiratory system organ class AEs that could suggest an effect on airways. Patients with both asthma and COPD had more airway-related AEs than healthy subjects and a significant number of Staccato Loxapine treated subjects did not complete the study through the 34 hours of assessment. Based on these findings, DPARP recommends that the risk benefit profile of Staccato Loxapine use in a psychiatric population who may have known or unknown pulmonary comorbidities may not be favorable for approval. The acute bronchospasm and related AEs seen in the patients with known pulmonary disease treated with Staccato Loxapine was clinically significant. We are particularly concerned regarding the safety of Staccato Loxapine in patients whose pulmonary history may not be known during treatment for acute agitation as well as the ability of health care or home personnel to recognize and respond to post-dosing respiratory distress. However, if the new formulation and delivery device provides a significant advance over current available treatment according to DPP, DPARP recommends including appropriate information (e.g. warnings, contraindications) in the product label along with implementation of a REMS to ensure safe use.

The pulmonary safety database consisted of serial spirometry, airway-related adverse event (AE) data, oxygen saturation measured by pulse oximetry, vital signs, rescue medication use and sedation. Exposure to Staccato Loxapine for the evaluation of pulmonary safety included a total of 135 either healthy subjects or patients with asthma or COPD that underwent a full pulmonary evaluation and over 1,500 patients including agitated patients, healthy volunteers, non agitated patients on stable antipsychotic regimens and patients with migraine headaches for whom respiratory related adverse events were evaluated. The sample population specifically in the pulmonary safety studies received two doses of 10 mg inhaled loxapine with 8-10 hours in between dosing to allow for the resolution of the sedating effects and serial evaluations were carried out to 32-34 hours after Dose 1.

In the clinical trial in healthy subjects, the largest mean change in FEV1 following Staccato Loxapine treatment was -0.10 L (-0.18, -0.03) [LSmean (90% LSmean CI)], which occurred 15 minutes after the second dose. The largest mean change following Staccato placebo treatment was very similar -0.10 L (-0.18, -0.02) [LSmean (90% LSmean CI)], which occurred 30 minutes after the second dose. The pattern of FEV1 vs. time curves for placebo treatment and Staccato Loxapine treatment showed a parallel decrease in FEV1 after treatment. Twenty five of the 30 randomized subjects completed the study. Of those that did not, 3 discontinued due to either a significant decrease in lung function or lack of return to $\geq 85\%$ predicted baseline spirometry values. There were no reported changes in pulse oximetry or airway-related AEs of bronchospasm, wheezing, cough or dyspnea or clinically significant decline in SpO2 or use of rescue medication in the healthy subjects. In the healthy population there were 7 subjects out of 26 with a decline of $> 10\%$ FEV1 from baseline in the spirometry population (for both loxapine and placebo treatment). However, maximum FEV1 decreases of $\geq 15\%$ or $\geq 20\%$ were more common after Staccato Loxapine treatment than placebo treatment. In addition, maximum decreases of $\geq 15\%$ or $\geq 20\%$ were more common after Dose 2 of Staccato Loxapine than after Dose 1. None of the healthy subjects had a maximum FEV1 decrease of $\geq 25\%$ with either treatment. During the 32 hour follow-up, most of the largest decreases in FEV1 were at 15 minutes post dose.

The population of stable asthmatics sampled had mild to moderate disease. In the asthma population, the largest mean changes from baseline FEV1 in the Staccato Loxapine group were -0.303 L (-0.378, -0.228) [LSmean (90% LSmean CI)] at 15 minutes post Dose 1 and -0.537 L (-0.696, -0.378) at 15 minutes post Dose 2. Overall, 85% of asthmatics had a $\geq 10\%$ decrease in FEV1, and 42% had a $\geq 20\%$ decrease. Fifty-four percent of Staccato Loxapine-treated and 11.5% placebo-treated patients experienced airway-related AEs of bronchospasm, chest discomfort, wheezing or dyspnea. Use of rescue medication occurred in 54% of Staccato Loxapine treated patients and 11.5% placebo-treated. Ten patients, 9 of which were in the Staccato Loxapine group, discontinued due to either bronchospasm, wheezing, dyspnea or decrease in FEV1 $\geq 20\%$ baseline. There were no clinically significant changes in pulse oximetry, respiratory rate or heart rate. Subjects who had both an airway-related AE and a maximum FEV1 decrease $\geq 20\%$, were identified and further grouped into a category called “notable respiratory signs or symptoms”. When the Staccato Loxapine-treated subjects were compared across strata (i.e. FEV1 strata of $<80\%$ or $\geq 80\%$), notable respiratory signs or symptoms occurred in a larger percentage of subjects in the FEV1 $<80\%$ stratum: 9 (52.9%) of 17 subjects in the FEV1 $\geq 80\%$

stratum, and 8 (80%) of the 10 subjects in the FEV1 <80% stratum. Finally, for the placebo treated subjects, 3 (11.5%) had notable respiratory signs or symptoms.

For the COPD patients, the largest mean change following Staccato Loxapine treatment was -0.125 L (-0.204, -0.045) and following placebo-treatment was -0.077 L (-0.195, 0.042) [LSmean (90% LSmean CI)]. Of the 53 subjects treated, 45 received the two planned doses according to the protocol and 8 received only Dose 1. The most common reason for those not receiving Dose 2 was due to $\geq 20\%$ decrease in FEV1 or an AE of dyspnea, wheezing, or bronchospasm. Airway-related AEs overall were found in 5 (19%) Staccato Loxapine treated patients and 3 (11%) placebo treated patients. These events included dyspnea, cough, wheezing, FEV1 decrease, pulmonary congestion, bronchospasm or productive cough. Evaluation of the group with notable respiratory signs or symptoms for the COPD patients showed that 15 (57.7%) Staccato Loxapine-treated subjects would be included in this group (with 6 of the 15 subjects requiring 1 dose of albuterol per episode) and 6 subjects (22.2%) from the placebo treated would be in this group (with 4 of the 6 requiring one or two doses of albuterol per episode). Overall, there were no clinically significant changes in pulse oximetry or vitals.

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4. Background Information

4.1. Rationale

The antipsychotic effects of loxapine are due to its action on dopamine D₂ receptors. As well, there is limited evidence that loxapine shares some of its clinical effects with atypical antipsychotics due to its unique binding profile, particularly to serotonin 5HT_{2A} receptors. In a

previously marketed intramuscular injection formulation not currently marketed in the US, loxapine was effective in the treatment of acute agitation. Staccato Loxapine (5 mg and 10 mg) has been developed for the treatment of agitation in patients with schizophrenia or bipolar disorder. Currently available therapies for agitation have the limitations of slow onset of action (oral and IM agents), pain from administration (IM agents) and risks to caregivers of needle stick injuries (IM agents). Staccato Loxapine attempts to address the unmet need for rapid onset of action combined with a noninvasive administration.

The product is a hand-held single administration device that releases the drug as an aerosol generated by rapid heating (up to 400°C) forming a vapor followed by condensation and aerosol particle formation. The vapor is quickly cooled by the airflow generated by the patient's inspiration and condenses to form the appropriate predetermined particle size (mass median aerodynamic diameter of 0.5-3µm), capable of penetrating to deep lung. The Staccato® technology delivers aerosolized drug that is absorbed with intravenous (iv)-like kinetics. The rapid onset of activity delivered by the Staccato® technology combined with loxapine has been developed as a noninvasively delivered, rapidly acting dosage form of loxapine for use in treating acute agitation in patients with schizophrenia or bipolar disorder.

4.2. Proposed Indication

Staccato® Loxapine is proposed for the rapid treatment of agitation associated with schizophrenia or bipolar disorder.

4.3. Proposed Dosing

Loxapine is proposed as a single use product at the recommended dose of 10 mg administered by oral inhalation using the Staccato® system.

4.4. Summary of Prior DPARP Consults

Reviewer's Comment: On March 15, 2010 the Division of Pulmonary and Allergy Products, (DPAP) was renamed to Division of Pulmonary, Allergy, and Rheumatology Products. Thus, the Division name will be referred to as DPAP when reviewing the earlier consults.

DPAP completed 4 prior consults (dated August 28, 2007, November 14, 2008, March 29, 2009 and June 29, 2009) for DPP regarding the assessment of pulmonary toxicity and recommendations for further evaluation of lung-associated adverse effects in the Staccato Loxapine development program.

4.4.1. DPAP consult dated August 28, 2007

An End of Phase 2 (EOP2) Information Package was submitted prior to an EOP2 meeting scheduled for September 13, 2007. Study AMDC-004-101 to evaluate pulmonary safety in healthy volunteers was included in this package and was reviewed by the Division. No pulmonary-related AEs except for one "pharyngeal hypoesthesia" were reported. Pulmonary function assessments consisted of assessing FEV1 and FVC by spirometry pre-treatment and at 2 and 6 hours post-treatment. A central tendency analysis of the spirometry data was presented

while the spirometry data for each individual subject was presented in an appendix. There were a few subjects with decline in FEV1 of >10% (i.e. one subject in the 10mg treatment group had FEV1 decline of 600mL, 18% at the 2 hour post-dose time-point). The Division recommended that a responder analysis would be more informative than the analysis of central tendency. However, in this Phase 1 study of safety, Alexza failed to adequately assess subjects for the possibility of Staccato Loxapine causing acute bronchospasm. The recommendation to assess for acute bronchospasm had been conveyed to the Sponsor in a 30-day IND letter dated February 8, 2006. At that time, the Division acknowledged that pulmonary safety data would be extremely difficult to obtain in a population of agitated patients with schizophrenia who were just treated with a drug that causes dizziness and somnolence. It was therefore recommended that Alexza gather additional pulmonary safety data in Phase 1 and 2 studies including spirometric data at earlier time points after drug administration to assess for acute bronchospasm. Also of note, there was the potential for Staccato Loxapine to be administered several times within hours of each other to manage the acutely agitated patient. Therefore, it was recommended that pulmonary function be assessed after each of two doses. Finally, the PK of other inhaled non-pulmonary drugs, most notably inhaled insulin (i.e. Exubera) was significantly altered (increased exposure) in patients who smoke cigarettes. The Sponsor was advised to assess whether smoking affects PK in patients who receive Staccato Loxapine, especially since the 10 mg dose proposed in future clinical trials appeared to be the maximally tolerated dose in healthy individuals. Because of the anticipated potential difficulties in assessing the pulmonary safety in the planned phase 3 studies with agitated patients, DPAP recommended evaluation of the change in pulmonary function instead in healthy subjects and subjects with pulmonary disease, namely asthma and COPD. Alexza was also conducting a multi-dose PK study (AMDC 004-102) to assess the safety and PK of a maximum of 3 doses of Staccato Loxapine given at 4 hour intervals within a 24 hour period in non-agitated schizophrenic patients. The plan to collect pulmonary safety data in the overall proposed development program was not outlined in the meeting package, and therefore only general comments regarding the adequacy of the proposed development plan could be conveyed at that time.

4.4.2. DPAP consult dated November 14, 2008

In response to recommendations from DPAP, the Sponsor submitted a protocol for a Phase 1 pulmonary safety study in healthy subjects to be reviewed. The proposed trial, study AMDC-004-104, was a randomized, placebo-controlled, cross-over design study in approximately 30 healthy subjects to assess the pulmonary safety of 2 inhaled doses of 10 mg of the Staccato Loxapine product in a 24 hour period. The dose selected was the highest dose proposed for clinical use, and the two doses of medication were to be separated by an 8 hour period again, so the sedative properties of Loxapine would not interfere with spirometry testing. In addition, spirometry would be assessed 24 hours after the second dose of Staccato Loxapine or placebo.

The inclusion/exclusion criteria as well as the washout period of at least 4 days before cross-over were deemed adequate by the DPAP. Spirometry was scheduled to be assessed just prior to study medication administration and at 15, 30, and 60 minutes and 2, 4, 6, and 8 hours after the first and second doses of study medication and additionally at 24 and 32 hours after the second dose. Subjects would be confined to a clinical study center until at least 24 hours after the second dose. Spirometry would be performed according to current ATS guidelines and adequate safety precautions were in place in case significant bronchospasm was detected in study subjects.

4.4.3. DPAP consult dated March 29, 2009

The prior pulmonary safety study, AMDC-004-104, was to be conducted in healthy subjects. The Sponsor subsequently submitted the proposed protocols to evaluate safety in patients with pulmonary disease; Studies AMDC-004-105 and AMDC-004-108 in patients with mild to moderate asthma and COPD, respectively. The study in asthmatics only tested a single dose of 10 mg of loxapine. The study in patients with COPD also tested only a single lower dose of 5 mg of loxapine. The Division again recommended that pulmonary safety be assessed after each of two 10 mg doses of Staccato loxapine separated by 6-12 hours and again at 24 hours after the second dose.

In addition, other recommendations included: adding a spirometry assessment at 10-15 minutes post-dose, assessing blood pressure serially out to 2-4 hours post dose, and limiting the age of the population to subjects ≥ 40 years of age in the COPD study. Given that current smokers would be allowed to enroll in study AMDC-004-108, the Division recommended that the Sponsor assess the pharmacokinetics of Staccato loxapine in subjects who smoke compared to nonsmokers.

4.4.4. DPAP consult dated June 29, 2009

Alexza did not incorporate some of the recommendations made in the March 29, 2009 consultation. Therefore, on April 6, 2009, the pulmonary medical reviewer, Dr. Anthony Durmowicz held a conference call with the Sponsor to clarify any misunderstanding regarding the dose and number of doses of Staccato loxapine to be used in the pulmonary safety studies. Subsequently, Alexza submitted revised versions of both protocols which incorporated DPAP’s previous comments and were consistent with previous discussions as to the extent of pulmonary safety information that would be required pre-approval. The amended safety protocols (studies AMDC-004-105 and AMDC-004-108) were acceptable to the Division.

5. Pulmonary Safety Studies

The pulmonary safety studies reviewed in this consult are shown in Table 1.

Table 1. Pulmonary Safety Studies

Study	Study Title	N	Number of doses 10 mg
004-104	Pulmonary Safety of Repeat Doses of Staccato Loxapine in Healthy Volunteers	30	2
004-105	Pulmonary Safety of Staccato Loxapine for Inhalation in Subjects with Asthma	52	2
004-108	Pulmonary Safety of Staccato Loxapine for Inhalation in Subjects with Chronic Obstructive Disease	53	2

5.1. Review of Individual Studies

5.1.1. Study AMDC-004-104

Title

Pulmonary Safety of Repeat Doses of Staccato® Loxapine for Inhalation in Healthy Volunteers

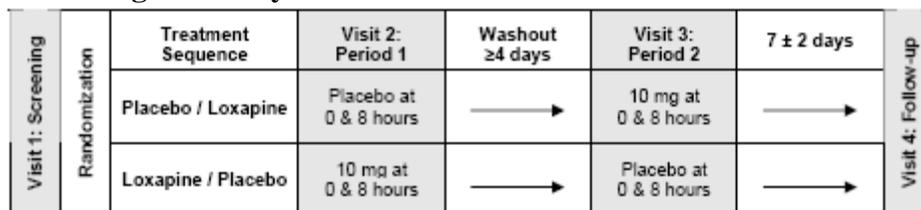
Primary Objective

The objective was to assess the pulmonary safety of 2 inhaled doses of 10 mg Staccato Loxapine within a day.

Study Design and Conduct

This Phase 1, single-center, randomized, double-blind, placebo-controlled, 2-period crossover study was designed to assess the pulmonary safety of Staccato Loxapine, 10 mg, administered as 2 doses within a day. Subjects were healthy, nonsmoking, males and females, 18 to 65 years old, with a body mass index (BMI) of 21 to 35. The study enrolled 30 subjects who were randomized to receive either Staccato Loxapine or Staccato Placebo (which was a functioning Staccato device with no reported excipients or loxapine) in Period 1 and the alternate treatment in Period 2 (1:1 randomization). There were 4 study visits. Screening took place at Visit 1. During Visit 2, the treatment assigned to Period 1 was administered (2 doses, 8 hours apart). During Visit 3, the treatment assigned to Period 2 was administered (2 doses, 8 hours apart). A washout period of at least 4 days separated Visits 2 and 3. Visit 4 was the end-of-study follow-up visit, which occurred 7±2 days after Visit 3. The study design is presented schematically in Figure 1.

Figure 1. Design of Study AMDC-004-104



Each treatment consisted of 2 doses given 8 hours apart; inhalation treatment occurred at 0 and 8 hours.

Source: CSR AMDC-004-104, Figure 1

Assessments (spirometry, SpO₂, respiratory rate, heart rate, and sedation) in each period were performed in the hour before the first dose and at 0.25, 0.5, 1, 2, 4, 6, 8, 8.25, 8.5, 9, 10, 12, 14, 16, 24 and 32 hours after the first dose. The 8-hour assessments were performed just before the second dose was administered. AEs were recorded before the first dose, at all assessment times from 0.25 to 32 hours after the first dose, and whenever volunteered by the subject or noted by study center staff. Additional safety assessments included periodic blood pressure measurements and physical examinations. The 8-hour interval between doses was selected to allow sedation from Dose 1 of Staccato Loxapine to subside before Dose 2 was administered. The washout (≥4 days) between treatment periods was selected based on the terminal half-life data from a single-dose pharmacokinetic study, AMDC-004-101. The mean half-life was 6.19 hours for loxapine and 9.55 hours for the metabolite, 7-OH-loxapine. Consequently, the 4-day washout period was greater than 5 half-lives. If a subject's FEV₁ decreased by ≥20% from the same-period baseline after any dose, or if there were any AEs of wheezing, dyspnea, or bronchospasm, the subject was not to receive additional doses of study treatment. Albuterol via metered-dose inhaler or nebulizer could be administered as clinically indicated. Subjects were to be followed with repeat

spirometry testing every 0.5 hour until the FEV1 returned to within 10% of same-period baseline, at which time spirometry testing continued on the routine schedule.

Inclusion Criteria

- Subjects who spoke, read and understood English and were willing and able to provide written informed consent.
- Subjects willing and able to be confined to a clinical research facility for approximately 48 hours (including 2 overnight stays) for each treatment visit and to comply with the study schedule and study requirements.
- Subjects in good health as determined by a complete medical history, PE, 12-lead electrocardiogram (ECG), blood chemistry profile, hematology and urinalysis.
- Subjects with normal spirometry at screening and baseline, as demonstrated by FEV1 \geq 85% of predicted and FVC \geq 85% of predicted and room air oxygen saturation \geq 95% as measured by pulse oximetry.
- Female subjects (if of child-bearing potential and sexually active) and male subjects (if sexually active with a partner of child-bearing potential) who agreed to use a medically acceptable and effective birth control method throughout the study and for 1 week following the end of the study.

Exclusion Criteria

- Subjects who had received an investigational drug within 30 days (or within 5 half-lives of the investigational drug, if >30 days) prior to Visit 2.
- History of asthma, COPD, or any other acute or chronic pulmonary disease.
- Subjects who had previously used a bronchodilator prescribed for a diagnosis of wheezing, bronchospasm, asthma, or COPD.
- Subjects who had an upper respiratory tract infection in the prior 6 weeks or bronchitis or pneumonia in the prior 6 months.
- History in the past year of a cough lasting more than 2 weeks following an upper respiratory tract infection.
- Subjects who had any acute illness within 5 days of either Visit 2 or Visit 3.
- Subjects who had hypotension (systolic blood pressure \leq 90 mm Hg, diastolic blood pressure \leq 50 mm Hg) or hypertension (systolic blood pressure \geq 140 mm Hg, diastolic blood pressure \geq 100 mm Hg) at screening or baseline.
- Subjects with significant hepatic, renal, gastroenterologic, cardiovascular (including ischemic heart disease and congestive heart failure), endocrine, neurologic (including history of seizures or stroke), or hematologic disease.
- Subjects who had taken prescription or nonprescription medication (with the exception of vitamins, acetaminophen, oral contraceptives, and ibuprofen) within 5 days of the first treatment day (Visit 2).
- Subjects who regularly consumed large amounts of xanthine-containing substances (i.e. more than 5 cups of coffee or equivalent amounts of caffeine- or xanthine-containing substances, including herbal supplements or energy drinks, per day).
- Subjects who reported any tobacco use within the last year or who had a positive urine cotinine test or exhaled carbon monoxide test for recent smoking.

- Subjects who had a history within the past 2 years of drug or alcohol dependence or abuse.
- Subjects who tested positive for alcohol or who had a positive urine screen for drugs of abuse at any visit.
- History of human immunodeficiency virus (HIV) positivity.
- History of allergy or intolerance to loxapine or amoxapine.
- Breastfeeding or had a positive pregnancy test at any visit.

Pulmonary Safety Assessments

Assessments were to be performed in the 5 minutes before the nominal time and in the order listed below:

- AE assessment
- SpO₂
- Respiratory rate, heart rate
- Sedation (VAS- Visual Analog Scale for Sedation)
- Spirometry (as close as possible to the nominal time point)
- In addition, in both Periods 1 and 2, post-treatment blood pressure measurements were obtained at 8 and 32 hours, and a brief physical examination was performed at 32 hours.

Reviewer's Comment:

The Sponsor used the term Airway related adverse events throughout the study to relate to a subset of the preferred terms (PT) under the respiratory, thoracic and mediastinal disorders system organ class (SOC) combined with one preferred term from the investigations SOC of MedDRA version 10.0 that could suggest an effect on airway, specifically: dyspnea, cough, wheezing, FEV1 decreased, pulmonary congestion, bronchospasm and productive cough.

Statistical Analyses

Spirometry tests were assessed for adequacy by an external blinded rater (using the ATS/ERS criteria), and for repeatability by the study center. Evaluation of spirometry data included determination of LSmeans and 90% LSmean confidence intervals (LSmean CIs) for differences between treatments in the change from same-period baseline to each assessment time, using a mixed-model analysis of variance (ANOVA) with fixed terms for treatment, period, and sequence, and a random term for subject. Similarly, LSmeans and 90% LSmean CIs were provided for sedation level, heart rate, respiratory rate, and SpO₂ at each time point using mixed-model ANOVAs at each time point for both the changes from same-period baseline and the post-treatment values. In the analyses of FEV₁, FVC, and FEV₁/FVC data, descriptive statistics were provided for the following: number of subjects with FEV₁ $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$ maximum change from same-period baseline after each dose and after either dose; number of subjects with FEV₁ $\geq 0\%$, $\geq 1\%$, $\geq 2\%$, $\geq 3\%$, $\geq 4\%$, $\geq 5\%$, $\geq 6\%$, $\geq 7\%$, $\geq 8\%$, $\geq 9\%$, $\geq 10\%$, $\geq 15\%$, $\geq 20\%$, or $\geq 25\%$ maximum percentage change from same-period baseline after each dose and after either dose; proportion of subjects with each FEV₁ change at each time point for each treatment; and FVC and FEV₁/FVC at each time point for each treatment (including LSmeans and 90% LSmean CIs for the changes from same-period baseline and post-treatment values). Summary statistics also were provided for the sedation level, heart rate, respiratory rate, and SpO₂ at each time point after each treatment; subject disposition; population demographics and study-baseline

characteristics; exposure to study medication; AEs; blood pressure; and concomitant medications.

5.1.2. Study AMDC-004-105

Title

Pulmonary Safety of Staccato® Loxapine for Inhalation in Subjects with Asthma

Primary Objective

The objective of this trial was to assess the pulmonary safety of 2 inhaled doses of 10 mg Staccato® Loxapine within a day in subjects with mild to moderate persistent asthma.

Study Design and Conduct

This was a Phase 1, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, of 2 inhaled doses of Staccato Loxapine 10 mg given 10 hours apart in 52 subjects with mild or moderate persistent asthma. Subjects were randomly assigned to Staccato Loxapine or Staccato Placebo. Randomization was stratified based on the subject's pre-bronchodilator forced expiratory volume (FEV1) at screening (i.e. <80% or ≥80% of predicted), and subjects were randomized 1:1 within each stratum. There were 3 study visits. At Visit 1, subjects were screened for eligibility. At Visit 2, continued eligibility was confirmed, subjects were randomized, baseline measurements were obtained, study treatments were administered and post-treatment assessments were performed; Visit 2 occurred ≤28 days after Visit 1. At Visit 3, end-of-study assessments were performed; Visit 3 occurred 7 ± 3 working days after Visit 2. Subjects were allowed to continue asthma controller medications; however, quick-relief agents were withheld during the entire 34-hour assessment period unless required as rescue medication. Permitted asthma control medications included long-acting β-2 agonists, methylxanthines, tiotropium, leukotriene modifiers and inhaled corticosteroids. Asthma medications were to be given ≥2 hours before Dose 1 of study medication. Short-acting β-2 agonists (i.e. albuterol, fenoterol, terbutaline, levalbuterol) or short-acting anticholinergic agents (i.e. ipratropium), were not allowed, unless medically required, from 6 hours before study medication administration through 24 hours after the last study medication treatment. Albuterol via metered-dose inhaler or nebulizer could be used as clinically indicated if a subject's FEV1 decreased ≥20% from baseline after any dose of study medication, or a subject had an AE of wheezing, dyspnea, or bronchospasm. Such subjects were not eligible to receive Dose 2.

Inclusion Criteria

Eligible subjects were male and female nonsmoking subjects, 18 to 65 years old (inclusive), with a history of mild to moderate persistent asthma, in good general health, with a BMI between 21 to 35 kg/m² (inclusive), a screening pre-bronchodilator FEV1 ≥60% of predicted value, a history of FEV1 reversibility of ≥10% after administration of a short-acting bronchodilator documented at screening, and on an asthma drug regimen stable for ≥2 weeks prior to study medication administration. Female subjects (if of child-bearing potential and sexually active) and male subjects (if sexually active with a partner of child-bearing potential) who agreed to use a medically acceptable and effective birth control method throughout the study and for 1 week following the end of the study.

Reviewer's Comment:

Accepted evidence of variable airway obstruction is usually indicated by an increase in FEV1 of $\geq 12\%$ and $\geq 200\text{mL}$ after short acting $\beta 2$ agonist (SABA) according to the American Thoracic Society.

Exclusion Criteria

Subjects were excluded if they had a ≥ 10 pack-year smoking history; an acute illness in the 5 days before Visit 2; an upper respiratory tract infection in the 4 weeks before Visit 2, or bronchitis/pneumonia within 3 months of Visit 2; a diagnosis of another pulmonary disease; lung resection or other thoracic operation within 12 months of Visit 1; treatment in an emergency room or hospital admission for asthma exacerbation within 3 months of Visit 2; history of ventilator support for respiratory failure secondary to asthma; acute worsening of asthma requiring systemic corticosteroids or antibiotics in the 6 weeks before Visit 1; drug or alcohol dependence in the prior year or positive drug or alcohol screening test results; hypotension or hypertension; a clinically significant ECG abnormality; HIV positive or other significant systemic disease or condition that would present undue risk to the subject or may confound interpretation of study results.

Pulmonary Safety Assessments

Spirometry, use of rescue medication, sedation assessment, AE, serious adverse events (SAE), laboratory tests, vital signs, oxygen saturation by pulse oximetry, 12 Lead ECG and PE were all measured according to the schedule of assessments. Specifically, spirometry tests were performed in the hour before the first dose of study treatment was administered and at 0.25, 0.5, 1, 2, 4, 6, 10, 10.25, 10.5, 11, 12, 14, 16, 24, and 34 hours after that dose. The 10-hour assessments were performed just before the second dose was administered. For each spirometry test analysis was based on FEV1, FVC, and FEV1/FVC, with FEV1 serving as the primary criterion. Furthermore, at the time of each spirometry assessment, respiratory rate, heart rate, blood pressure (excluding the 6-, 14-, and 16-hour assessment), and oxygen saturation by pulse oximetry (SpO2) were measured; treatment-emergent adverse events (AEs) were recorded (excluding the 0.25-hour assessment); and sedation was assessed using a visual analog scale (VAS). Brief physical exams (PEs) were done upon entry to the study center before study medication administration (Visit 2) and full PEs were to be done at follow-up (Visit 3). Spirometry tests were performed according to ATS/ERS standards, using NHANES III predicted values. For each test, the largest FVC and the largest FEV1 were recorded from among the acceptable maneuvers. Tests were scored for adequacy by an independent physician reviewer, who remained blinded to treatment, and for repeatability by the study staff.

Statistical Analyses

Evaluation of spirometry data included determination of LSmeans and 90% LSmean confidence intervals (LSmean CIs) for differences between treatments in the change from baseline to each assessment time, using a 2-factor ANOVA model including terms for stratum and treatment. Descriptive statistics and graphical presentations were provided along with 90% confidence intervals (CIs) for the spirometry data (FEV1, FVC, and FEV1/FVC). All CIs were based on the LSmeans and residual sums of squares from the corresponding ANOVA models. Similarly, vital signs, oxygen saturation, and sedation VAS data were examined as secondary analyses. LSMeans and 90% CIs for the differences between treatments were calculated for the change

from baseline for each quantitative safety measure for each post-baseline time point. All CIs were based on 2-factor ANOVA models including terms for stratum and treatment. Descriptive statistics were calculated for all general quantitative safety measures (systolic and diastolic blood pressure, heart rate, respiration rate, temperature, SpO₂, and visual analog scale for sedation). Summary statistics were provided for subject disposition; population demographics and study-baseline characteristics; exposure to study medication; AEs; and concomitant medications.

5.1.3. Study AMDC-004-108

Title

Pulmonary Safety of Staccato® Loxapine for Inhalation in Subjects with Chronic Obstructive Pulmonary Disease

Primary Objective

The objective of this trial was to assess the pulmonary safety of 2 doses of 10 mg Staccato Loxapine within a day in subjects with chronic obstructive pulmonary disease.

Study Design and Conduct

This was a Phase 1, multicenter, randomized, double-blind, placebo-controlled, parallel-group pulmonary safety study of 2 inhaled doses of Staccato Loxapine 10 mg given 10 hours apart to subjects with an established history of chronic obstructive pulmonary disease (COPD). Fifty-three subjects were in the safety population, and 52 subjects were in the spirometry population. The safety population included all randomized subjects who received any study medication. The spirometry population included all subjects who received study medication, had a baseline FEV₁ measurement, and had at least 1 post-baseline FEV₁ measurement that was obtained before the use of rescue medication. Subjects were randomly assigned to Staccato Loxapine or Staccato Placebo and randomization was stratified based on the subject's post-bronchodilator FEV₁ at screening (i.e. <50% or ≥50% of predicted), and subjects were randomized 1:1 within each stratum. There were 3 study visits: Visit 1, subjects were screened for eligibility; Visit 2, continued eligibility was confirmed, subjects were randomized, baseline measurements were obtained, study treatments were administered, and post-treatment assessments were performed; and at Visit 3, end-of-study assessments were performed.

Inclusion Criteria

Eligible subjects were males and females 40 to 70 years old, with a history of established COPD, in good general health and on a stable COPD drug regimen for ≥2 weeks before Dose 1 of study medication. They were to have a >15 pack-year history of cigarette smoking, a BMI between 21 and 35, and a screening post-bronchodilator FEV₁ ≥40% of predicted and FEV₁/FVC <0.70.

Exclusion Criteria

Subjects were excluded if they had any acute illness in the 5 days before Dose 1, an upper respiratory tract infection in the 4 weeks before Dose 1, or pneumonia in the 3 months before Dose 1; acute worsening of COPD requiring systemic corticosteroids or antibiotics in the 6 weeks before screening, hospital treatment for COPD in the 3 months before Dose 1, or a history of requiring ventilator support for COPD; a diagnosis of another pulmonary disease; thoracic surgery or sleep apnea in the year before screening; current use or a history of chronic use of supplemental oxygen; a clinically significant electrocardiographic (ECG) abnormality;

hypotension or hypertension; HIV-positive or other significant systemic disease; drug or alcohol dependence in the prior year; or positive drug or alcohol screening test results.

Pulmonary Safety Assessments

Safety was assessed by serial spirometry testing (15 post-treatment assessment times over 34 hours), and each spirometry test was accompanied by assessment of AEs, SpO₂, respiratory rate, heart rate, and sedation. Additional safety evaluations included ongoing monitoring of AEs, assessments of blood pressure, and PE.

Statistical Analyses

Evaluation of spirometry data (FEV₁, FVC, and FEV₁/FVC) included determination of LSmeans and 90% confidence intervals (CIs) for (1) the change from baseline in each treatment group at each assessment time, and (2) the differences between treatments in the change from baseline to each assessment time, using a 2-factor analysis of variance (ANOVA) model, including terms for stratum and treatment. Descriptive statistics and graphical presentations were provided for the spirometry data. All CIs were based on the LSmeans and residual sums of squares from the corresponding ANOVA. Similarly, vital signs, SpO₂, and sedation VAS data were examined as secondary analyses. For each quantitative safety measure, LSmeans and 90% CIs for the differences between treatments were calculated for the change from baseline to each post-baseline time point and for the differences between treatments in the change from baseline to each post-baseline time point. All CIs were based on 2-factor ANOVA models, including terms for stratum and treatment. Descriptive statistics were calculated for all general quantitative safety measures (systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, SpO₂, and the sedation VAS). Summary statistics were provided for subject disposition, population demographics and study-baseline characteristics, exposure to study medication, AEs, and concomitant medications.

6. Pulmonary Safety Results

6.1. Safety in Healthy Subjects (Study AMDC-004-104)

6.1.1. Disposition of Subjects

Of 45 individuals screened, 30 were randomized and 25 of them completed the study, receiving all planned doses of study treatment. Five subjects discontinued prematurely for the following reasons: FEV₁ <85%, hospitalization for a SAE of perforated appendicitis 5 days after placebo treatment, personal problems, FVC < 85% predicted, and 24% decrease in FEV₁ after Dose 2 in Period 1. Four of the subjects who discontinued prematurely were randomized to the placebo-loxapine sequence. Of the 111 Staccato systems used in the study (combining Staccato Loxapine and Staccato Placebo), none were reported to have malfunctioned, and none were returned via Alexza's device complaint system.

6.1.2. Demographics

See Table 2 below for details.

Table 2. Study AMDC-004-104, Demographics and Baseline Characteristics (Safety Population)

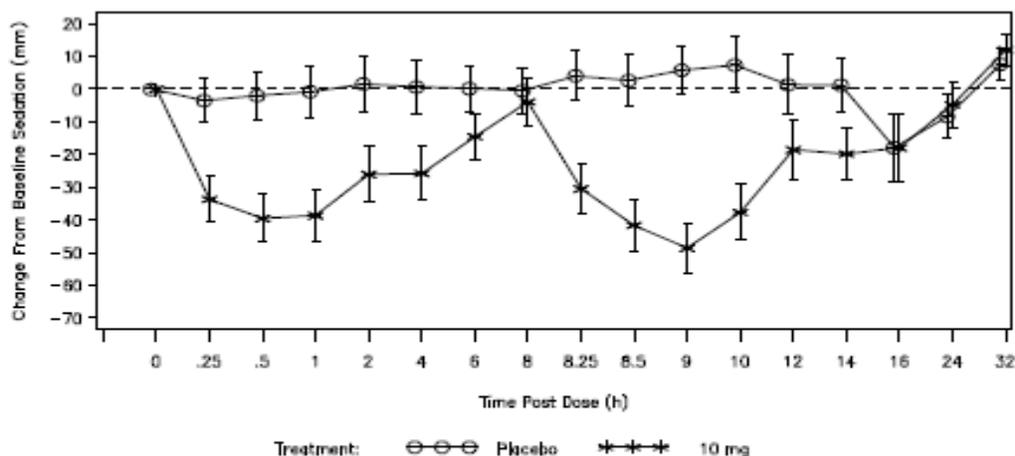
Demographic or Baseline Characteristic	Placebo/Loxapine Sequence (N=15)	Loxapine/Placebo Sequence (N=15)	Total (N=30)
Gender, n (%):			
Female	5 (33.3%)	5 (33.3%)	10 (33.3%)
Male	10 (66.7%)	10 (66.7%)	20 (66.7%)
Age (years):			
Mean (SD)	31.4 (13.65)	28.7 (9.75)	30.0 (11.74)
Median	25	24	24.5
Minimum, maximum	20, 63	20, 55	20, 63
Race, n (%):			
Caucasian	14 (93.3%)	14 (93.3%)	28 (93.3%)
Other	1 (6.7%)	1 (6.7%)	2 (6.7%)
Height (cm):			
Mean (SD)	171.0 (9.19)	171.3 (8.10)	171.2 (8.51)
Median	175.3	170.2	170.2
Minimum, maximum	157.5, 185.4	158.8, 190.5	157.5, 190.5
Weight (kg):			
Mean (SD)	80.12 (15.248)	77.49 (13.976)	78.80 (14.434)
Median	78.2	76.4	77.3
Minimum, maximum	55, 112.7	58.6, 104.5	55, 112.7
Smoking history, n (%):			
Never smoked	12 (80.0%)	14 (93.3%)	26 (86.7%)
Ex-smoker	3 (20.0%)	1 (6.7%)	4 (13.3%)

Section 10.1, Table 1.6.1., 1.7

6.1.3. Sedative Effects

As sedation is a known effect of loxapine, the Sponsor evaluated the potential contribution of sedation on pulmonary function test performance. The level of sedation was assessed immediately before each spirometry assessment using a visual analog scale (VAS) with ranges from “sleepy” (0) to “awake” (100). Baseline sedation scores were 83.5 (78.2, 88.8) before placebo treatment and 78.3 (73.0, 83.6) before loxapine treatment [LSmean (90% LSmean CI)]. Sedation was apparent after each dose of loxapine (Figure 2). The maximum mean sedation occurred 30 minutes to 1 hour after each dose of loxapine and was greater after the second dose. Sedation was also observed in the placebo group at 16 hours, corresponding to typical bed-time hours. Refer to Figure 2 for the pattern and duration of sedative effects for both Staccato placebo and Staccato Loxapine treated healthy subjects.

Figure 2. Study AMDC-004-104, Sedation Change from Same-Period Baseline, by Treatment (Spirometry Population)



LSMean, 90% LSMean CI

Program Name:f-3-19.sas Date:19AUG2009: 7:35:41 Source Data:Table 3.25

LSmean and 90% LSmean CI; a negative excursion indicates a sedative effect

Source: Section 10.1, Table 3.25

Reviewer’s Comment:

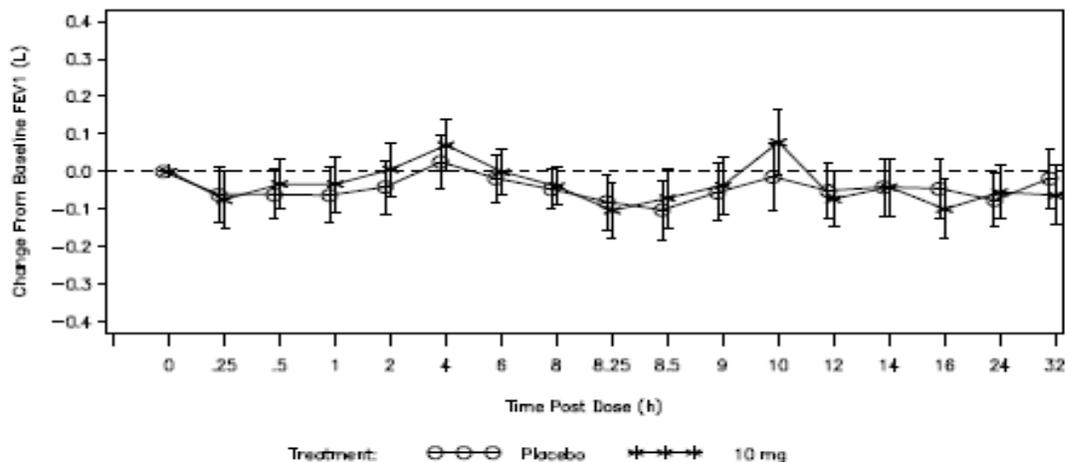
The data for defining cut off points or clinically significant sedation scores in the VAS are not provided.

6.1.4. Spirometry Findings

• **FEV1**

Measurement of the pulmonary function following treatment with either Staccato Loxapine or Staccato Placebo revealed the following results. Baseline pulmonary function measures, FEV1, FVC, FEV1/FVC were all similar before administration of Staccato Placebo and Staccato Loxapine. Specifically, the FEV1 was 4.07 L (3.78, 4.36) before Dose 1 of placebo, and 4.01 L (3.72, 4.30) before Dose 1 of loxapine [LSmean (90% LSmean CI)]. The changes from same-period baseline FEV1 after placebo and loxapine treatment had similar profiles over the 16 assessment times in the 32-hour observation period, as seen in Figure 2. The largest change in FEV1 following loxapine treatment was -0.104 L (-0.178, -0.031) [LSmean (90% LSmean CI)], which occurred 8.25 hours after the first dose (i.e. 15 minutes 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 (i.e. 30 minutes after the second dose). Also of note, there were no significant changes in SpO2 or airway-related AEs (i.e. no bronchospasm, wheezing, cough, dyspnea).

Figure 3. Study AMDC-004-104, FEV1 Change from Same-Period Baseline, by Treatment (Spirometry Population)



LSMean, 90% LSMean CI

Program Name:f-3-3.sds Date:19AUG2009: 7:34:10 Source Data:Table 3.15

LSmean and 90% LSmean CI

Source: Section 10.1, Table 3.15

Reviewer’s Comment:

In the healthy subjects, there was a loss of ~100 ml FEV1 after treatment with both loxapine and placebo. This 100 ml represents a 2.5% fall from baseline FEV1. To interpret the clinical significance of the change, the transient decrease in FEV1 seen during a bronchoprovocation diagnostic test may be used to provide a context. A fall in FEV1 that is accepted as significant for bronchial hyperresponsiveness is dependent on the bronchoprovocation test used: Methacholine Aerosol Challenge (20% fall of FEV1 at a dose of <4mg/ml); Exercise Challenge Tests (10% fall of FEV1); Histamine challenge (20% fall of FEV1 at a histamine concentration of 8mg/ml); Mannitol Inhalation (15% fall of FEV1); Hypertonic Saline Aerosol Challenge (15% fall of FEV1); Eucapnic Voluntary Hyperpnea (EVH) Test (10% fall of FEV1). The final three tests are unapproved methods of conducting airway hyper-responsiveness; however, the cutoff values for fall in FEV1 for these tests are provided, so that the reader can have some clinical context to apply the reported decreases in FEV1 observed in these studies. The 2.5% decrease in FEV1 falls short of the 10-20% decrease in FEV1 defined as clinically significant in these bronchoprovocation tests. Because these are mean numbers for the entire treatment group, it may be more relevant to look at number of patients with significantly decreased values as in the “responder analysis” shown below.

The results were subcategorized based on the range of maximal FEV1 ($\geq 10\%$, 15% and 20%) decrease at 8 hours after each dose and presented in Table 2. There were no differences in the percentage of subjects between placebo and loxapine at the $\geq 10\%$ category; however, there were a larger number of patients with decreases in FEV1 of $\geq 15\%$ or 20% after loxapine treatment than placebo, 5 and 1 respectively. These greater falls in FEV1 were observed after Dose 2 of loxapine. No subject had a maximum FEV1 decrease of $\geq 25\%$.

Table 3. Study AMDC-004-104, Maximum FEV₁ Decrease from Same-Period Baseline in the 8 Hours After Dosing-Decreases of at Least 10%, 15% or 20% (Spirometry Population)

	Maximum FEV ₁ decrease in the 8 hours after each dose ^{a,b}	Staccato Placebo (N=26)	Staccato Loxapine (N=26)
After either dose	≥10%	7	7
	≥15%	1	5
	≥20%	0	1
After Dose 1	≥10%	4	5
	≥15%	1	2 ^c
	≥20%	0	0
After Dose 2	≥10%	5	6
	≥15%	0	5
	≥20%	0	1

Table presents the number of subjects.

- This analysis was based on the 8 hours after each dose (ie, Hours 0.25 to 16) and excludes Hours 24 and 32. However, these two 8-hour windows included all subjects with an FEV₁ decrease of ≥15%.
- FEV₁ categories are cumulative (eg, a subject with a maximum decrease of 21% would be included in the ≥10%, ≥15%, and ≥20% categories)
- Subject 01-008 had a maximum decrease of 14.5% after Dose 1 of loxapine, which was rounded to 15% and resulted in his inclusion in this category. (His maximum decrease after Dose 2 of loxapine was 17%.)

Source: Section 10.1, Table 3.19

Using the safety population to look at all significant FEV₁ decreases, there were 3 more subjects (n=26 vs. 29) evaluated in the placebo group and 1 more (n=26 vs. 27) in the loxapine group. See Table 3. Overall, there were 3 more subjects that had decreases in FEV₁ ≥10% in the placebo group and 2 more in the loxapine group in the safety population. There was one additional subject captured with a decrease in the FEV₁ ≥ 15% and also ≥ 20% in the safety population. Looking over the course of the study, the largest change from baseline in a placebo treated subject was -40% associated with an AE of bronchospasm. The largest change in a loxapine treated subject was -46.1%, which was not associated with any airway AE.

Table 4. Study AMDC-004-104, Maximum FEV₁ Decrease from Same-Period Baseline at Any Assessment – Decreases of at Least 10%, 15%, or 20% (Safety Population)

	Maximum FEV ₁ decrease at any assessment ^a	Staccato Placebo (N=29)	Staccato Loxapine (N=27)
After either dose	≥10%	10	9 ^b
	≥15%	1	6
	≥20%	0	2

Table presents the number of subjects.

- FEV₁ categories are cumulative (eg, a subject with a maximum decrease of 21% would be included in the ≥10%, ≥15%, and ≥20% categories)
- Includes 1 test that was assessed as not adequate and not repeatable (Subject 01-025, Hour 16).

Source: Appendix 11.2

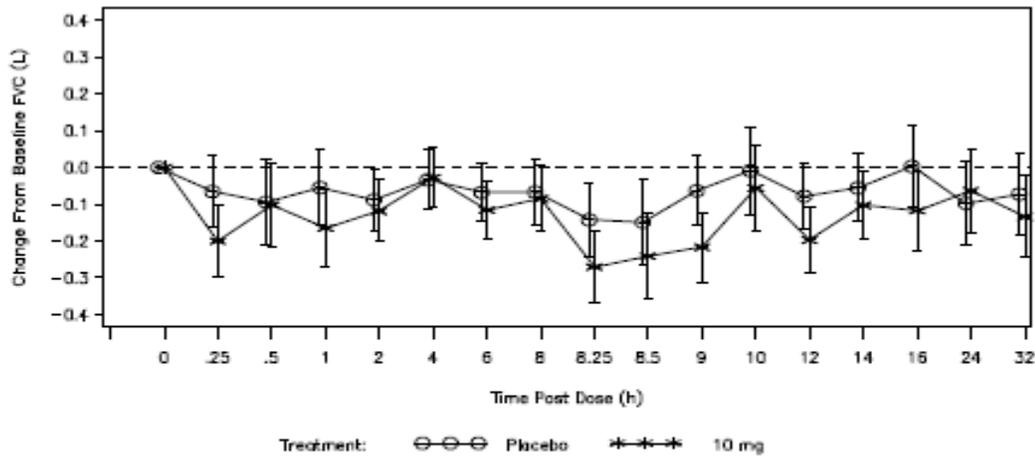
Reviewer's Comment:

Although the decrease in FEV1 for the group as a whole did not show a clinically significant decrease in FEV1, it is notable that in a “responder analysis” there were more patients with significant decreases in FEV1 in the loxapine group than in the placebo group, suggesting that loxapine induces some degree of airway hyperresponsiveness in a subgroup of normal people.

- **FVC**

The LSmean FVC decreased from same-period baseline at all assessment times after loxapine treatment and at most of the assessment times after placebo treatment, as seen in Figure 4. These systematic decreases were numerically larger after loxapine treatment than after placebo treatment, particularly after Dose 2. See Figure 4.

Figure 4. Study AMDC-004-104, FVC Change from Same-Period Baseline, by Treatment (Spirometry Population)

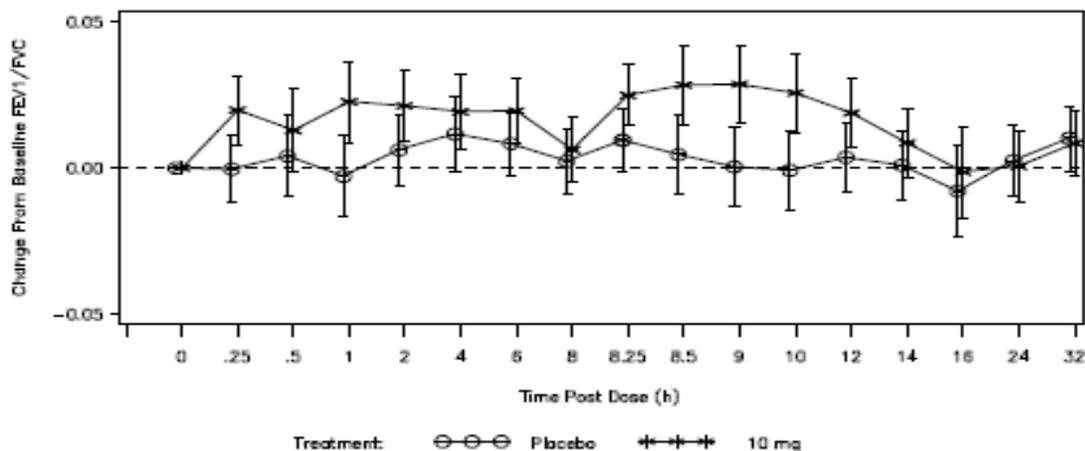


LSMean, 90% LSMean CI
 Program Name:f-3-61.sas Date:19AUG2009: 7:36:35 Source Data:Table 3.17
 LSmean and 90% LSmean CI
 Source: Section 10.1, Table 3.17

- **FEV1/FVC**

LSmean FEV1/FVC increased from same-period baseline at 15 of the 16 assessment times after loxapine treatment, and at 12 of the 16 assessment times after placebo treatment, as seen in Figure 5. These increases were larger after loxapine treatment than after placebo treatment, particularly after Dose 2.

Figure 5. Study AMDC-004-104, FEV1/FVC Change from Same-Period Baseline, by Treatment (Spirometry Population)



LSMean, 90% LSmear CI
 Program Name:f-3-63.sas Date:19AUG2009: 7:36:44 Source Data:Table 3.18
 LSmear and 90% LSmear CI
 Source: Section 10.1, Table 3.18

Reviewer’s Comment:

There appears to be a consistent increase in the change of the ratio of FEV1/FVC that returns to baseline in a similar time scale as the previous measures. It is unclear if this is consistent with noise; however, it is clearly the opposite of what would be expected in a mostly obstructive disease.

6.1.5. Treatment Emergent Adverse Events

Verbatim AE terms were translated to preferred terms and body systems according to the Medical Dictionary for Regulatory Activities (MedDRA® Version 10.0). MedDRA® terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). All AEs presented in this study report were treatment emergent. Adverse experiences that occurred before administration of Dose 1 in Period 1 are referred to as interim medical events. Investigators assessed treatment-emergent AEs for severity (mild, moderate, or severe) and relationship to study treatment (unrelated, possibly related, or probably related). More subjects had an AE after loxapine treatment compared with placebo treatment (placebo, 31.0%; loxapine, 59.3%). Dysgeusia was the only AE reported for more than 2 subjects after loxapine treatment (placebo, 3.4%; loxapine, 44.4%). There were no reports of bronchospasm, wheezing, cough, dyspnea, or other AEs. Most AEs were assessed as possibly or probably related to study medication. All AEs after loxapine treatment were mild or moderate, and there were no SAEs or withdrawals for AEs after loxapine treatment. The only SAE in the study was a perforated appendix that occurred 5 days after placebo treatment and led to early discontinuation; the subject did not receive loxapine. Dizziness, a known effect of oral loxapine, was reported after Staccato Loxapine treatment by 2 subjects (7.4%). Both events resolved without intervention in less than 30 minutes and were judged to be probably treatment related. No subject reported dizziness after placebo treatment. One subject, reported moderate anxiety

(verbatim, apprehensive) starting 1 minute after the first dose of loxapine, which was administered in Period 1. It was judged possibly treatment related and resolved without treatment in approximately 2 hours.

6.1.6. Deaths

There were no deaths.

6.1.7. Clinical Laboratory Evaluations

Blood chemistry, hematology, and urinalysis tests were completed only to screen potential study subjects; no post-treatment laboratory assessments were performed.

6.1.8. Vital Signs and Oxygen Saturation

Baseline heart rates were similar before treatment with Staccato Placebo and Staccato Loxapine. Using the spirometry population to measure changes over time, there were no clinically significant changes in heart rate with either treatment. As well, baseline respiratory rates were also similar before treatment and there were no clinically significant changes in respiratory rates observed in the healthy subjects exposed to loxapine and placebo. Specifically, using the spirometry population, the largest changes from the baseline respiratory rate occurred 16 hours after Dose 1 for both placebo and loxapine (i.e. 8 hours after Dose 2): -1.03 breaths/min (-1.64, -0.41) for placebo, and -0.53 breaths/min (-1.15, 0.08) for loxapine [LSmean (90% LSmean CI)]. No clinically significant findings were identified in blood pressure data, and there were no AEs related to blood pressure. Finally, as with HR and RR, there were no clinically significant changes in SpO₂ with either treatment and no clinically significant differences between treatments. Looking at the Spirometry population, the ranges of LSmean SpO₂ values were similar after both treatments (97.0% to 97.5% after placebo, and 96.6% to 97.6% after loxapine). The largest changes from baseline SpO₂ were -0.94% (-1.39%, -0.49%) 32 hours after Dose 1 of placebo, and -1.05% (-1.48%, -0.63%) 0.25 hours after Dose 1 of loxapine [LSmean (90% LSmean CI)]. Looking at individual subject changes, there were no AEs related to SpO₂ and the lowest SpO₂ value after Staccato Placebo treatment and Staccato Loxapine treatment was 94%.

6.1.9. Pregnancies

No pregnancies were reported.

6.2. Safety in Subjects with Asthma (Study AMDC-004-105)

6.2.1. Disposition of Subjects

On review of the pulmonary safety data in patients with asthma, 51 of the 52 randomized subjects completed the study. The remaining subject received Dose 1 of study medication but chose to leave the study center before receiving the second dose of loxapine because of a death in the family. Of the 52 treated subjects, 42 received both planned doses of study treatment (i.e. 2 doses of Staccato Loxapine or 2 doses of Staccato Placebo), and 10 received only the first dose (9 Staccato Loxapine subjects, 1 Staccato Placebo subject). The most common reason subjects did not receive Dose 2 were due to a respiratory tract-related AE (i.e. bronchospasm, wheezing, or dyspnea) in combination with an FEV₁ decrease of $\geq 20\%$ from baseline.

6.2.2. Demographics

Of the 52 subjects, 43 (82.7%) had never smoked and 9 (17.3%) were ex-smokers. The prebronchodilator FEV1 at screening was $\geq 80\%$ in 67.3% of the subjects. See Table 5 for details.

Table 5. Study AMDC-004-105, Demographics and Baseline Characteristics (Safety Population)

Demographic or Baseline Characteristic	Staccato Placebo (N=26)	Staccato Loxapine (N=26)	Total (N=52)
Gender, n (%)			
Female	11 (42.3%)	16 (61.5%)	27 (51.9%)
Male	15 (57.7%)	10 (38.5%)	25 (48.1%)
Age (years)			
Mean (SD)	33.2 (11.46)	40.0 (11.53)	36.6 (11.88)
Median	29	38.5	35.5
Minimum, maximum	18, 61	18, 57	18, 61
Race, n (%)			
Caucasian	20 (76.9%)	21 (80.8%)	41 (78.8%)
Black	5 (19.2%)	0 (0.0%)	5 (9.6%)
Hispanic	1 (3.8%)	4 (15.4%)	5 (9.6%)
Other	0 (0.0%)	1 (3.8%)	1 (1.9%)
Height (cm)			
Mean (SD)	172.8 (10.46)	168.8 (10.72)	170.8 (10.68)
Median	174.6	168.0	169.1
Minimum, maximum	154.9, 190.5	150, 196	150, 196
Weight (kg)			
Mean (SD)	84.4 (14.33)	77.4 (16.76)	80.9 (15.8)
Median	82.7	73	79.8
Minimum, maximum	60, 110	55.3, 110	55.3, 110
Smoking history, n (%)			
Never smoked	23 (88.5%)	20 (76.9%)	43 (82.7%)
Ex-smoker	3 (11.5%)	6 (23.1%)	9 (17.3%)
Enrollment stratum, n (%)			
FEV1 $\geq 80\%$	18 (69.2%)	17 (65.4%)	35 (67.3%)
FEV1 $< 80\%$	8 (30.8%)	9 (34.6%)	17 (32.7%)

Source: Section 10.1, 1.6.1, 1.7

Reviewer's Comment:

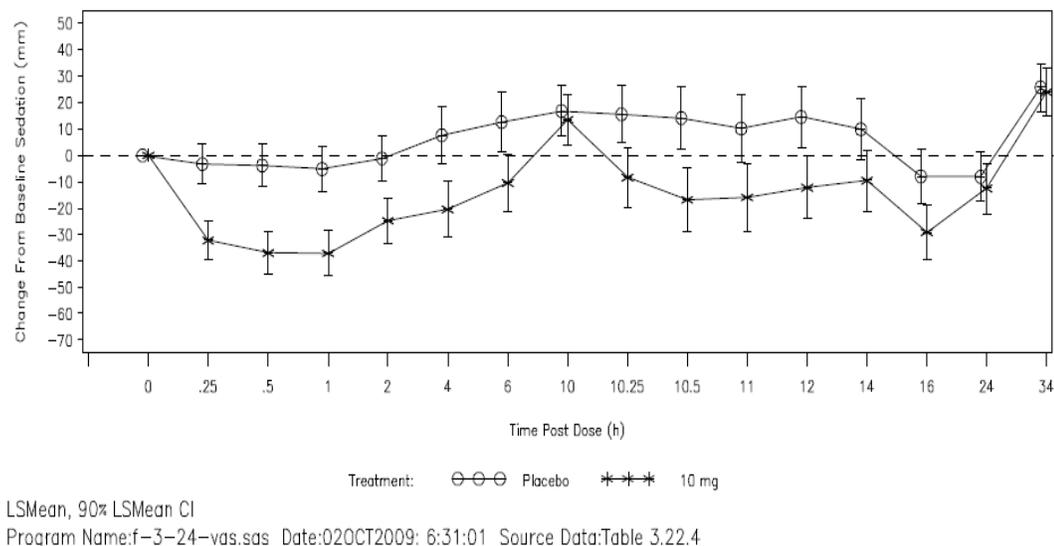
It is concerning that a significant number of different severities of asthmatics were not represented in the population: 69.2% of placebo treated and 65.4 of loxapine treated subjects were in the $\geq 80\%$ stratum while 30.8% in the placebo treated and 34.6% in the loxapine treated group were in the $\leq 80\%$ FEV1 stratum. Mean baseline FEV1 in the FEV1 $\geq 80\%$ stratum was 3.52 L for the Staccato Placebo subjects and 3.03 L for the Staccato Loxapine subjects. In the FEV1 $< 80\%$ stratum, mean baseline FEV1 values were 2.90 L and 2.73 L for the Staccato Placebo and Staccato Loxapine subjects, respectively.

6.2.3. Sedative Effects

The same visual analog scale to assess sedation used in Study AMDC-004-104 was used in this study in asthmatics. Clinically significant sedation was observed after each dose of loxapine as seen in Figure 6. The maximum change in LSmean VAS score occurred 30 minutes to 1 hour after each dose of loxapine (1 hour post-dose and 10.5 hour time points). In the loxapine group, the maximum change in VAS score after Dose 1 was -41.5 (-50.2, -32.7) at 1 hour, and the

maximum change in VAS score after Dose 2 was -41.3 (-58.2, -24.3) at 10.5 hours (i.e. 0.5 hours after Dose 2) [LSmean (90% LSmean CI)]. The largest treatment-group difference (loxapine – placebo) in sedation after Dose 1 was -36.9 (-47.4, -26.4) and it occurred at 30 minutes. The largest difference after Dose 2 was -51.6 (-70.0, -33.2) and it occurred at 10.5 hours (i.e. 30 minutes after Dose 2).

Figure 6. Study AMDC-004-105, Sedation VAS Change from Baseline, by Treatment (Spirometry Population)

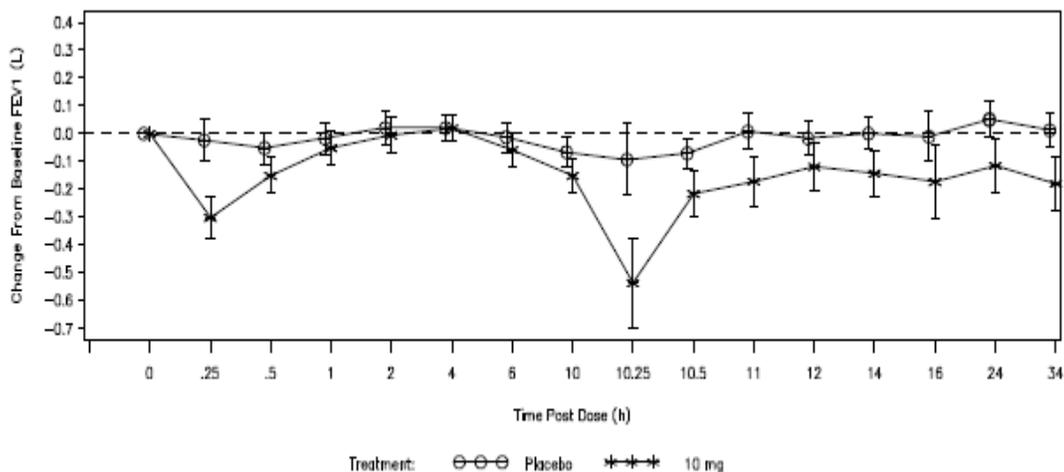


6.2.4. Spirometry Findings

- **FEV1**

Baseline FEV1 values were generally similar before administration of Staccato Placebo, 3.33±0.74 L and Staccato Loxapine, 2.92±0.69 L [mean±SD]. Decreases in FEV1 were observed after both loxapine and placebo treatment in subjects with asthma with the largest decreases seen 15 minutes after each dose. The largest changes from baseline FEV1 in the loxapine group were -0.303 L (-0.378, -0.228) [LSmean (90% LSmean CI)] 15 minutes after Dose 1 and -0.537 L (-0.696, -0.378) 15 minutes after Dose 2, both statistically significantly lower than the decrease in placebo at this same time point. Figure 7 demonstrates the changes in FEV1 for both groups over the full assessment period. The decreases seemed to return to baseline by 2 hours after Dose 1 and appeared to have a slower full recovery after Dose 2, not evident during the 24 hours depicted in the graph.

Figure 7. Study AMDC-004-105, FEV1 Change from Baseline, by Treatment (Spirometry Population)



LSMean, 90% LSMean CI
 Program Name:f-3-3-fev.sas Date:02OCT2009: 6:29:54 Source Data:Table 3.15.1
 Source: Section 10.1, Table 3.15.1

Reviewer’s Comment:

Since rescue albuterol was immediately given per protocol to any subject who had respiratory symptoms or a decrease of $\geq 20\%$ in FEV1 the true nadir of FEV1 following Staccato Loxapine treatment is unknown.

As indicated in the time course chart below, the number of subjects represented in this figure and many other figures represents a decreasing number of subjects from left to right due to the exclusion of subjects who received rescue medication or did not receive Dose 2 at Hour 10 from the spirometry population at all subsequent time points; therefore, the population size represented on the figure decreases over time.

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. Active:	26	26	22	22	22	21	20	20	17	12	12	12	12	12	11	10

LSmean and 90% LSmean CI
 Note: Placebo=Staccato Placebo, 10 mg=Staccato Loxapine 10 mg.
 Source: Section 10.1, Table 3.15.1

Reviewer’s Comment:

It is concerning that the population size decreases significantly in the loxapine treated asthmatic group vs. the placebo asthma group, with only 10/26 patients completing both doses in the loxapine group. This was also seen in the COPD group study where 19/26 or 73.1% of loxapine treated subjects received Dose 2, while 26/27 or 96.3% of placebo treated subjects received Dose 2. It is unclear if 10 of 26 patients with asthma is a sufficient sample size to evaluate the effects of multiple dosing with Staccato Loxapine on the pulmonary safety in this target population.

As presented previously, the results were subcategorized based on the maximum FEV1 decrease and presented in Table 6. As well, the categories are cumulative; for example, a subject with a

maximum decrease of 21% is included in the $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$ categories. More loxapine-treated subjects had decreases of $\geq 10\%$, $\geq 15\%$ and $\geq 20\%$ compared with placebo-treated subjects after Dose 1, Dose 2 and at any time. Among subjects with an FEV₁ decrease of $\geq 20\%$, the largest change in the loxapine group was one subject with a decrease of 50.1% and one subject in the placebo group had a decrease of 23.0% from baseline. The results of this analysis were similar when assessed in the safety population; however, there was one more patient in the $>15\%$ and $>20\%$ loxapine group.

Table 6. Study AMDC-004-105, Maximum FEV₁ Decrease from Baseline – Decreases of at Least 10%, 15%, or 20% FEV₁ (Spirometry Population)

	Maximum % FEV ₁ Decrease ^c	Staccato Placebo (N=26)	Staccato Loxapine (N=26)
After either dose (ie, at any time)		n=26	n=26
	$\geq 10\%$	3	22
	$\geq 15\%$	1	16
	$\geq 20\%$	1	11
After Dose 1 ^a		n=26	n=26
	$\geq 10\%$	2	16
	$\geq 15\%$	1	8
	$\geq 20\%$	1	6
After Dose 2 ^b		n=25	n=17
	$\geq 10\%$	3	12
	$\geq 15\%$	1	9
	$\geq 20\%$	1	5

Table presents number of subjects with indicated percentage decrease.

a. Dose 1 captures time points of 15 minutes through 10 hours after Dose 1.

b. Dose 2 captures time points of 10.25 minutes through 24 hours after Dose 1. Data obtained at 34 hours were not included.

c. FEV₁ categories are cumulative (eg, a subject with a maximum decrease of 21% would be included in the $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$ categories)

Source: Section 10.1, Table 3.1

Reviewer’s Comment:

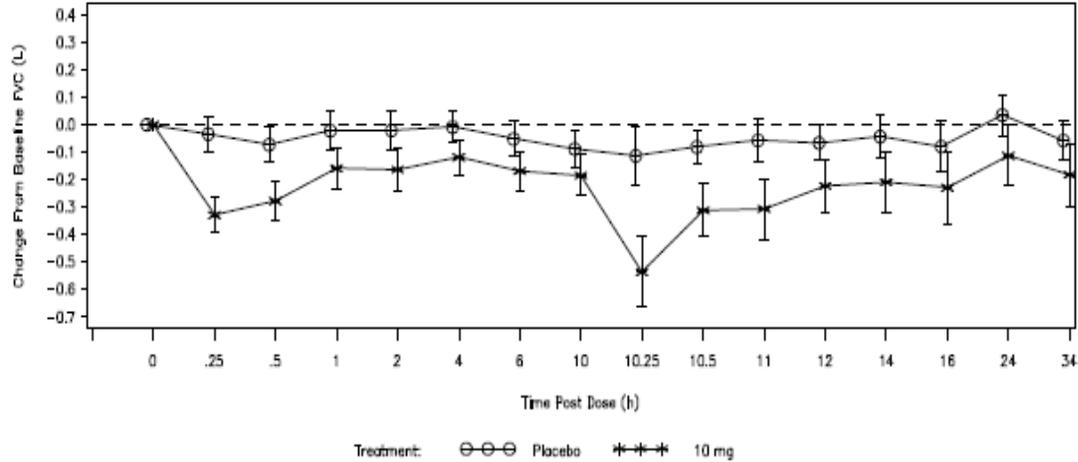
These results are quite concerning regarding the pulmonary safety of Staccato Loxapine, since 85% of stable asthmatics receiving loxapine had $\geq 10\%$ decrease in FEV₁ and 42% had a decrease of $\geq 20\%$. It is even more concerning that the decrease was markedly larger and did not show recovery after the second dose, which was given 8 hours after the first dose. The proposed dosing interval for Staccato Loxapine is every 2 hours up to 3 times per day, which would imply repeat dosing prior to FEV₁ recovery. In addition, this product will be used in acutely agitated patients who may be unable to give a clear history of asthma and may be noncompliant with asthma controller medications. Further, patients who are sedated may be unable to report respiratory symptoms following dosing.

• **FVC**

A decrease from baseline in the LSmean FVC was observed at most assessment times after placebo. The decreases from baseline after loxapine were greater at all time points, particularly 15 minutes after each dose. The largest change from baseline FVC in the loxapine group was -

0.537 L (-0.667, -0.407) [LSmean (90% LSmean CI)]. The largest change in the placebo group was -0.114 L (-0.218, -0.009). See the change in FVC over time in Figure 8.

Figure 8. Study AMDC-004-105, FVC Change from Baseline, by Treatment (Spirometry Population)

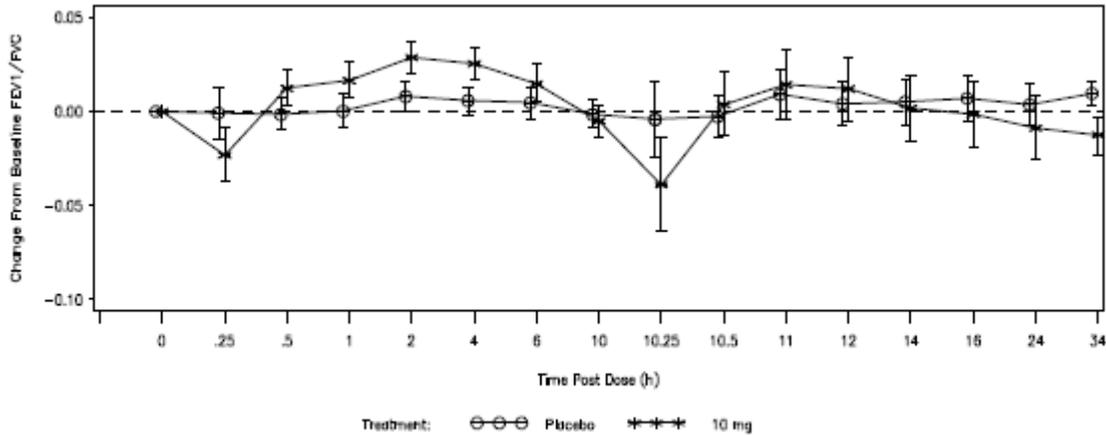


LSMean, 90% LSMean CI
 Program Name:f-3-5-fvc.sas Date:02OCT2009: 6:29:59 Source Data:Table 3.16.1

• **FEV1/FVC**

After loxapine treatment, FEV1/FVC decreased to below baseline, again with a similar pattern as before with the greatest decreases occurring 15 minutes after each dose. However the values were above baseline at several other time points, particularly from 30 minutes to 6 hours as seen in Figure 9 below.

Figure 9. Study AMDC-004-105, FEV1/FVC Change from Baseline, by Treatment (Spirometry Population)



LSMean, 90% LSMean CI
 Program Name:f-3-7-fevfv.sas Date:02OCT2009: 6:30:04 Source Data:Table 3.17.1

Reviewer's Comment:

The pattern observed here, with a decreased FEV1/FVC ratio observed after dosing in the Staccato Loxapine group, is consistent with airway obstruction.

6.2.5. Treatment Emergent Adverse Events

The treatment emergent AEs seen in the asthma population were similar to those seen in the healthy subjects; however, the numbers of airway related AEs were greater in the asthmatic population. Sedation, which is a known effect of loxapine, was seen in 69.2% of the loxapine treated subjects. AEs seen in > 10% of the loxapine treated subjects include: dysgeusia (30.8%), bronchospasm (26.9%), chest discomfort (23.1%), dizziness, headache and wheezing 15.4% each and dyspnea (11.5%). The AEs seen in > 10% of placebo treated subjects include: headache (30.8%) and sedation (23.1%). Ten subjects (9 loxapine, 1 placebo) did not receive Dose 2 because of an AE of dyspnea, wheezing, or bronchospasm or a decrease from baseline FEV1 of $\geq 20\%$. The protocol required that Dose 2 not be administered to such subjects. Two loxapine-treated subjects (03-027, 03-113) did not receive Dose 2 because of an FEV1 decrease of $\geq 20\%$, and 2 loxapine-treated subjects did not receive Dose 2 because of AEs (02-117: chest discomfort and cough; 04-104: chest discomfort). The other 5 loxapine-treated subjects did not receive Dose 2 because of an FEV1 decrease of $\geq 20\%$ and AEs (01-025: wheezing; 02-106, bronchospasm; 03-008: chest discomfort, dyspnea, FEV decreased, wheezing, throat tightness; 02-116: bronchospasm; 03-112: wheezing). The placebo-treated subject (02-012) had an AE of chest discomfort.

Reviewer's Comment: Four subjects (3 loxapine treated and 1 placebo treated) had severe sedation. One subject had severe sedation starting 6 minutes after Dose 1 of loxapine and resolved 5 hours later. The VAS score went from baseline 97 to 73 fifteen minutes post dose and 31 at four hours post dose. A second subject experienced severe sedation 28 minutes after Dose 2 of placebo and resolved 17 hours later. The baseline VAS was reported at 21 which decreased to 6 after Dose 1 and 10 after Dose 2. The third subject reported severe sedation 35 minutes after Dose 1 of loxapine which resolved 5 hours later. This same subject reported severe sedation 15 minutes after Dose 2 which didn't resolve until 15.5 hours. The fourth subject had severe sedation 20 minutes after Dose 1 of loxapine and resolved 5 hours later, she again reported severe sedation 15 minutes after Dose 2 which resolved 4 hours later. The range of sedative effects seems to be as short as 6 minutes after loxapine lasting to as long as 15.5 hours. The potential complications that could occur in an asthmatic patient that may develop bronchospasm as well as a prolonged sedative effect could result in the need for intubation and mechanical ventilation with intensive care management.

6.2.6. Deaths

There were no deaths.

6.2.7. Clinical Laboratory Evaluations

Blood chemistry, hematology, and urinalysis tests were completed only to screen potential study subjects. There were no post-treatment assessments.

6.2.8. Vital Signs and Oxygen Saturation

There were no clinically significant changes, treatment differences, or AEs associated with heart rate, respiratory rate or SpO₂. There was a small treatment group difference in systolic and diastolic blood pressures (both lower after Staccato Loxapine) notable from hours 10 to 14 in those subjects who received Dose 2. There was 1 subject who had a clinically significant

decrease in blood pressure and 1 subject who had a clinically significant decrease in heart rate and blood pressure; no AEs related to these changes were reported. There were no AEs related to SpO₂. There were 4 subjects with SpO₂ values <90% at any time point: 1 placebo subject (04-105, 89% 11 hours after Dose 1) and 3 loxapine subjects (01-025, 89% 4 hours after Dose 1; 03-113, 88% 15 minutes after Dose 1; 04-006, 89% 1 hour after Dose 1). Specifically, none of these SpO₂ values <90% were temporally associated with AEs. One of the subjects, 03-113, had a corresponding decrease in FEV₁ of 24.8% from baseline.

6.2.9. Pregnancies

No pregnancies were reported.

6.2.10. Notable Respiratory Signs or Symptoms

To further explore potential pulmonary effects of Staccato Loxapine in asthmatics, all safety-population subjects who had “notable respiratory signs or symptoms” (defined as an FEV₁ decrease from baseline of $\geq 20\%$, an airway AE, or use of rescue medication) were closely evaluated for acute effects of study treatment. Eighteen (69%) loxapine-treated subjects and 3 (12%) placebo-treated subjects had notable respiratory signs and/or symptoms. Of the 18 loxapine-treated subjects, all but 1 (who withdrew for personal reasons) completed the spirometry testing. The specific notable respiratory signs and symptoms were as follows:

- **FEV₁ Decreases $\geq 20\%$:** Decreases $\geq 20\%$ occurred in 12 (46.2%) loxapine-treated asthmatic subjects and 1 (3.8%) placebo-treated subject. Eight of these loxapine-treated subjects had an FEV₁ $\geq 20\%$ below baseline just before rescue with albuterol.
- **Airway Adverse Events:** Airway AEs were reported by 14 (53.8%) loxapine-treated subjects and 3 (11.5%) placebo-treated subjects. Airway AEs that occurred in more than a single loxapine-treated subject were bronchospasm (7 subjects), chest discomfort (6 subjects), wheezing (4 subjects), and dyspnea (3 subjects). Airway AEs were also reported for 3 (11.5%) placebo-treated subjects (chest discomfort in 2 subjects; bronchospasm in 1 subject). All airway AEs were assessed as mild or moderate; and none was serious, led to withdrawal from the study, prevented a subject from completing the spirometry testing regimen, or delayed discharge at the end of the treatment day. In the loxapine group, airway AEs in 13 loxapine-treated subjects required treatment with albuterol by metered-dose inhaler or nebulizer, the 1 remaining resolved without treatment. In the 3 placebo-treated subjects, the AEs were treated with albuterol by metered-dose inhaler.
- **Use of Rescue Medication:** A larger percentage of loxapine-treated subjects (53.8%) received rescue medication compared with placebo-treated subjects (11.5%). Several loxapine-treated subjects received rescue medication only after Dose 2. Among the 14 loxapine-treated subjects who required rescue medication, 10 received a single albuterol dose via metered-dose inhaler, 2 subjects received 2.5 mg albuterol by nebulizer, and 2 subjects received albuterol by both metered-dose inhaler and nebulizer.

Table 7. Study AMDC-004-105, Adverse Events Related to Airways (Safety Population)

Adverse Event, n (%)	Staccato Placebo (N=26)	Staccato Loxapine (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.

Source: Section 10.1, Table 3.2.1

6.3. Safety in Subjects with COPD (Study AMDC-004-108)

6.3.1. Disposition of Subjects

Fifty-two of the 53 randomized subjects with COPD completed the study. The remaining subject received Dose 1 of study medication but withdrew consent after the 4-hour assessments (no AEs), refusing to complete the remaining treatment-day assessments or return for the Visit 3 end-of-study assessments. Of the 53 treated subjects, 45 subjects received both planned doses, while 8 received only Dose 1 (1 placebo subject, 7 loxapine subjects). The most common reason that a subject did not receive Dose 2 was an FEV1 decrease from baseline of $\geq 20\%$ after Dose 1. Specifically, one placebo-treated subject had an AE of bronchospasm and an FEV1 decrease of $\geq 20\%$, two loxapine-treated patients had an FEV1 decrease of $\geq 20\%$, one loxapine-treated patient had AEs of wheezing and dyspnea and the final loxapine-treated patient while the FEV1 was -8.1% change from baseline, other spirometry parameters had a $\geq 20\%$ decrease from baseline.

6.3.2. Demographics

The mean age was 57.1 with a range from 40 to 68; 59.3% of those treated with placebo were current smokers while 65.4% of loxapine treated subjects were current smokers; 69.8% of the population had FEV1 $\geq 50\%$ and 30.2% had $\leq 50\%$. In the FEV1 $\geq 50\%$ stratum, the mean FEV1 in the placebo group was 1.784 L (range, 1.1 to 3.0), and the mean FEV1 in the loxapine group was 1.703 L (range, 1.0 to 2.2). In the FEV1 $< 50\%$ stratum, the mean FEV1 in the placebo group was 1.174 L (range, 0.8 to 2.2), and the mean FEV1 in the loxapine group was 1.161 L (range, 0.9 to 1.9). All FEV1 results are reported as post-bronchodilator. See Table 8 for further details.

Table 8. Study AMDC-004-108, Demographics and Baseline Characteristics (Safety Population)

Demographic or Baseline Characteristic	Staccato Placebo (N=27)	Staccato Loxapine (N=26)	Total (N=53)
Gender, n (%)			
Female	15 (55.6%)	15 (57.7%)	30 (56.6%)
Male	12 (44.4%)	11 (42.3%)	23 (43.4%)
Age (years)			
Mean (SD)	56.7 (6.50)	57.5 (6.58)	57.1 (6.49)
Median	57	58.5	58
Minimum, maximum	40, 68	40, 66	40, 68
Race, n (%)			
Caucasian	20 (74.1%)	24 (92.3%)	44 (83.0%)
Black	7 (25.9%)	2 (7.7%)	9 (17.0%)
Height (cm)			
Mean (SD)	169.1 (10.20)	167.0 (10.59)	168.0 (10.33)
Median	168.9	167.95	168.3
Minimum, maximum	155.6, 190.5	137.2, 186.1	137.2, 190.5
Weight (kg)			
Mean (SD)	76.87 (16.981)	79.54 (14.141)	78.18 (15.561)
Median	77.3	78.65	77.5
Minimum, maximum	52.7, 113.6	52.8, 110.9	52.7, 113.6
Smoking history, n (%)			
Current smoker	16 (59.3%)	17 (65.4%)	33 (62.3%)
Ex-smoker	11 (40.7%)	9 (34.6%)	20 (37.7%)
Screening post-bronchodilator FEV ₁ stratum, n (%)			
FEV ₁ ≥50%	19 (70.4%)	18 (69.2%)	37 (69.8%)
FEV ₁ <50%	8 (29.6%)	8 (30.8%)	16 (30.2%)

Source: Section 10.1, 1.6.1, 1.7

The reviewer categorized patients based on the published guidelines from Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2009 (<http://www.goldcopd.org>) or American Thoracic Society/European Respiratory Society Task Force Guidelines (Celli, B.R. and MacNee, W., ATS/ERS Task Force. Eur Respir J 2004;23:932-946). Based on this analysis, there were 3 patients, 2 in the placebo group and 1 in the loxapine group, who did not meet the inclusion criteria of FEV₁/FVC ratio of <70% (the criteria for obstruction), thus may not have had COPD. Overall, 15% of patients had mild disease (Gold Stage I), 56% had moderate disease (Gold Stage II), and 30% had severe disease (Gold Stage III). Due to the enrollment criteria excluding patients with FEV₁ <40% predicted, no patients with very severe disease (Gold Stage IV) were included. The distribution of disease severity was generally balanced between the treatment groups. See Table 9. [NDA 22-549, Protocol AMDC-004-108, Listing 3.1.6]

Table 9. COPD Severity by Treatment Group (Safety Population)

	Placebo N=27	Loxapine N=26	Overall N=53
Gold Stage I	4 (14.8%)	2 (7.7%)	6 (11.3%)
Gold Stage II	15 (55.6%)	25 (57.7%)	30 (56.6%)
Gold Stage III	8 (29.6%)	9 (34.6%)	17 (32.1%)

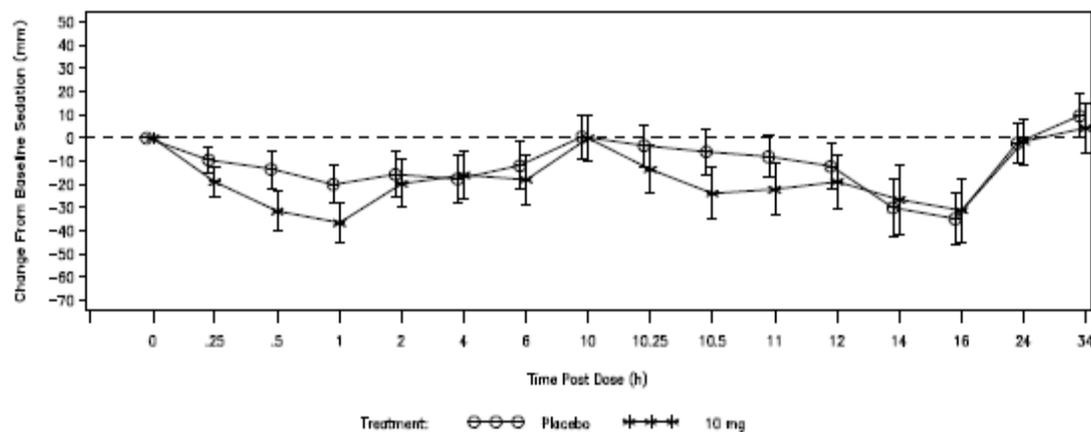
Reviewer’s Comment:

The sponsor claims that the population for this study is moderate to severe COPD patients. However, the average baseline post-bronchodilator FEV1 (1.8L, 52% predicted) is significantly higher than in most COPD trials, indicating milder disease. For example, the mean post-bronchodilator FEV1 in the Spiriva HandiHaler UPLIFT trial was 1.3L (47% predicted) and in the Advair TORCH trial was 1.2L (44% predicted) (Tashkin DP, Celli B, Senn SDB, et al. A 4-year trial of tiotropium in Chronic Obstructive Pulmonary Disease. *N Engl J Med.* 2008;359:1543–1554 and Calverley PMA, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease *N Engl J Med.* 2007;356:775–789, respectively.) Further, 15% of patients had mild disease by GOLD criteria, suggesting that the population is more mixed than the sponsor claims.

6.3.3. Sedative Effects

As in the prior to two studies, clinically significant sedation was observed after each dose of placebo and a greater effect after each dose of loxapine as seen in Figure 10. Baseline sedation scores were 73.0 ± 26.2 before placebo treatment and 79.0 ± 23.6 before loxapine treatment (mean \pm SD). Again, a score of 100 was consistent with ‘wide awake’. In the placebo group, the maximum change from baseline in the sedation VAS was -34.9 (-46.24, -23.52) at 16 hours [LSmean (90% LSmean CI)]. In the loxapine group, after Dose 1, the maximum change from baseline in the sedation VAS was -36.6 (-45.5, -27.8) at 1 hour after that dose and after Dose 2 of loxapine, the changes in the sedation VAS at 10.5 hours [-23.9 (-35.1, -12.8)], which was 30 minutes after Dose 2, and at 11 hours [-22.2 (-33.1, -11.4)], which was 1 hour after Dose 2. Changes from baseline in the sedation VAS were evident in both groups at the late night assessment times, 14 and 16 hours.

Figure 10. Study AMDC-004-108, Sedation VAS Change from Baseline, by Treatment (Spirometry Population)



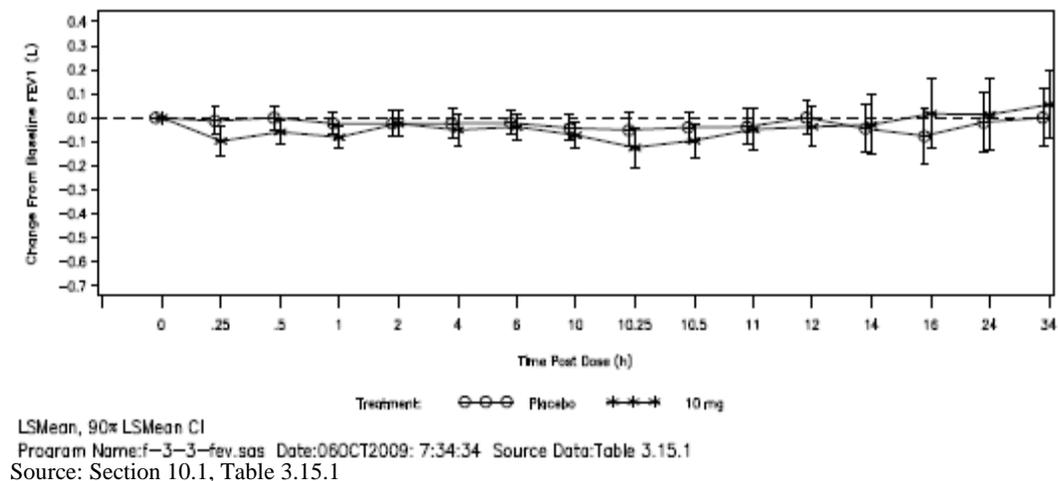
LSMean, 90% LSMean CI
 Program Name:f-3-24-vds.sas Date:06OCT2009: 7:35:44 Source Data:Table 3.22.4
 VAS=visual analog scale
 A negative excursion indicates a sedative effect
 Source: Section 10.1, Table 3.22.4

6.3.4. Spirometry Findings

- **FEV1**

The baseline FEV1 was similar before administration of Staccato Placebo and Staccato Loxapine. The FEV1 was 1.603 ± 0.588 L before placebo treatment, and 1.551 ± 0.411 L before loxapine treatment (mean \pm SD). There were decreases from baseline in the LSmean FEV1 at most assessment times after placebo or loxapine treatment, with a larger decrease after loxapine treatment (Figure 11). Again, of note, there is a decrease in the number of subjects over time in the analysis due to the exclusion of that data from subjects who used rescue medication. The largest difference was in the hour after each dose. The largest change following placebo treatment was -0.077 L ($-0.195, 0.042$) [LSmean (90% LSmean CI)], which occurred at a late-night assessment, 16 hours after Dose 1 (i.e. 6 hours after Dose 2). The largest change from baseline FEV1 following loxapine treatment was -0.125 L ($-0.204, -0.045$), which occurred 10.25 hours after Dose 1 (i.e. 0.25 hours after Dose 2) [LSmean (90% LSmean CI)]. The value of 0.125 L represents 8% of the average baseline FEV1 and could represent up to 18% based on the upper confidence interval for the largest change from baseline FEV1 after loxapine treatment and the lower standard deviation of the baseline FEV1 before loxapine treatment.

Figure 11. Study AMDC-004-108, FEV1 Change from Baseline, by Treatment (Spirometry Population)



As with the previous two studies, the results were subcategorized based on the maximum FEV1 decrease and presented in Table 10. Again, the categories are cumulative. More loxapine-treated subjects had decreases of >10%, 15% and 20% compared with placebo-treated subjects after either dose.

Table 10. Study AMDC-004-108, Maximum FEV₁ Decrease from Baseline – Decreases of at Least 10%, 15% or 20% (Spirometry Population)

	Maximum FEV ₁ Decrease ^c	Staccato Placebo (N=27)	Staccato Loxapine (N=25)
After either dose (ie. at any time)	—	n=27	n=25
	≥10%	18	20
	≥15%	9	14
	≥20%	3	10
After Dose 1 ^a	—	n=27	n=25
	≥10%	8	16
	≥15%	4	10
	≥20%	2	9
After Dose 2 ^b	—	n=26	n=19
	≥10%	15	12
	≥15%	6	10
	≥20%	1	5

Table presents the number of subjects.

- "After Dose 1" captures time points from 0.25 through 10 hours after Dose 1.
- "After Dose 2" captures time points from 10.25 through 24 hours after Dose 1. Data obtained at 34 hours are not included.
- FEV₁ categories are cumulative (eg. a subject with a maximum decrease of 21% would be included in the ≥10%, ≥15%, and ≥20% categories).

Source: Section 10.1, Table 3.18.1

Among subjects with an FEV₁ decrease of ≥20%, the largest change from baseline in a placebo-treated subject was -40.0% associated with an AE of bronchospasm and the largest change in a loxapine-treated subject was -46.1% without any reported airway AEs. The numbers reported were similar for the safety population. The sponsor did not analyze the data based on smoking history.

Reviewer's Comment:

It is not surprising that smaller decreases in FEV₁ were seen in the COPD population compared to the asthma population since by definition COPD patients have some degree of fixed rather than reversible airway obstruction. In addition, starting from a lower baseline, a smaller decrease may be sufficient to cause respiratory compromise. Since many patients with schizophrenia and bipolar disease smoke, it is likely that a large portion of patients receiving this drug will have some degree of respiratory disease at baseline.

Dr. Yeh-Fong Chen, FDA biometrics reviewer, performed an analysis of pulmonary function by smoking history. See Table 11 representing the percent of current smokers vs. former smokers with decreases in FEV₁ of ≥10, ≥15 and ≥20% after treatment with Staccato Loxapine or Placebo. For both time points a greater percentage of current smokers in the Staccato Loxapine group have a clinically significant FEV₁ decrease than current smokers in the placebo group, but no significant differences are observed between current smokers and former smokers within the Staccato Loxapine group.

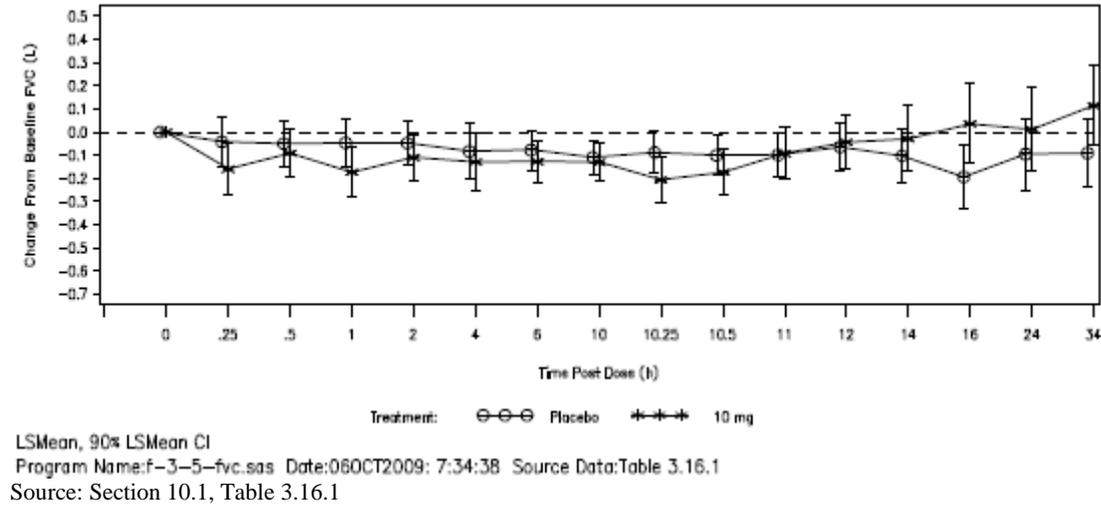
Table 11. Pulmonary Function in Current Smokers vs. Former Smokers

FEV1 Decrease After Dose 1	Staccato Loxapine %		Placebo %	
	Current smoker N = 16	Former smoker N = 9	Current smoker N = 16	Former smoker N = 11
≥ 10%	69	56	25	36
≥ 15%	44	33	19	9
≥ 20%	38	33	6	9
FEV1 Decrease After Dose 2	Staccato Loxapine %		Placebo %	
	Current smoker N = 11	Former smoker N = 8	Current smoker N = 14	Former smoker N = 11
≥ 10%	64	63	71	45
≥ 15%	55	5	29	18
≥ 20%	18	38	7	0

- **FVC**

The baseline FVC was similar before administration of Staccato Placebo and Staccato Loxapine. The FVC was 2.904 ± 0.786 L before placebo treatment and 2.831 ± 0.707 L before loxapine treatment (mean \pm SD). There were decreases from baseline in the LSmean FVC at all assessment times after placebo treatment and at most assessment times after loxapine treatment, as seen in Figure 11. The decreases were larger after loxapine treatment than after placebo treatment. The largest change from baseline in the placebo group was -0.194 L ($-0.335, -0.053$), which occurred at a late-night assessment, 16 hours after Dose 1 (i.e. 6 hours after Dose 2) [LSmean (90% LSmean CI)]. The largest change from baseline FVC in the loxapine group was -0.208 L ($-0.311, -0.106$), which occurred 10.25 hours after Dose 1 (i.e. 0.25 hours after Dose 2).

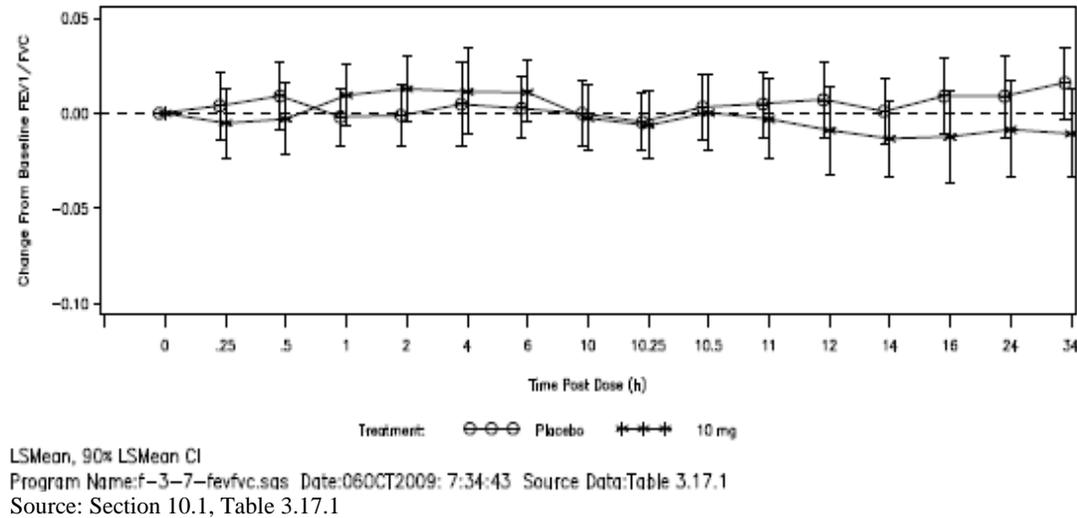
Figure 11: Study AMDC-004-108, FVC Change from Baseline, by Treatment (Spirometry Population)



- **FEV1/FVC**

The baseline FEV1/FVC was similar before administration of Staccato Placebo and Staccato Loxapine. FEV1/FVC was 0.552 ± 0.129 before placebo treatment and 0.555 ± 0.108 before loxapine treatment (mean \pm SD). As seen in Figure 12, there was no systematic pattern of change in either group after dosing.

Figure 12: Study AMDC-004-108, FEV1/FVC Change from Baseline, by Treatment (Spirometry Population)



6.3.5. Treatment Emergent Adverse Events

The pattern of reported AEs was similar to those seen in the previous two studies. See below for a discussion of the pulmonary adverse events.

6.3.6. Vital Signs and Oxygen Saturation

The safety population was used in the examination of heart rate, respiratory rate, and blood pressure data from individual subjects. However, the spirometry population was used in the treatment-group analyses to help control for variation that would be introduced by use of rescue medication and the failure of some subjects to get Dose 2. In the spirometry population analyses, measurements obtained after use of rescue medication were excluded, as were measurements obtained after Hour 10 in subjects who did not receive Dose 2. At baseline in the spirometry population, SpO₂ was 96.3% ± 2.18% in the placebo group and 96.0% ± 2.15% in the loxapine group (mean ± SD). The ranges of mean post-treatment SpO₂ values were 96.2% to 96.9% in the placebo group, and 95.3% to 96.3% in the loxapine group. In the placebo group, the largest negative change from baseline SpO₂ was -0.2% (-1.0%, +0.5%) at 16 hours after Dose 1 [LSmean (90% LSmean CI)]. In the loxapine group, the LSmean SpO₂ was below baseline at each post-treatment assessment in the first 2 hours after Dose 1; the largest negative change from baseline was -0.7% (-1.5%, +0.1%) at 1 hour after Dose 1. Using the safety population for the examination of SpO₂ data from individual subjects no AE associated with changes in SpO₂ were observed. The lowest SpO₂ measurement in a placebo-treated subject was 85%, occurring at 6 hours, and the lowest in a loxapine-treated subject was 88%, occurring at 10 hours, just before Dose 2. Data from subjects who used rescue medication were excluded at time points after rescue; data from subjects who did not receive Dose 2 were excluded after Hour 10, and 1 subject withdrew consent after the Hour 4 assessments. There was no systematic pattern of changes or clinically significant changes in the heart rate or respiratory rate.

Reviewer's Comment:

An oxygen saturation of ≤88% corresponds to a SaO₂ of 55 mm Hg and is the cut-off required by Medicare and most insurance agencies to reimburse for chronic oxygen therapy. A higher cut off (89%, PaO₂ 59 mm Hg) is used for patients with symptoms of CHF, pulmonary hypertension, or polycythemia. Since patients who received rescue medication were excluded from the analysis of oxygen levels, the occurrence of hypoxia was not adequately evaluated in this trial and remains a concern for patients treated with Staccato Loxapine.

In placebo-treated subjects, the LSmean systolic and diastolic blood pressure was at or above baseline at most assessment times. In loxapine-treated subjects, there were decreases in LSmean systolic and diastolic blood pressure, with a more consistent effect on diastolic blood pressure. For systolic blood pressure, the largest change in the 4 hours after either dose was -7.1 mm Hg (-11.12, -3.14) at 1 hour after Dose 1. For diastolic blood pressure, all values were below baseline in the 4 hours after each dose. During that period, the largest changes from baseline were -4.2 mm Hg (-6.70, -1.77) at 0.5 hours after Dose 1 and -3.8 mm Hg (-8.29, +0.62) at 11 hours. Two loxapine-treated subjects had an AE of hypertension (1 of which was coded to the preferred term, blood pressure increase). One of these AEs started days after study treatment in the subject with a history of hypertension. Her baseline BP 138/90 and on Visit 3 her BP was 180/120. She was treated; however, according to the narrative, the event was ongoing at the end of the study. The second subject had a baseline BP of 116/72 mm Hg and 30 minutes after Dose 1 it was 140/82 and resolved without medication. In addition, a review of the vital signs data by the medical monitor identified a clinically significant increase in blood pressure in 1 placebo-treated subject and clinically significant decreases in blood pressure in 4 loxapine-treated and 2 placebo-treated

subjects; all were asymptomatic. There were no clinically important changes in individual loxapine-treated subjects in other vital signs parameters.

6.3.7. Notable Respiratory Signs or Symptoms

Again, as with the asthma study, with the COPD study the Sponsor explored the potential pulmonary effects of Staccato loxapine as manifested by “notable respiratory signs or symptoms” (defined as an FEV1 decrease from baseline of $\geq 20\%$, an airway AE or use of rescue medication) in the all safety-population. Airway AEs were reported for 5 (19.2%) loxapine-treated subjects, which includes 1 subject whose airway AE was a “greater than 20% decrease in FEV1 from baseline”. Airway AEs that occurred in more than a single loxapine-treated subject were dyspnea (3 subjects), cough (3 subjects), and wheezing (2 subjects). Airway AEs were also reported for 3 (11.1%) placebo-treated subjects. No airway AE occurred in more than a single placebo-treated subject. In the loxapine-treated subjects, all airway AEs were mild or moderate. No airway AE led to discontinuation of the study. The events resolved without treatment in 3 of the 5 loxapine-treated subjects with airway AEs. In the remaining 2 subjects, the AEs were treated with albuterol by metered dose inhaler. The specific notable respiratory signs and symptoms were as follows:

- **FEV1 Decreases of $\geq 20\%$:** FEV1 decreases of at least 10% from the baseline FEV1 were seen in the majority of COPD patients in both groups, 66.7% of placebo treated subjects and 80.8% of Staccato Loxapine treated subjects. Decreases of $\geq 20\%$ occurred in 11.1% (3) placebo treated subjects and 38.5% (10) Staccato Loxapine treated subjects. The largest change from baseline in FEV1 in any subject in the loxapine group was -46.1%, but reportedly, there were no airway AE associated with this decline. The largest for the placebo group was -40% which was associated with moderate bronchospasm. In 3 of the loxapine-treated subjects, there was no airway AEs or clinically significant changes in respiratory rate or SpO2. Seven of the 10 loxapine-treated subjects with FEV1 decreases of $\geq 20\%$ received no rescue medication. In the 3 who did receive rescue medication, their FEV1 measurements returned to within 10% of baseline within an hour of the use of rescue medication.
- **Airway Adverse Events:** Airway AEs were reported for 5 (19.2%) loxapine-treated subjects and 3 (11.1%) placebo-treated subjects. The AEs were similar in loxapine treated and placebo-treated subjects. All were mild or moderate; and none was serious, led to withdrawal from the study, prevented a subject from completing the spirometry testing regimen, or delayed discharge at the end of the treatment day. Airway AEs that occurred in more than a single loxapine-treated subject were dyspnea (3 subjects), cough (3 subjects), and wheezing (2 subjects). No airway AE occurred in more than a single placebo-treated subject. In the loxapine group, airway AEs resolved without treatment in 3 of 5 subjects. In the remaining 2 loxapine-treated subjects, the AEs were treated with 1 dose of albuterol by metered-dose inhaler per episode. In the placebo group, airway AEs resolved without treatment in 1 of 3 subjects. In the remaining 2 placebo-treated subjects, the AEs were treated with 1 or 2 doses of albuterol by metered-dose inhaler per episode.
- **Use of Rescue Medication:** Rescue medication was used by a larger percentage of loxapine-treated subjects (6 subjects, 23.1%) compared with placebo-treated subjects (4 subjects, 14.8%). Of the 6 loxapine-treated subjects who received rescue medication, albuterol by metered-dose inhaler sufficed in 5 of them; the remaining subject received 2.5 mg of albuterol by nebulizer. All 6 loxapine-treated subjects received only a single

dose of albuterol per episode. Of the 4 placebo-treated subjects who received rescue medication, all received albuterol by metered-dose inhaler. Three of the subjects received a single dose per episode. The remaining subject received 2 doses for an AE of bronchospasm and later received another dose for an FEV1 decrease. Table 13 below is a synopsis of the all COPD patients (safety population) with the details of the notable respiratory signs or symptoms, the screening FEV1 stratum and total doses of study drug.

Table 12. Study AMDC-004-108, Subjects with Notable Respiratory Signs or Symptoms (Safety Population)

Screening FEV ₁ Stratum	Subject No.	Treatment	Most Recent Dose	Airway AE	AE Severity	AE Resolved by Scheduled Discharge	FEV ₁ Δ ≥20% (Maximum Δ) ^a	Rescue Tx (No. Doses) ^b	Total Doses of Study Drug
≥50%	02-008	Placebo	1	Bronchospasm	Moderate	Yes	—	MDI (2)	1
			1	—	—	—	-40.0%	MDI (1)	
	02-015	Placebo	1	Productive cough	Moderate	Yes	—	—	2
			1	—	—	—	—		
	02-022	Placebo	1	—	—	—	—	MDI (1)	2
			1	—	—	—	—	MDI (1)	
			2	—	—	—	—	MDI (1)	
			2	—	—	—	—	MDI (1)	
	02-026	Placebo	2	Dyspnea	Mild	Yes	—	MDI (1)	2
	01-007	Loxapine	1	—	—	—	-24.4%	—	2
	01-011 ^c	Loxapine	1	—	—	—	-21.5%	—	1
	01-014	Loxapine	2	—	—	—	-28.4%	—	2
	01-018	Loxapine	1	—	—	—	-24.4%	—	1
	02-001	Loxapine	1	Cough Wheezing Pulmonary congestion	Mild	Yes	—	—	—
					Mild	Yes			
	02-023	Loxapine	2	—	—	—	—	MDI (1)	2
	02-027	Loxapine	2	Dyspnea	Mild	Yes	—	—	—
					2	—			
03-010	Loxapine	2	—	—	—	-46.1%	MDI (1)	2	
05-033	Loxapine	1	FEV ₁ decrease ≥20%	Mild	Yes	-28.7%	MDI (1)	1	
05-036	Loxapine	1	—	—	—	-32.4%	—	2	
<50%	01-105	Placebo	1	—	—	—	-24.5%	—	2
	03-111	Placebo	2	—	—	—	-20.6%	MDI (1)	2
	01-110	Loxapine	1	Cough Dyspnea	Moderate	Yes	—	—	—
					Moderate	Yes			
	02-102	Loxapine	2	Cough	Mild	Yes	—	—	—
					—	—			
	02-106	Loxapine	2	—	—	—	-31.6%	—	2
	02-114	Loxapine	1	Dyspnea + Wheezing	Mild	Yes	—	—	MDI (1)
					Moderate	Yes			
					Mild	Yes			
					Mild	Yes			
	03-112	Loxapine	2	—	Mild	Yes	—	—	MDI (1)
—					—				
03-112	Loxapine	2	—	—	—	-28.4%	Nebulizer (1)	2	

Δ=change from baseline; MDI=metered-dose inhaler; notable respiratory sign/symptom=use of rescue drug, airway AE, or FEV₁ decrease of ≥20% from baseline; tx=treatment
a. Maximum decrease in FEV₁ was not always concurrent with administration of rescue medication for a decrease in FEV₁.
b. All subjects received albuterol as a rescue medication. One or more puffs administered at the same time from a metered-dose inhaler were considered 1 dose.
c. Subject withdrew consent during Visit 2 after the 4-hour assessments

Source: Appendix 11.3, Listings 1.2, 1.15, 1.16, 3.1, 3.17, 3.20

6.4. Safety in Subjects with Agitation or Migraine Headaches

The studies submitted in support of efficacy and safety for the NDA were carried out in agitated patient populations, subjects on stable antipsychotic regimens, patients with migraine headaches and healthy volunteers with agitation. Review of the respiratory related AE reveals the following incidences of respiratory related AEs. In controlled studies in agitated patient (CSAP) population the AE were summarized using MedDRA preferred terms as follows: for those who received 10 mg Staccato loxapine, throat irritation 2.7%, bronchospasm 0.4%, and cough 0.4%. For those who received 5 mg Staccato loxapine wheezing 0.8%. Respiratory AEs reported by subjects on stable antipsychotic regimens, included cough experienced by 1 subject (13%) in the Staccato Loxapine 20 mg group and 2 subjects (25%) in the Staccato Loxapine 30 mg group vs. none in the placebo or Staccato Loxapine 15 mg group. There were two studies carried out on patients

with migraine headaches (Study 104-201 and Study 104-202). Respiratory, thoracic and mediastinal AEs experienced by patients in Study 104-201 included throat irritation by 3 patients (7%) in the Staccato Loxapine 1.25 mg group and pharyngeal hypoesthesia by 3 patients (7%) in the Staccato Loxapine 5 mg group. Moderate cough was reported by 2 patients, 1 following administration of Staccato Placebo and 1 following Staccato Loxapine 1.25 mg. These events resolved without treatment and there were no reports of dyspnea, wheezing, or bronchospasm. In Study 104-202, among treatment-related respiratory AEs, 2 cases of dyspnea were reported after Staccato Loxapine 1.25 mg. Moderate cough was reported after Staccato Loxapine 1.25 mg and mild cough was reported after Staccato Placebo. All four cases resolved spontaneously without medical intervention. There were no reports of wheezing or bronchospasm.

In the studies on healthy volunteers with agitation, cough was the most frequently reported respiratory system AE, experienced by 13 subjects (9.8%) in the Staccato Loxapine 10 mg group vs. 2 subjects (2.2%) in the placebo group, and no subjects in the lower Staccato Loxapine dose groups. Pharyngeal hypoesthesia was experienced by 2 subjects (1.5%) in the Staccato Loxapine 10 mg group and 1 subject (4.3%) in the Staccato Loxapine 5 mg group. Pharyngitis was experienced by 3 subjects (2.3%) in the Staccato Loxapine 10 mg group and in no other groups. Three subjects (2.3%) in the Staccato Loxapine 10 mg group experienced pharyngolaryngeal pain compared with 2 subjects (2.2%) in the placebo group. Other respiratory, thoracic and mediastinal disorder AEs included: nasal congestion by 2 subjects (1.5%) in the Staccato Loxapine 10 mg group, rhinitis allergic, sinus headache, throat irritation, and upper respiratory tract infection by 1 subject each in the Staccato Loxapine 10 mg group; and sinus headache by 1 subject (1.1%) in the placebo group.

Amongst these studies there was only one AE that led to withdrawal. In the narrative, the patient was a 59 year old black woman in the CSAP population, diagnosed with schizophrenia in 1990. She was randomized and received Staccato Loxapine 10 mg. At screening, the patient was taking aripiprazole, 10 mg daily, and she was an active cigarette smoker (25 years, average of 10/day). Approximately 5 minutes after her first dose of Staccato Loxapine, the patient developed labored breathing with wheezing that was audible without a stethoscope, although she did not complain of shortness of breath. She was given albuterol (2 puffs, via metered-dose inhaler) and oxygen by nasal cannula, and she responded promptly. She was stable when discharged. She had no other AEs. The patient was subsequently withdrawn from the study due to this AE.

7. Summary and Conclusions

Evaluation of the pulmonary function parameters FEV1 and FVC revealed a decline across all three pulmonary safety studies performed in healthy subjects and patients with asthma or COPD. Consistently, however, there was greater and more clinically significant pulmonary toxicity seen in those with asthma and COPD. In the asthmatic population treated with Staccato Loxapine, 84% had clinically significant decreases in $FEV1 \geq 10\%$ and 42% had decreases $\geq 20\%$. In the COPD population treated with Staccato Loxapine, 80% exhibited decreases of $\geq 10\%$ and 40% had decreases $\geq 20\%$. While these numbers represent significant pulmonary toxicity, the true nadir of the FEV1 following Staccato Loxapine treatment is not known since rescue albuterol was immediately given per protocol to any subject who had respiratory symptoms or a decrease in FEV1. The second dose of Staccato Loxapine also appeared to have a greater impact on pulmonary function. There was a greater reduction in population size over time in patients who

received the second dose of Staccato Loxapine than placebo. The timing of pulmonary effects was consistent over the pulmonary safety studies. The decline in FEV1 occurred approximately 15 to 30 minutes after dosing and while none of the healthy subjects required rescue medication, 54% asthmatic patients and 23% of COPD patients receiving Staccato Loxapine required rescue medication.

The largest changes from baseline in FEV1 in the healthy subjects represented a small portion of the mean baseline FEV1 and there were no clinically significant airway-related adverse events associated with the decline in FEV1. However, asthmatics treated with Staccato Loxapine exhibited the largest declines of 0.303 L (0.378, 0.228) at 15 minutes post Dose 1 and 0.537 L (0.696, 0.378) 15 minutes post Dose 2. For FVC values, the largest decrease from baseline in Staccato Loxapine treated asthmatics was 0.537 L (0.667, 0.407) 15 minutes after Dose 2. Of the patients with asthma treated with Staccato Loxapine, ten discontinued due to either bronchospasm, wheezing, dyspnea or a decrease in $FEV1 \geq 20\%$ baseline. At the end of the 34 hour pulmonary assessment of these patients with asthma, 10 of the original 26 of Staccato Loxapine treated and 23 of the original 26 of the Staccato placebo treated patients completed the two dose protocol. For the COPD group, 19 out of 26 of the Staccato Loxapine treated subjects received Dose 2 while 26 out of 27 of placebo treated subjects received Dose 2.

The same level of decline in FEV1 observed in the asthma population was not seen in the COPD patients which is consistent with the pathophysiology of COPD where a significant degree of the airway obstruction is fixed rather than reversible. The largest mean decline from baseline was 0.125 ml (0.204, 0.045) in the Staccato Loxapine treated subjects and the largest change following Staccato placebo-treatment was -0.077 L (-0.195, 0.042). The COPD patients in the study seemed to represent a mixed population in terms of the severity of disease based on the baseline post bronchodilator FEV1 of approximately 1.8L. This is significantly higher than many of the large COPD trials such as TORCH and UPLIFT. Of the Staccato Loxapine treated COPD subjects 70% were in the $FEV1 > 50\%$ category. The occurrence of hypoxia was not adequately evaluated and remains a concern for patients treated with Staccato Loxapine because again, patients that received rescue medication were excluded from the analysis of oxygen levels. Evaluation of the notable respiratory signs and symptoms revealed a greater percentage seen in Staccato Loxapine treated asthmatics and patients with COPD than placebo. In the asthmatic population, 54% of Staccato Loxapine treated and 11.5% placebo treated patients experienced airway-related AEs of bronchospasm, chest discomfort, wheezing or dyspnea. For the COPD patients, airway-related AE were found in 19% Staccato Loxapine treated patients and 11% placebo-treated patients. The large numbers of patients with COPD exhibiting pulmonary toxicities raises the concern over the necessary skill and preparedness of the staff in administering rescue medication in patients with acute respiratory distress in the setting of agitation.

The sedative effects of Staccato Loxapine were apparent within 15 minutes post dose and lasting anywhere from 5 hours post Dose 1 to 12 hours post Dose 2. However, a clinically significant value or cutoff of the VAS score was not clearly described to thoroughly evaluate the clinical changes that may be associated with these VAS scores.

In conclusion, the apparent unfavorable risk benefit profile seen in patients with known pulmonary disease who were administered Staccato Loxapine raises concern over an approval action. If Staccato Loxapine were to be approved, appropriate pulmonary information and contraindications in the product label along with implementation of a REMS to ensure safe use is recommended.

8. Proposed Product Labeling, REMS and PMR

Minimal language regarding pulmonary toxicity is included in the Applicant's proposed labeling for Staccato Loxapine. **Section 5.7 Use in Patients with Concomitant Illness** describes the potential for bronchospasm in patients with asthma or COPD. **Section 8.6 Use in Specific Populations/ Patients with Underlying Lung Disease** describes the studies performed to evaluate subjects with mild-to-moderate persistent asthma and moderate-to-severe COPD. No warnings, REMS or PMR have been proposed.

Due to the unfavorable risk-benefit profile of Staccato Loxapine in a population with a significant smoking and pulmonary disease burden, the reviewer did not make specific labeling comments. If labeling negotiations are undertaken, DPARP is prepared to offer recommendations at that time.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22549	ORIG-1	ALEXZA PHARMACEUTICA LS INC	Staccato (loxapine) for Oral Inhalation

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/s/

ANYA C HARRY
08/27/2010

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08/27/2010

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08/27/2010
I concur