

# Multiple Dose Pharmacokinetics of Inhaled Loxapine in Subjects on Chronic, Stable Antipsychotic Regimens

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## Abstract

This randomized, double-blind, placebo-controlled, parallel-group study was to determine the pharmacokinetic characteristics, safety, and tolerability of multiple doses of inhaled loxapine aerosol in subjects on a stable, oral, chronic antipsychotic regimen. Loxapine was delivered by means of a unique thermally generated aerosol comprising drug particles of a size designed for deep lung delivery and absorption. Thirty-two subjects were randomized 1:1:1:1 to receive inhaled loxapine (total doses of 15, 20, or 30 mg) or inhaled placebo administered in 3 divided doses, given 4 hours apart. Following inhalation, the median  $T_{max}$  was 2 minutes, and concentrations declined to about half  $C_{max}$  approximately 5 minutes later across the 3 dose levels. The dose proportionality across data from this study combined with data from the single-dose study showed a slope (90%CI) of log  $AUC_{inf}$  versus log dose of 0.818 (0.762–0.875) across the 8 doses ( $n = 60$  subjects) studied, indicating reasonable dose proportionality. The most common adverse events were cough (3 of 32, 9%), sedation (3 of 32, 9%), and dysgeusia (2 of 32, 6%). The inhalation of multiple doses of inhaled loxapine were well tolerated in study subjects and provided a safe, well-tolerated means for rapidly and reliably achieving therapeutic plasma concentrations of loxapine. ClinicalTrials.gov identifier: NCT00555412

## Keywords

inhaled loxapine, ADASUVE, multiple dose, pharmacokinetics, pharmacodynamics, agitation, *Staccato*

Acute agitation is a serious complication of many chronic mental illnesses, including schizophrenia,<sup>1</sup> bipolar disorder,<sup>2</sup> and dementia.<sup>3</sup> Broadly defined as a state of motor restlessness associated with mental tension, agitation may include hand-wringing, fist clenching, pacing, pressured speech, yelling, or threatening other persons.<sup>4</sup> Acute agitation associated with psychiatric diseases often results in severe distress to patients and their caregivers and is a major contributor to the ongoing stigmatization of mental illness.<sup>5</sup>

Oral loxapine, introduced more than 35 years ago in the United States, Canada, and Europe, has a well-established efficacy and safety profile in the treatment of schizophrenia,<sup>6,7</sup> and an intramuscular formulation was previously approved for the treatment of agitation.<sup>8–11</sup> Its antipsychotic effects are similar to those of other antipsychotics such as haloperidol and are likely attributable to its action at dopamine D2 receptors.<sup>1</sup> Loxapine shares some of its clinical effects with atypical antipsychotics such as clozapine and olanzapine,<sup>12</sup> likely because of its antagonism of 5-hydroxytryptamine 2A receptors. Oral loxapine is used for the treatment of schizophrenia in the United States. The intramuscular form of loxapine is no longer marketed in the United States, but is frequently used in France for the acute treatment of agitation.<sup>13</sup> Intramuscular antipsychotics have a  $T_{max}$  of 90 minutes and can take up to 60 minutes to reduce agitation,<sup>14–17</sup> and symptoms can

escalate during this period. Moreover, intramuscular administration is often resisted by patients. To address these concerns, an inhaled formulation of loxapine has been developed that has a  $T_{max}$  of 2 minutes and has been shown in clinical trials to begin controlling agitation of patients with schizophrenia<sup>18</sup> or bipolar I disorder<sup>19</sup> within 10 minutes. This inhaled loxapine formulation (ADASUVE) uses breath-actuated delivery, the *Staccato* system, which delivers loxapine with a pharmacokinetic profile comparable to that of intravenous administration, providing peak plasma levels in systemic circulation within minutes after administration.<sup>20</sup> ADASUVE was approved by the US Food and Drug Administration in 2012 for a single dose and by the European Medicines Association in

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2013 for 2 doses. In the United States, it is “indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults.” ADASUVE became commercially available in the European Union in 2013 and in the United States in 2014.

The objective of this phase 1, randomized, double-blind, placebo-controlled, parallel-group study was to determine the pharmacokinetic characteristics, safety, and tolerability of multiple doses of inhaled loxapine aerosol in subjects on a stable, oral, chronic antipsychotic medication regimen.

## Methods

### Human Subject Protection

The protocol for this study was reviewed and approved by the Sterling Institutional Review Board (Atlanta, Georgia). Prior to enrollment in the study, written informed consent was obtained from each subject.

### Subjects

Participants in this study were male and female subjects between 18 and 65 years of age, inclusive, who were on a stable, oral, chronic (more than 2 months) antipsychotic medication regimen and who were able to tolerate the rapid oral dose taper and substitution regimen (half their usual oral dose  $\times$  1 day, followed by a quarter oral dose  $\times$  1 day, followed by inhaled loxapine or placebo  $\times$  1 day).

Subjects provided written informed consent prior to the initiation of any study procedures and expressed willingness to comply with all requirements of the study. Subjects were excluded from the study if they were currently being treated with injectable depot neuroleptics within a 1-dose

interval, had a history of drug or alcohol dependence or abuse within the preceding year, had a history of asthma or chronic obstructive lung disease or a known allergy or intolerance to amoxapine or loxapine, or were currently taking medications that prolong the QT/QTc interval. Female subjects of childbearing potential (and male participants if sexually active with a partner of childbearing potential) agreed to use a medically accepted method of contraception during the study and for 1 week after.

### Study Center and Dates

The study was conducted at Atlanta Center for Medical Research (Atlanta, Georgia) between October and December 2007.

### Study Medication

The Staccato System (Alexza Pharmaceuticals, Inc., Mountain View, California) is designed to provide rapid drug delivery via inhalation of thermally generated aerosols. This handheld device and its development have been described elsewhere.<sup>21,22</sup> To summarize, the flow of inspired air through the delivery device is detected by a breath sensor, causing rapid activation of a sealed, drug-coated heat source resulting in complete drug vaporization in less than 1 second. The vaporized drug quickly cools and condenses into aerosol particles with a mass median aerodynamic diameter between 1 and 3.5  $\mu\text{m}$  before leaving the device via the inspired air. Drug particles of this size are optimal for deep lung delivery and rapid systemic drug absorption.<sup>23</sup> Figure 1 shows the delivery system before and during an inhalation. The placebo used in this study was identical

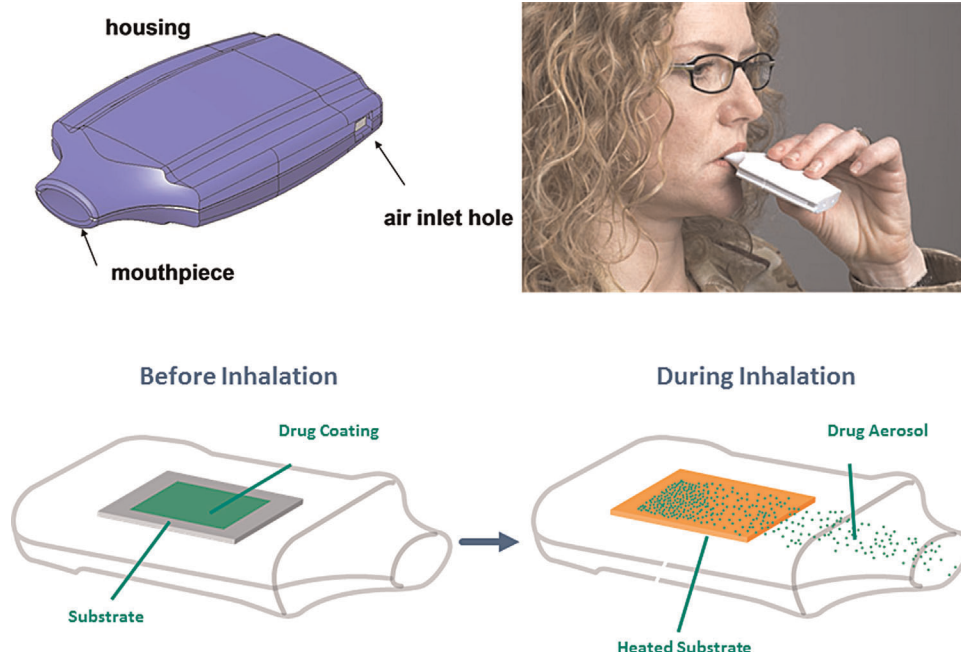


Figure 1. Staccato drug-device combination product.

to the active treatments except there was no drug coated onto the heat package.

### Study Design

This phase 1, single-center, randomized, double-blind, multiple-dose, placebo-controlled safety and pharmacokinetic study of inhaled loxapine enrolled subjects on a chronic, stable antipsychotic regimens. Adult subjects (18–65 years, inclusive) were randomized to 1 of the 4 parallel groups: inhaled loxapine 15, 20, or 30 mg (total daily dose) or inhaled placebo (1:1:1:1). Subjects received 3 doses of study drug in a 24-hour evaluation period: 3 doses of 5 mg for the 15-mg group, 1 dose of 10 mg and 2 doses of 5 mg for the 20-mg group, and 3 doses of 10 mg for the 30-mg dose group. The doses were separated by 4 hours. Each of the 5- and 10-mg inhaled loxapine doses were administered during a single inhalation.

The study enrolled 32 subjects, 8 per treatment group. Subjects were on stable, oral, chronic (more than 2 months) antipsychotic medication regimens. In addition, subjects were able to tolerate the rapid oral dose taper and substitution regimen (half oral dose for 1 day, followed by a quarter oral dose for 1 day, followed by loxapine or placebo for 1 day). Only subjects who were willing and able to comply with the study schedule and requirements and stay at the Clinical Research Unit for approximately 36 hours were enrolled.

Subjects signed an informed consent form before any protocol-related assessments or procedures. As part of the screening process, subjects were trained in the use of the delivery system, and their ability to use the device properly was evaluated. Screening and baseline evaluations were performed during a 3-week period. After eligibility was confirmed, each subject was enrolled in the study, randomized to 1 of the 4 dose regimens, and dose 1 of study medication was administered. Doses 2 and 3 were administered 4 and 8 hours later

### Pharmacokinetic Assessments

Blood samples (4 mL each) were collected into evacuated dipotassium ( $K_2$ ) EDTA tubes from each subject at the specified times (predose, 2, 5, 10, and 20 minutes, 1 and 2 hours after each dose, and 12, 16, and 20 hours). Tubes were gently inverted 8 to 10 times and placed on ice, centrifuged (within 30 minutes) for 15 minutes (1000g) at 4°C–10°C, plasma was split into 2 equal volume samples (set A and set B) and stored upright at –70°C or below for storage. Set A was sent to the analytical laboratory, and set B was retained at the study site until the end of the study. Plasma loxapine, 7-OH-loxapine, 8-OH-loxapine, and amoxapine concentrations were measured using a validated method by Tandem Labs (Salt Lake City, UT). Analytical quality controls (QCs) at the low (0.150 ng/mL), medium (20.0 ng/mL), and high (40.0 ng/mL) levels were assayed in duplicate in each

analytical run. For each dilution level, dilution QCs (200 ng/mL,  $df=10$ ) were run in triplicate in any analytical run that contained diluted subject samples. Each internal standard (loxapine-d8, amoxapine-d8, 7-hydroxyloxapine-d8, and 8-hydroxyloxapine-d8) was added to all samples (except blanks). Calibration standards had to be within  $\pm 15\%$  of target ( $\pm 20\%$  for the method lower limit of quantification [LLOQ]) to be acceptable. The samples were prepared by a solid-phase extraction procedure and analyzed by liquid chromatography–tandem mass spectrometry. The API 5000 was operated in the selected reaction monitoring mode under optimized conditions for detection of loxapine, amoxapine, 7-OH-loxapine, and 8-OH-loxapine, as well as the internal standards loxapine-d8, amoxapine-d8, 7-OH-loxapine-d8 and 8-OH-loxapine-d8 positive ions formed by electrospray ionization. The LLOQ of the assay was 0.05 ng/mL for all analytes.

Individual plasma concentration (C) versus time (t) data across the 3 doses were analyzed by model-independent methods to obtain the pharmacokinetic parameters for loxapine and its metabolites, where appropriate, using WinNonlin software (version 5; Pharsight Corporation, Mountain View, California). The maximum concentration ( $C_{max}$ ) and the time to  $C_{max}$  ( $T_{max}$ ) were the observed values. The time when the concentration fell to half of  $C_{max}$ ,  $T_{half-max}$ , was calculated based on linear interpolation from the mean concentration profiles. The area under the concentration–time curve to the last measurable concentration,  $AUC_{last}$ , was estimated by the linear trapezoidal rule. The  $AUC_{inf}$  was calculated as  $AUC_{last} + C_{last}/k_e$ , where  $C_{last}$  is the last measurable plasma concentration and  $k_e$  is the terminal rate constant. The half-life was calculated as  $\ln(2)/k_e$ . Clearance uncorrected for bioavailability of loxapine (CL/F) was calculated as total dose/ $AUC_{inf}$ . For each of the 3 metabolites (7-OH-loxapine, 8-OH-loxapine, and amoxapine), the  $AUC_{inf}$  ratio of each metabolite to loxapine was calculated for each subject.

In the phase 3 trials, it was planned to give the second dose, if needed, 2 hours after the first dose, so the difference between the 4-hour and 2-hour concentrations as a percentage of  $C_{max}$  was calculated from the mean concentration profiles:  $C_{2h} - C_{4h}$  as a percentage of  $C_{max}$ .

### Safety Assessments

Safety measurements included clinical laboratory evaluation (blood chemistry, hematology, and urinalysis), physical examination, 12-lead electrocardiogram (ECG), and sedation assessments. Vital signs (systolic and diastolic blood pressure, pulse rate, and respiratory rate) were measured immediately before dosing, 10 minutes after each dose, and at 24 and 48 hours.

Sedation was measured with a 100-mm visual analog scale (VAS) between the verbal anchors extremely sleepy

(0) and wide awake (100) immediately before dosing, at 10 and 20 minutes, 1, 2, and 4 hours after each dose, and at 24 hours.

Treatment-emergent adverse events (AEs) were recorded throughout the study period, with the investigator reporting an assessment of the severity of each AE and its relationship to the study drug. AEs were classified according to Medical Dictionary for Regulatory Activities (MedDRA), version 10.0, system organ class and preferred terms.

### Analyses of Quantitative Safety Measures

Eleven quantitative safety measures, including vital signs, ECG intervals, and sedation scale, were examined across the dose groups. Vital signs and ECG intervals were measured at 1 time (10 minutes) after each of the 3 doses. Sedation was measured at 4 times after each dose.

The dose effect was evaluated using the following steps:

- The dose response for each measure was examined based on the most recent dose (0, 5, or 10 mg) and cumulative dose (0, 5, 10, 15, 20, or 30 mg) by visual inspection, linear regression, and analysis of variance (ANOVA) with dose as a nominal variable to avoid assumptions on the dose relationship).
- For sedation, the dose response was examined for 1, 2, 3, and all 4 time points.
- The following descriptive statistics were computed by dose group for each measure: number of subjects (n), mean, standard deviation (SD), standard error of the mean (SEM), and 90% confidence interval (CI).
- Graphic displays of each time-averaged measure were then generated and examined, and representative graphics were chosen to summarize the quantitative safety results.

### Statistical Analyses

The results of clinical laboratory tests, vital signs, ECGs, and VAS sedation were summarized by treatment group. AEs were coded by body system and preferred term using MedDRA version 10.0 and summarized by frequency counts and incidence percentages. Subjects with multiple episodes of a single AE or multiple AEs that coded to the same preferred term or body system were counted only once in the event summary. The relation of the quantitative safety measures to dose was assessed via ANOVA versus last dose received (as a nominal variable).

The dose proportionality for loxapine was examined across the dose groups using the power model (linear regression of  $\log AUC_{inf}$  vs  $\log$  dose). A slope of 1.00 would indicate “perfect” dose proportionality (double the

dose = double the exposure). Because within this study, the dose range was only 2-fold (30 vs 15 mg), an additional power analysis was done including the 16-fold dose range (10 vs 0.625 mg) from the single-dose study.<sup>20</sup>

Statistical analyses and preparation of summary tables and graphics were performed using Statistical Analysis System (SAS, version 9.1.3 for Windows) and SAS JMP (version 9.0.0 for Windows). No imputation of missing data was performed.

## Results

In all, 37 subjects were screened, 32 were enrolled and randomly assigned to the 4 treatment groups, and all 32 completed the study (Figure 2). The safety analyses included the 32 subjects enrolled into this study and pharmacokinetic analyses on the 24 subjects who received inhaled loxapine. The age of the 32 subjects (mean  $\pm$  SD) was  $44.5 \pm 10.0$  years, weight was  $85.6 \pm 14.6$  kg, 10 (31.3%) were female, 28 (87.5%) were smokers, 30 (94%) were black, 1 was white, and 1 was Native American. The characteristics by treatment group and for all subjects are shown in Table 1.

### Pharmacokinetics

Following repeat administration every 4 hours for 2 additional doses, the shape of the plasma concentration–time profiles was similar to that following administration of the first dose (Figure 3). Table 2 summarizes the pharmacokinetic (PK) parameters by dose group, and Table 3 shows the PK parameters across all 3 dose groups. The loxapine plasma concentration–time profiles showed rapid absorption and distribution across the 3 dose regimens administered (total dose range of 15 to 30 mg). The median (min, max)  $T_{max}$  for the 72 doses was 2 minutes (2, 120 minutes). Mean peak plasma concentrations across all 3 dose groups (mean  $\pm$  SD, normalized to 10 mg) were  $69.3 \pm 55.0$ ,  $101 \pm 78.5$ , and  $107 \pm 82.6$   $\mu\text{g/mL}$  after the first, second, and third doses, respectively.

The loxapine half-life,  $T_{max}$ , and CL/F were similar across the 3 dose regimens studied. The terminal half-life across all doses was  $7.1 \pm 1.9$  hours, and CL/F was  $103 \pm 51.7$  mL/h.

For the 9 mean postdose profiles (Table 2), the difference between the 4- and 2-hour concentrations as a percentage of  $C_{max}$  was  $7.6\% \pm 1.9\%$ . The median (min, max) time to half-max ( $T_{half-max}$ ) was 6.8 minutes (4.9, 8.4 minutes). Time after  $T_{max}$  ( $T_{half-max} - T_{max}$ ) was 4.6 minutes (2.9, 6.4 minutes).

The PK parameters  $AUC_{inf}$ ,  $AUC_{last}$ , and  $C_{max}$  increased with increasing loxapine dose (Table 1). The slope of  $\log AUC_{inf}$  versus  $\log$  total dose of the 3 doses in this study (power analysis) was 0.661,  $P = .328$ . As seen in Figure 4, loxapine  $AUC_{inf}$  was dose-proportional across

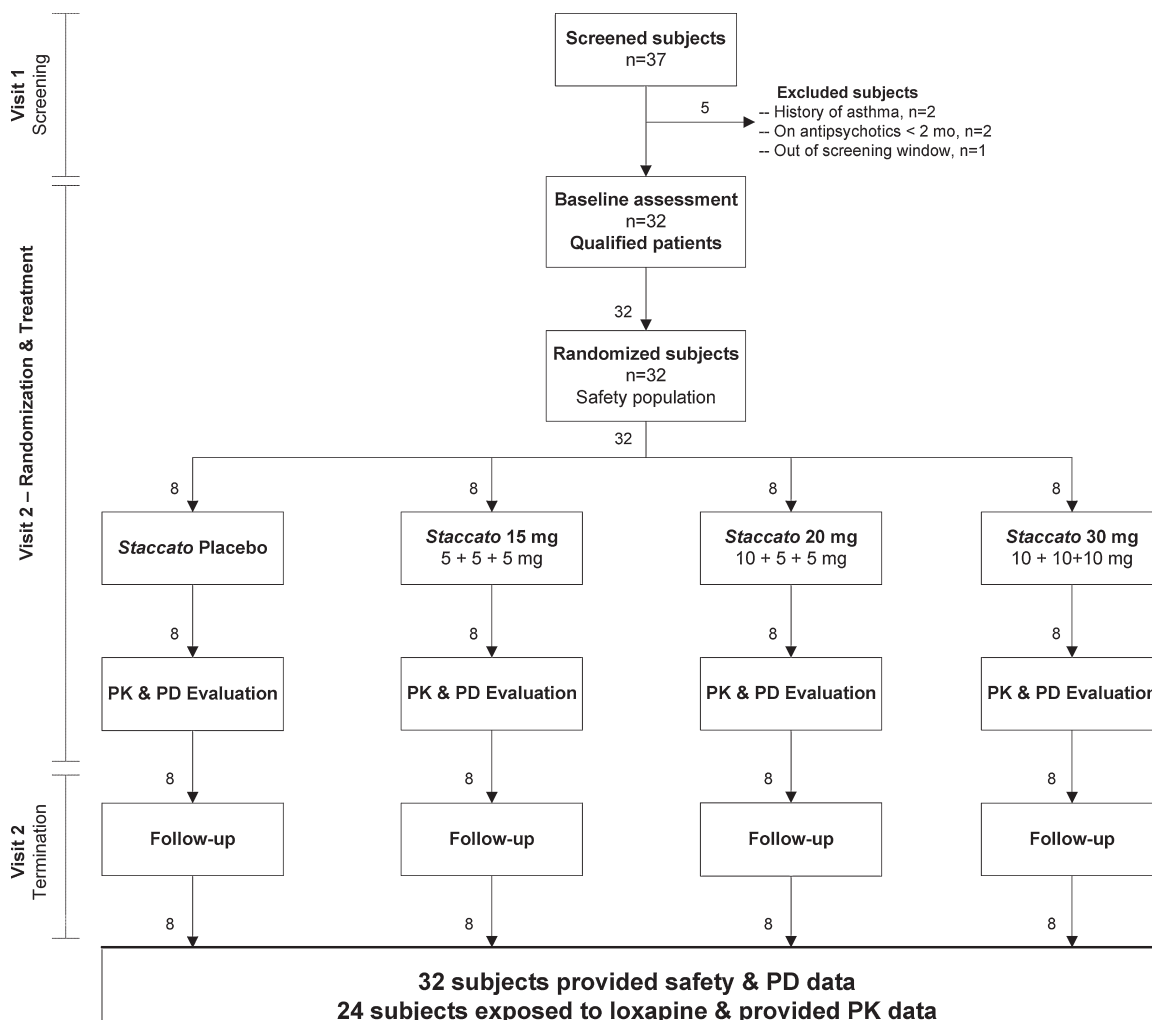


Figure 2. Subject disposition (safety population).

the 8 doses (3 doses studied in this multidose study and the 5 doses studied from the single-dose study).<sup>20</sup> The slope (90%CI) of log AUC<sub>inf</sub> versus log dose was 0.818 (0.762–0.875),  $P < .0001$ , across the 8 dose groups.

For the 3 metabolites measured, the mean AUC<sub>inf</sub> ratio to loxapine was 15.0% for 7-OH-loxapine, 103% for 8-OH-loxapine, and 6.1% for amoxapine (Table 2).

**Safety**

All 32 subjects completed all 3 doses; there were no premature discontinuations. There were no deaths, serious adverse events (AEs), or early study discontinuations because of AEs. AEs were reported by 31% of subjects (10 of 32); all were mild or moderate in intensity. All AEs are tabulated in Table 4. AEs were reported by 0%, 38%, 38%, and 50% of those who received placebo and total doses of 15, 20, and 30 mg of inhaled loxapine, respectively. The most common adverse events were cough (3 of 32, 9%), sedation (3 of 32, 9%), and dysgeusia (2 of 32, 6%). One subject

had an episode of tachycardia, dizziness, and hypotension, which occurred 31 hours after the last inhaled loxapine dose and was judged by the investigator to be associated with the restarting of the subject’s quetiapine 750 mg. One subject reported a history of high blood sugar for 1 year, had a glucose at screening of 129 mg/dL, 295 mg/dL at baseline (day -2), 318 mg/dL on day +1, and 446 mg/dL at follow-up. A clinic appointment was arranged, and the importance of follow-up was stressed to the subject.

For laboratory tests (hematology, blood chemistry, or urinalysis), the majority of subjects had results that were within the normal reference ranges at baseline and on day 1. No individual results were judged clinically significant by the investigator (with 1 exception), and no results were deemed to be adverse events. The exception was the subject with high blood glucose described above. There were no clinically significant mean changes from baseline through the end of the study for any parameter, and no means were outside the reference range. All

**Table 1.** Patient Characteristics (Safety Population, N = 32)

Demographic or Baseline Characteristic	StaccatoPlacebo (N = 8)	StaccatoLoxapine 15 mg (N = 8)	StaccatoLoxapine 20 mg (N = 8)	StaccatoLoxapine 30 mg (N = 8)	Overall Study Population (N = 32)
Sex, n (%):					
Female	3 (37.5%)	2 (25.0%)	3 (37.5%)	2 (25.0%)	10 (31.3%)
Male	5 (62.5%) <sup>a</sup>	6 (75.0%)	5 (62.5%)	6 (75.0%)	22 (68.8%)
Age (years)					
Mean (SD)	40.4 (10.8)	42.5 (7.7)	44.3 (8.1)	50.9 (11.3)	44.5 (10.0)
Median	40.5	43.5	45.0	53.0	44.5
Min, max	24, 56	27, 52	33, 56	34, 65	24, 65
Height (cm)					
Mean (SD)	169 (5.6)	164 (15.2)	173 (6.7)	175 (9.0)	170 (10.2)
Median	169	165	173	175	170
Min, max	160, 175	137, 183	165, 183	163, 185	137, 185
Weight (kg)					
Mean (SD)	79.0 (12.8)	91.2 (13.8)	82.6 (13.2)	89.4 (17.2)	85.6 (14.6)
Median	74.6	95.1	80.3	92.9	86.8
Min, max	63.5, 95.5	63.0, 106	62.5, 104	61.4, 111	61.4, 111
Race, n (%)					
Caucasian	0	0	1 (12.5%)	0	1 (3.1%)
Black	8 (100%)	7 (87.5%)	7 (87.5%)	8 (100%)	30 (93.8%)
Hispanic	0	0	0	0	0
Asian	0	0	0	0	0
Native American	0	1 (12.5%)	0	0	1 (3.1%)
Smoking history, n (%)					
Current smoker	7 (87.5%)	7 (87.5%)	7 (87.5%)	7 (87.5%)	28 (87.5%)

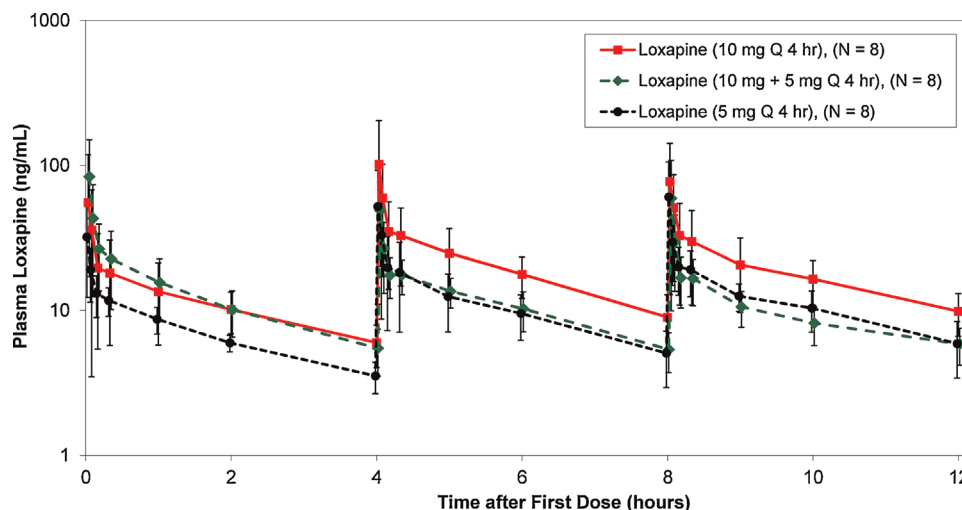
physical examinations were normal at screening and at the end of the study.

Based on the methods outlined above (Analyses of Quantitative Safety Measures section), the most recent dose response was statistically stronger in virtually all analyses than the cumulative dose, and are reported hereafter. The strongest relationship to dose for sedation was for the mean of the first 3 times (10, 20, and 60 minutes). Figure 5 shows 6 plots that are representative of the results for the 11 quantitative safety measures.  $R^2$  is

shown in each panel of the ANOVA —  $R^2$  of 0.185 means the dose group explained 18.5% of the observed variation. All but the QTcF ANOVAs showed statistically significant dose-related effects ( $P < .05$ ).

## Discussion

Acute agitation generally requires prompt pharmacological intervention to minimize the likelihood of patient injury and distress and to ensure the safety of other



**Figure 3.** Plasma concentrations of loxapine by dose regimen, first 12 h. Mean  $\pm$  1 SD by dose group, all PK subjects (N = 24).

**Table 2.** Pharmacokinetic Parameters for Inhaled Loxapine by Dose Group. All subjects receiving loxapine (N = 24 subjects)

Parameter	15 mg (5 + 5 + 5 mg) (N = 8)	20 mg (10 + 5 + 5 mg) (N = 8)	30 mg (10 + 10 + 10 mg) (N = 8)
T <sub>max</sub> (min) <sup>a</sup>	2 [2, 5] (8)	2 [2, 60] (8)	10 [2, 120] (8)
Dose 1			
Dose 2	2 [2, 5] (8)	2 [2, 20] (8)	2 [2, 120] (8)
Dose 3	2 [2, 13] (8)	2 [2, 60] (8)	2 [2, 120] (8)
All Doses	2 [2, 13] (24)	2 [2, 60] (24)	2 [2, 120] (24)
Half-life (h) <sup>b</sup>	6.6 ± 2.0 (8)	7.9 ± 2.3 (8)	6.75 ± 1.3 (8)
CL/F (mL/h) <sup>b</sup>	86.6 ± 22.6 (8)	101 ± 42.4 (8)	122 ± 75.8 (8)
AUC <sub>inf</sub> (ng · h/mL) <sup>b</sup>	184 ± 49.6 (8)	226 ± 82.7 (8)	315 ± 145 (8)
AUC <sub>last</sub> (ng · h/mL) <sup>b</sup>	167 ± 46.0 (8)	197 ± 71.8 (8)	284 ± 129 (8)
C <sub>max</sub> (ng/mL) <sup>b</sup>	32.7 ± 19.1 (8)	84.8 ± 65.0 (8)	57.8 ± 61.7 (8)
Dose 1			
Dose 2	52.3 ± 40.6 (8)	48.8 ± 28.2 (8)	102 ± 102 (8)
Dose 3	62.2 ± 48.9 (8)	59.4 ± 49.0 (8)	78.4 ± 63.5 (8)

a = Median [Min, Max] (N)

b = Arithmetic mean ± standard deviation (N)

patients and staff in the treatment setting. Currently available treatments for acute agitation include oral or intramuscular formulations of conventional and atypical antipsychotics, often used in combination with a benzodiazepine.<sup>24–26</sup> ADASUVE was the first inhaled product for the acute treatment of agitation in patients with schizophrenia or bipolar I disorder and has demonstrated onset of an antiagitation effect in 10 minutes.<sup>18,19</sup>

**Table 3.** Pharmacokinetic Parameters for Loxapine and Metabolites Across Dose Groups. All subjects receiving loxapine (72 doses in 24 subjects receiving 3 doses each)

Parameter	Observations	All 3 Doses
T <sub>max</sub> (min) <sup>a</sup>	72	2 [2, 120]
C <sub>max</sub> (Dose 1) <sup>b</sup> (ng/mL) <sup>c</sup>	24	69.3 ± 55.0
C <sub>max</sub> (Dose 2)(ng/mL) <sup>c</sup>	24	101 ± 78.5
C <sub>max</sub> (Dose 3)(ng/mL) <sup>c</sup>	24	107 ± 82.6
AUC <sub>inf</sub> 7-OH-loxapine (%) <sup>cd</sup>	24	15.0 ± 7.7
AUC <sub>inf</sub> 8-OH-loxapine (%) <sup>cd</sup>	24	103 ± 45.0
AUC <sub>inf</sub> Amoxapine (%) <sup>cd</sup>	24	6.1 ± 3.5
Half-life (h) <sup>c</sup>	24	7.1 ± 1.9
CL/F (mL/h) <sup>c</sup>	24	103 ± 51.7
C <sub>2hr</sub> - C <sub>4hr</sub> (% of C <sub>max</sub> ) <sup>ce</sup>	9	7.6 ± 1.9%
T <sub>half-max</sub> (min) <sup>ae</sup>	9	6.8 [4.9, 8.4]
T <sub>half-max</sub> - T <sub>max</sub> (min) <sup>ae</sup>	9	4.8 [2.9, 6.4]

a = Median [Min, Max]

b = Normalized to 10 mg dose

c = Arithmetic mean ± standard deviation

d = As a percent of the loxapine AUC<sub>inf</sub>

e = From mean concentration profiles (3 doses in each of the 3 dose groups)

Loxapine aerosol for inhalation thus appears to offer a number of benefits compared with currently available oral and intramuscular treatments for acute agitation in patients with schizophrenia, both in terms of speed of onset and acceptability to patients, who are often reluctant to accept an injection.<sup>10</sup> Oral administration of a single 25-mg dose of loxapine resulted in a mean C<sub>max</sub> of 20 ng/mL after approximately 2 hours,<sup>27</sup> whereas oral administration of a 50-mg dose of loxapine resulted in a mean C<sub>max</sub> of 33 ng/mL after approximately 1.5 hours.<sup>28</sup> Intramuscular administration of 20 mg of loxapine resulted in a C<sub>max</sub> of 17.8 ng/mL after approximately 1 hour.<sup>29</sup>

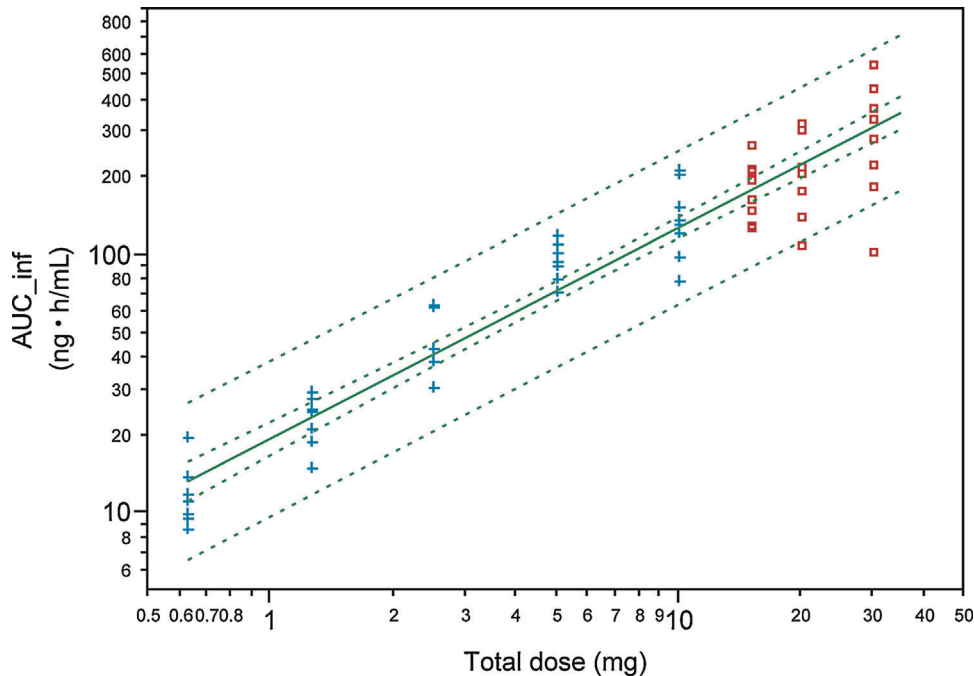
By comparison, inhalation of 5 or 10 mg (normalized to 10 mg loxapine) produced a mean C<sub>max</sub> of 69.3 ng/mL at a median time of 2 minutes (Table 2) following inhalation, so that clinical effects would be expected to occur very quickly. The <8% difference between the 4- and 2-hour concentrations in this study (Table 2) supports the administration of a second dose 2 hours after the first dose. Onset of a statistically significant reduction in agitation at 5 minutes has been demonstrated with this formulation in agitated patients with schizophrenia<sup>18</sup> and bipolar disease.<sup>19</sup>

The lungs contain most of the same drug-metabolizing enzymes found in the liver.<sup>30</sup> However, based on the loxapine levels achieved in this study, loxapine does not appear to be extensively metabolized in the lung. Although the peak plasma concentrations immediately following inhalation are higher than for oral loxapine, the concentration of loxapine and its metabolites after the distribution phase were similar to those reported following oral administration.<sup>27,31,32</sup>

We were able to locate 12 articles that reported measured loxapine blood concentrations. Only Midha et al<sup>28</sup> reported a loxapine half-life or AUC measured over 100 hours after an oral dose. They reported a half-life mean (CV%) of 7.6 hours (121%) compared with 6.2 hours (27%) in our single-dose study and 7.1 hours (27%) in the present study. They likewise reported a dose-normalized (per milligram) AUC<sub>inf</sub> of 3.4 ng · h/mL (59%) compared with 17.8 ng · h/mL (27%) and 11.4 ng · h/mL (50%) in the present study. Thus, both AUC and half-life following inhaled administration exhibited less (or similar) variability compared with oral administration.

The loxapine metabolites, 8-OH-loxapine and amoxapine, have little pharmacological activity at the concentrations observed in this study. Although 7-OH-loxapine has a 5-fold higher affinity for the dopamine D2 receptor compared with loxapine,<sup>33</sup> concentration showed no relation to QTc in a thorough QT/QTc study.<sup>34</sup>

Our data also showed that inhaled loxapine at doses up to 10 mg every 4 hours is safe and well tolerated in subjects on a stable, oral, chronic antipsychotic medication



**Figure 4.** Dose proportionality based on AUCinf for all 8 dose groups. Slope (90%CI) = 0.818 (0.762–0.875) across the 8 doses. (Regression [95% CI], R<sup>2</sup> = 0.911, N = 60). + from single dose study, □ from this study.

regimen. Among the 11 quantitative safety measures studied, none showed clinically important dose-related changes, even though the prescribing information for loxapine lists possible cardiovascular effects such as tachycardia, hypotension, hypertension, orthostatic hypotension, lightheadedness, and syncope.

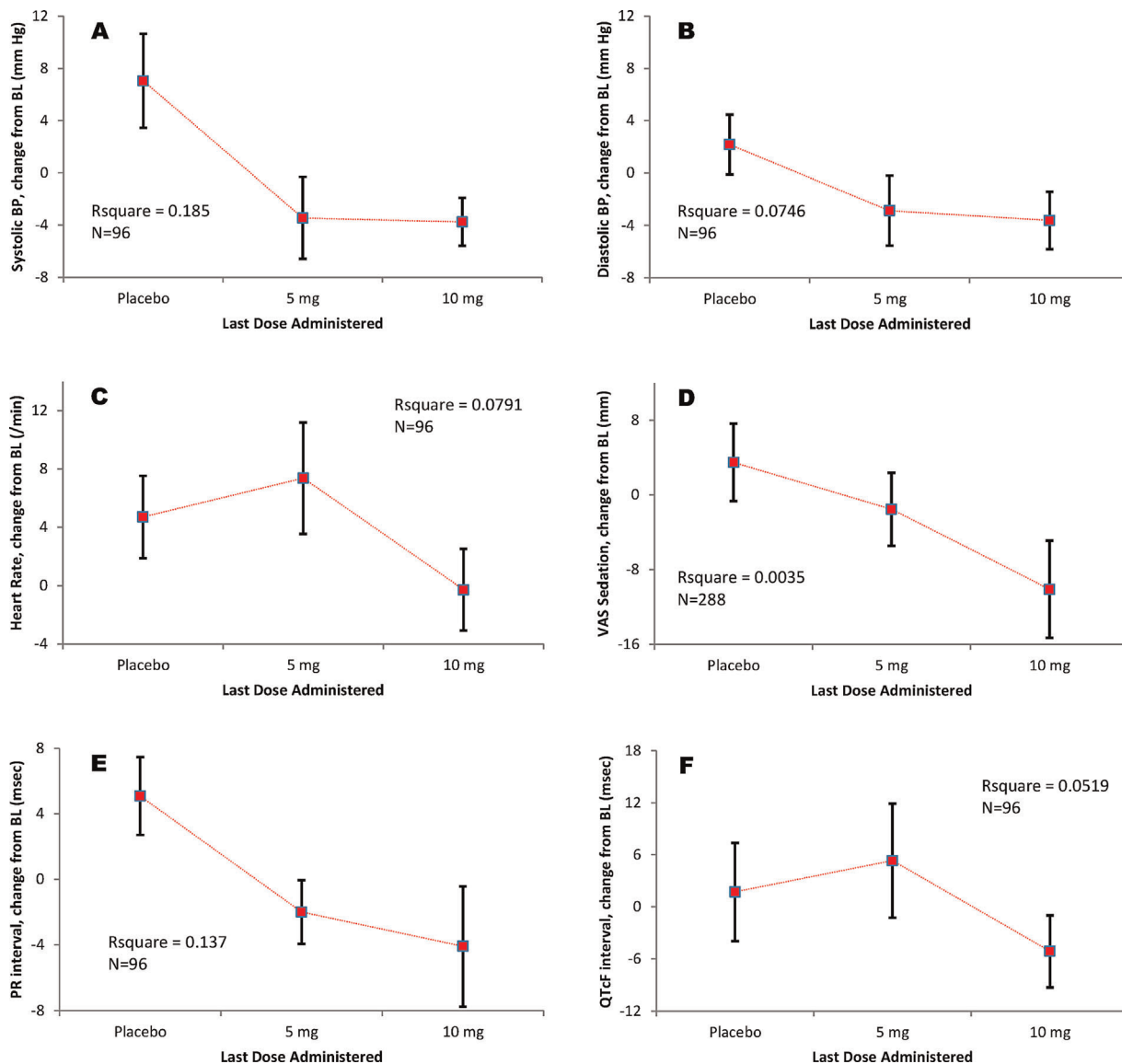
Overall, the most frequently reported AEs among the 24 subjects receiving loxapine were sedation and cough, each reported by 3 subjects. None of the AEs were serious; all events were mild to moderate in severity, and all events resolved without sequelae except for elevated blood glucose in 1 subject (Table 4).

**Table 4.** Number (%) of Subjects with Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Population, N = 32)

SYSTEM ORGAN CLASS Adverse Event	Placebo (N = 8)	Inhaled Loxapine 15 mg (N = 8)	Inhaled Loxapine 20 mg (N = 8)	Inhaled Loxapine 30 mg (N = 8)	All subjects (N = 32)
ANY PRIMARY SYSTEM ORGAN CLASS	0	3 (38%)	3 (38%)	4 (50%)	10 (31%)
CARDIAC DISORDERS	0	0	0	1 (13%)	1 (3%)
Tachycardia <sup>a</sup>	0	0	0	1 (13%)	1 (3%)
GASTROINTESTINAL DISORDERS	0	2 (25%)	2 (25%)	0	4 (13%)
Constipation	0	1 (13%)	0	0	1 (3%)
Dysgeusia	0	1 (13%)	1 (13%)	0	2 (6%)
Hypoesthesia oral	0	1 (13%)	0	0	1 (3%)
Toothache	0	0	1 (13%)	0	1 (3%)
INVESTIGATIONS	0	1 (13%)	0	0	1 (3%)
Blood glucose increased	0	1 (13%)	0	0	1 (3%)
NERVOUS SYSTEM DISORDERS	0	1 (13%)	1 (13%)	2 (25%)	4 (13%)
Dizziness <sup>a</sup>	0	0	0	1 (13%)	1 (3%)
Sedation	0	1 (13%)	1 (13%)	1 (13%)	3 (9%)
RESPIRATORY, THORACIC, & MEDIASTINAL DISORDERS	0	0	1 (13%)	2 (25%)	3 (9%)
Cough	0	0	1 (13%)	2 (25%)	3 (9%)
VASCULAR DISORDERS	0	0	0	1 (13%)	1 (3%)
Hypotension <sup>a</sup>	0	0	0	1 (13%)	1 (3%)

<sup>a</sup> This episode of tachycardia, dizziness, and hypotension occurred 31 hours after the last *Staccato* Loxapine dose and was judged by the investigator to be associated with the restarting of the subject's quetiapine 750 mg.





**Figure 5.** Safety summaries, change from baseline by last dose administered. Arithmetic mean [90% confidence interval] (safety population). A: Sitting systolic BP (mmHg); B: Sitting diastolic BP (mmHg); C: Sitting heart rate (/min); D: VAS sedation (mm); E: PR interval (msec); F: QTcF, Fridericia corrected QT (msec).

### Conclusion

Inhaled loxapine administered every 4 hours at doses of 5 or 10 mg up to a total of 30 mg (10 + 10 + 10 mg) was safe and well tolerated in subjects on chronic, stable antipsychotic regimens. Following inhalation, loxapine was rapidly absorbed and rapidly distributed and exhibited minimal accumulation during a 3-dose regimen with a 4-hour dosing interval. Relative to  $C_{max}$ , there were small differences in loxapine concentration between 2 and 4 hours after dosing, supporting the administration of a second dose 2 hours after the first dose with an expected minimal increase in  $C_{max}$ . The results of this multidose study support repeat dosing of inhaled loxapine after an interval of 2 to 4 hours.

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### Declaration of Conflicting Interests

D.A.S. was an employee during execution of this study and is currently a paid consultant of Alexza Pharmaceuticals. R.A.R. was the principal investigator for this study and was paid by Alexza Pharmaceuticals to carry out this study. J.V.C. is an employee of Alexza Pharmaceuticals. D.A.S. and J.V.C. own stock and stock options.

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