

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022549Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## Clinical Pharmacology/Biopharmaceutics Review

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PRODUCT (Generic Name):	Loxapine
PRODUCT (Brand Name):	Staccato Loxapine for Inhalation
DOSAGE FORM:	Inhalation powder
DOSAGE STRENGTHS:	5 mg and 10 mg delivery devices
NDA:	22549
SUBMISSION DATE:	December 11, 2009
SPONSOR:	Alexza Pharmaceuticals
INDICATION:	Agitation in Schizophrenia or Bipolar Disorder
REVIEWER	Andre Jackson

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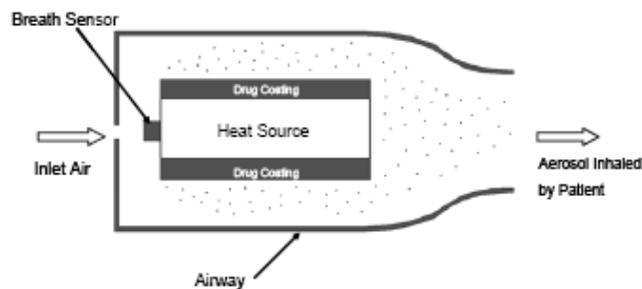
### REVIEW OF A NEW NDA

EXECUTIVE SUMMARY .....	2
RECOMMENDATION .....	3
COMMENTS TO THE MEDICAL OFFICER .....	3
QUESTION BASED REVIEW .....	4
FIRM'S LABEL .....	20
FDA LABEL.....	22
APPENDIX I .....	25
ASSAY VALIDATION.....	25
STUDY PROTOCOL AMDC-004-101 .....	27
STUDY NUMBER: AMDC-004-102 .....	34
STUDY NUMBER: AMDC-004-106 .....	40
PROTOCOL NUMBER: AMDC-004-103 .....	48
ADDENDUM REPORT ON PHARMACOKINETICS AND RACE.....	53
SIGNATURES.....	60
APPENDIX II .....	60
REVIEW OF IN VITRO STUDIES SUBMITTED BY FIRM.....	60
INSPECTION REPORT .....	73
OCP COMMENTS-INSPECTION REPORT .....	84
CONSULTS .....	86
STATISTICAL REVIEW.....	86
ELECTRONIC SIGNATURES.....	99

## EXECUTIVE SUMMARY

The firm is seeking approval of *Staccato* Loxapine which is a hand-held drug-device product that produces a thermally generated aerosol of the dopamine-blocking agent, loxapine, for rapid delivery to the systemic circulation via the lungs. (b) (4)

The principal components of the single-dose drug product, which are shown below



are as follows:

- Heat source (“heat package”) consisting of a battery-activated, hermetically sealed package, with a stainless steel substrate on 1 side
- Thin coating of pure loxapine on the stainless steel substrate
- Surrounding airway with airflow inlets
- Breath-activated mechanism for initiating the heating, and thus, aerosol generation

Loxapine has a half-life of 7 hours and is metabolized to amoxapine, 7-OH loxapine and 8-OH loxapine. The metabolite 7-OH loxapine has been shown to be active.

The sponsor has conducted the following Clinical Pharmacology studies:

1. Study AMDC-004-101  
This was a single-center, randomized, double-blind, placebo-controlled, dose escalation study of 0.625 mg, 1.25 mg, 2.5 mg, 5.0 mg, and 10 mg administered as 1 or 2 puffs done in healthy volunteers.
2. Study AMDC-004-102  
A safety, tolerability, and pharmacokinetics study of multiple doses of Staccato® Loxapine for inhalation in subjects on chronic, stable antipsychotic regimens.

3. Study AMDC-004-103  
This study was designed as 2-treatment, 4-period, dose-stratified, replicate-design to assess the single-dose bioequivalence of the Commercial Product Design vs. the Current Clinical Version.
4. Study AMDC-004-106  
The study assessed the pharmacokinetics of a single dose of 10 mg *Staccato* Loxapine administered to smokers compared to nonsmokers.

The exposure to *Staccato* Loxapine with respect to dose is dose proportional.

Two phase III studies were conducted by the firm:

1. Study 004-301 was an inpatient, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study that evaluated *Staccato* Loxapine 5 or 10 mg or matching placebo in schizophrenic patients with acute agitation.
2. Study 004-302 was an inpatient, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study that evaluated *Staccato* Loxapine 5 or 10 mg or matching placebo in bipolar I disorder (manic or mixed episodes) patients with acute agitation.

## **RECOMMENDATION**

The clinical pharmacology studies have been found to be acceptable to OCP. The NDA 22549 is acceptable to OCP.

## **COMMENTS TO THE MEDICAL OFFICER**

OCP has concluded that study 103 is not a traditional “BE” study as a consequence of the traditional metrics of C<sub>max</sub> and AUC<sub>inf</sub> not being primary metrics for this study. The sponsor has conducted the bioequivalence analysis by combining data from the 5 mg and 10 mg study. Loxapine exhibits dose proportional pharmacokinetics so combining doses is scientifically acceptable. However, sufficient data is available at each dose to independently assess equivalent exposure. The primary metric was AUC(0-2h) for the comparison of the to-be-marketed and clinical formulations. Based upon AUC(0-2h), equivalent exposure for study 103 was evaluated.

1. A separate analysis of the 5 mg dose comparing the Test product (Commercial Version 1) to the Reference product (Clinical Version 2) was found to have equivalent exposure for AUC(0-2hr) with a 90% CI=[0.999-1.238].
2. A separate analysis of the 10 mg dose comparing the Test product (Commercial Version 1) to the Reference product (Clinical Version 2) had an inequivalent exposure for AUC(0-2hr) with a

90% CI=[1.095-1.535]. Although the upper limit of 1.535 exceeds the established limit for conventional equivalence, it does not present a safety concern. An oral capsule formulation of loxapine is administered at doses of 60-100mg/day which is much higher than the 10 mg dose for Staccato loxapine.

3. The 10 mg dose efficacy response did not show any increase in efficacy over the 5 mg dose for schizophrenia or bipolar disorder. Therefore, OCP does not support marketing the 10 mg dose.

4. There was no efficacy vs. dose response between the 5 mg and 10 mg dosage strengths, therefore a lower strength of 2.5 mg of Staccato loxapine should be studied since it may be effective yet provide a greater margin of safety.

5. Based upon the higher exposure to Staccato loxapine observed in Caucasians compared to African Americans, the Medical Officer should determine if the drug shows more efficacy/toxicity in Caucasians for the 5 mg and 10 mg doses.

## QUESTION BASED REVIEW

WHAT ARE THE CURRENTLY APPROVED DRUG PRODUCTS FOR AGITATION?

Name	Initial	Maximum	Route
Aripiprazole	9.75 mg	30 mg/day	IM
Ziprasidone	10-20 mg	40 mg/day	IM
Olanzapine	10 mg	30 mg	IM

WHAT IS THE ACTIVE MOIETY FOR THIS NDA?

The active moiety is loxapine.

DID THE SUBMITTED STUDY 103 COMPARING CLINICAL VERSION 2 TO COMMERCIAL VERSION 1 MEET THE REGULATORY REQUIREMENTS TO BE CONSIDERED A BIOEQUIVALENCE STUDY?

No, BE analysis requires that at least two parameters be evaluated (i.e., AUC<sub>inf</sub> and C<sub>max</sub>). For study 103 C<sub>max</sub> was not evaluated as a primary metric therefore, data from this study can only be used to determine equivalent exposure not true BE.

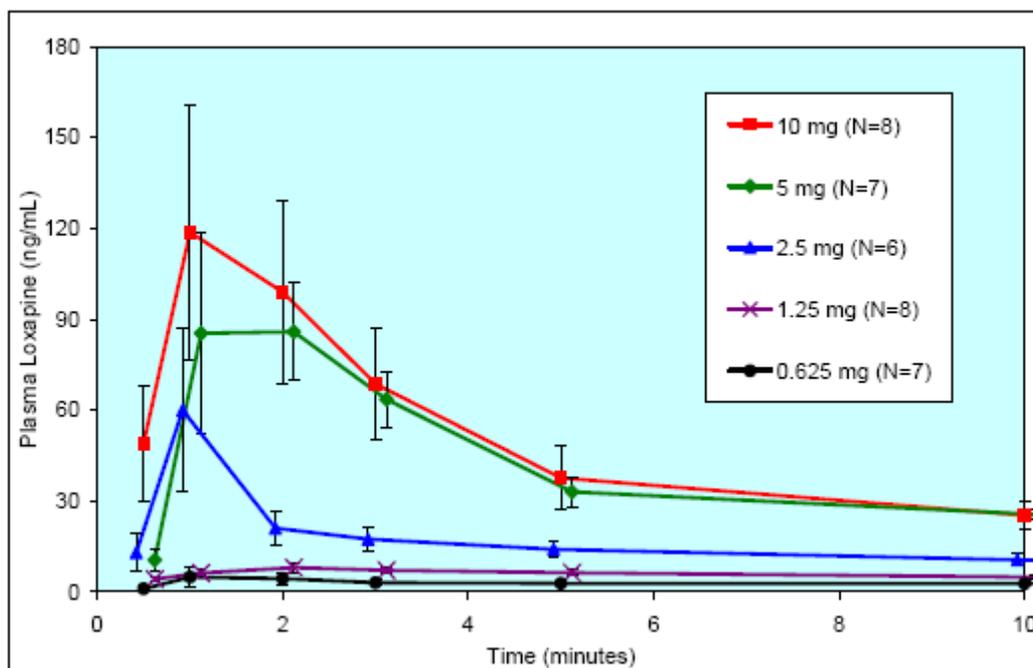
WHAT ARE THE PARAMETERS FOR DETERMINING EQUIVALENT EXPOSURE FOR THIS NDA?

The primary parameter for determination of equivalent exposure is AUC(0-2h). A secondary parameter would be AUC<sub>inf</sub>.

WHY IS AUC(0-2hr) CONSIDERED THE PRIMARY METRIC FOR AGITATION?

Agitation is a condition that requires an immediate onset of clinical intervention. Therefore, based upon the desired Clinical response it was decided by the Division of Psychiatry Drug Products that early exposure within 2 hrs was most relevant. Cmax was not expected to be Bioequivalent since it is a discrete variable that occurs within 2 min of drug administration, which makes it difficult to accurately measure. It was considered a secondary measure.

Figure 1. Plasma Concentrations of Loxapine by Dose Group, First 10 min. All PK Subjects (N=36), Mean  $\pm$  1 SEM



#### DOES STACCATO LOXAPINE EXHIBIT LINEAR PHARMACOKINETICS?

A study done in 36 normal subjects, study 101, investigated the pharmacokinetics of Staccato loxapine at doses from 0.625 mg to 10 mg. The doses of 0.625 mg, 2.5 mg, and 5 mg were administered as 1 single puff, whereas the doses of 1.25 mg and 10 mg were administered as 2 puffs of either 0.625 mg or 5 mg of *Staccato* Loxapine.

Figure 2. AUC<sub>0-inf</sub> vs. dose for subjects in Study 101.

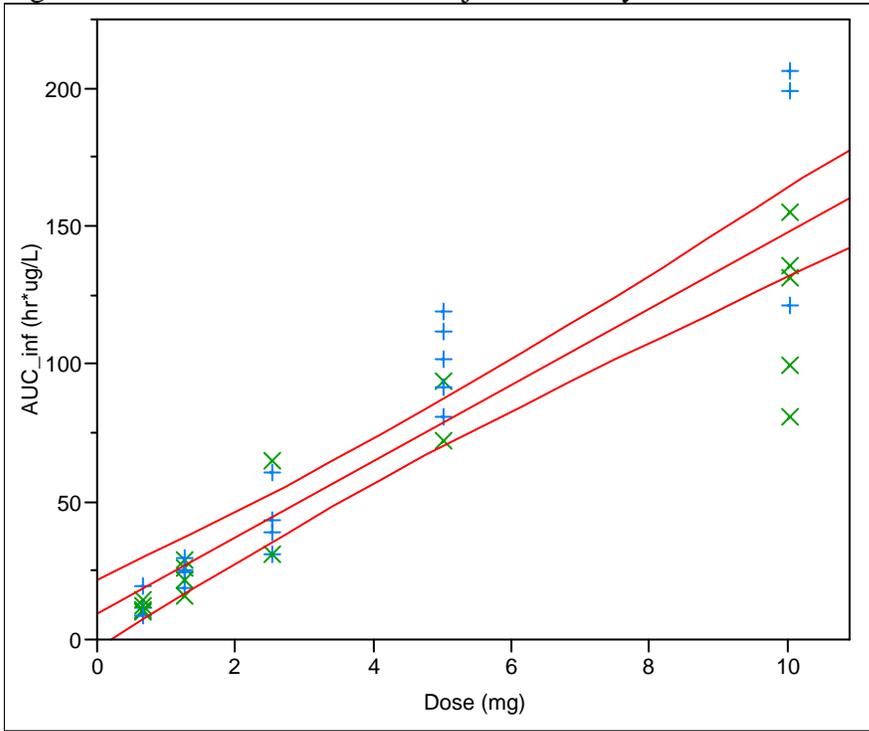
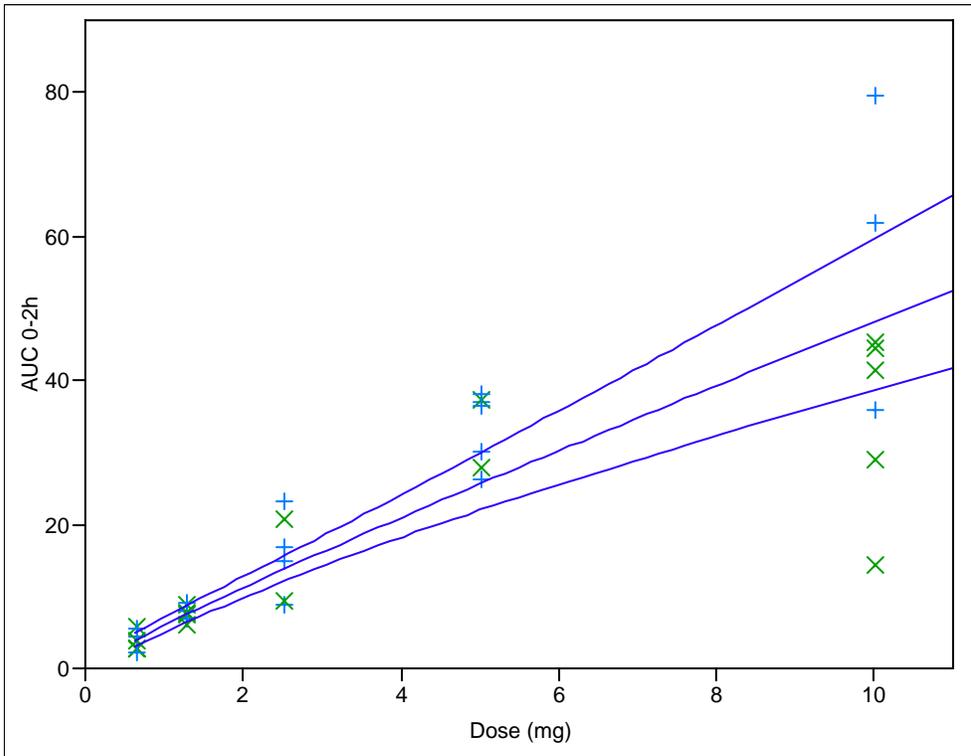


Figure 3. AUC(0-2hr) vs. dose for subjects in study 101.



+ = Female, x = Male

Table 1. Data from single dose Studies 004-103 (BE) and 004-106 (Smokers) were combined for the 10 mg dose. For each study a 5 mg delivery device and a separate 10 mg delivery device were used for dosing.

Parameter	5 mg (N=31)	10 mg (N=65)
AUC <sub>0-2h</sub> (ng·h/mL) Mean ± SD	25.6 ± 7.31	60.5 ± 15.4
AUC <sub>inf</sub> (ng·h/mL) Mean ± SD	70.1 ± 17.8	178 ± 43.8
C <sub>max</sub> (ng/mL) Mean ± SD	116 ± 85.1	217 ± 208

The top graph, Figure 2, shows that the increase in AUC<sub>inf</sub> with dose was less than dose proportional with 95% CI for the slope of 0.832-0.987 and does not include 1. The lower graph, Figure 2, is the same analysis for the BE parameter AUC(0-2h). The 95% CI were 0.77-1.03 indicating that it includes 1. The lack of apparent dose proportionality in study 101 is due to the use of 2 devices (2 puffs) for the 10 mg dose. If one looks at single puff data for the 5 mg vs. 10 mg products (i.e., studies 103 and 106) the data appears to be proportional. However there are no lower doses available to conduct a power analysis for these studies. It also appears that males have lower AUC values than females at the 10 mg dose (study 101), although the N=6 is small.

The pharmacokinetics for the parameters measuring extent of exposure for loxapine exhibit linear pharmacokinetics.

#### WAS THERE ANY ACCUMULATION OBSERVED FOR THE STACCATO LOXAPINE FORMULATION FOLLOWING MULTIPLE DOSING?

A single-center, randomized, double-blind, multiple dose, placebo-controlled, safety and pharmacokinetic study was conducted in subjects on a chronic, stable antipsychotic regimen that could tolerate a rapid oral dose taper and substitution of their current antipsychotic medication. Adult subjects (18-65 years, inclusive) were randomized to 1 of the 4 parallel groups *Staccato* Loxapine 15, 20, or 30 mg (total daily dose) or *Staccato* Placebo (1:1:1:1).

AUC values were collected for study 102 over a 24 hr dosing period (N=24 subjects). Doses were administered at time=0, time= 4h and time=8 h. Doses were 15 mg (5+5+5mg), 20 mg (10+5+5mg) , or 30 mg(10+ 10+ 10mg). Three AUC values were measured over three 4 hour periods-(0-4hr), (4-8), and (8-12hr).

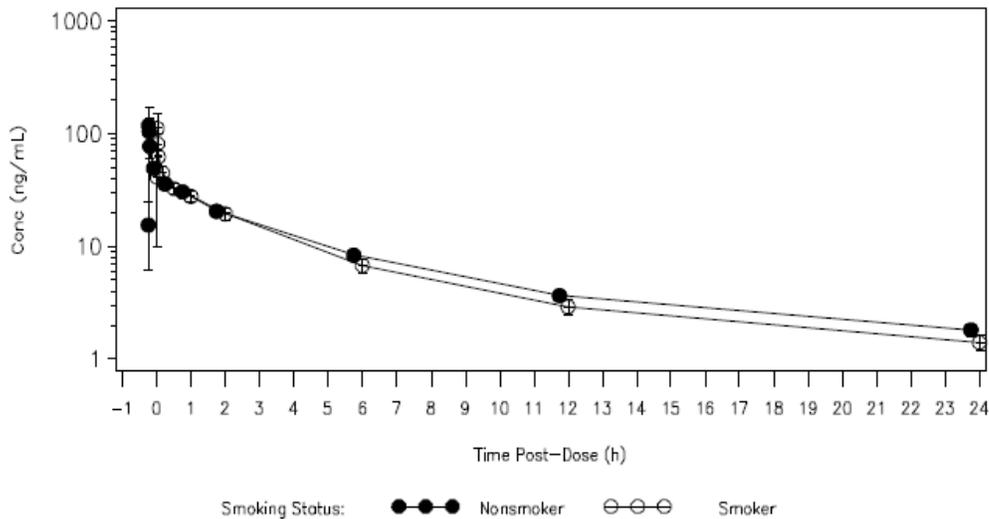
Table 2. AUC values for the 15 mg, 20 mg and 30 mg Multiple Dose treatment regimens

	Staccato Loxapine 15mg=5mg+5mg+5mg	Staccato Loxapine 20 mg=10mg+5mg+5mg	Staccato Loxapine 30mg=10mg+10mg+10mg
AUC(0-4) ng*hr/ml	34.3	63.9	50.3
AUC(4-8) ng*hr/ml	47.6	48.6	95.1
AUC(8-12) ng*hr/ml	48.1	41.6	76.7
Accumulation Dose2/Dose1	1.38	-----	1.89
Accumulation Dose3/Dose1	1.40	-----	1.52

The accumulation ratios measured for the comparable doses were less than 2 at the doses of 5 mg and 10 mg.

#### WAS THE PHARMACOKINETICS FOR STACCATO LOXAPINE THE SAME FOR SMOKERS AND NON SMOKERS?

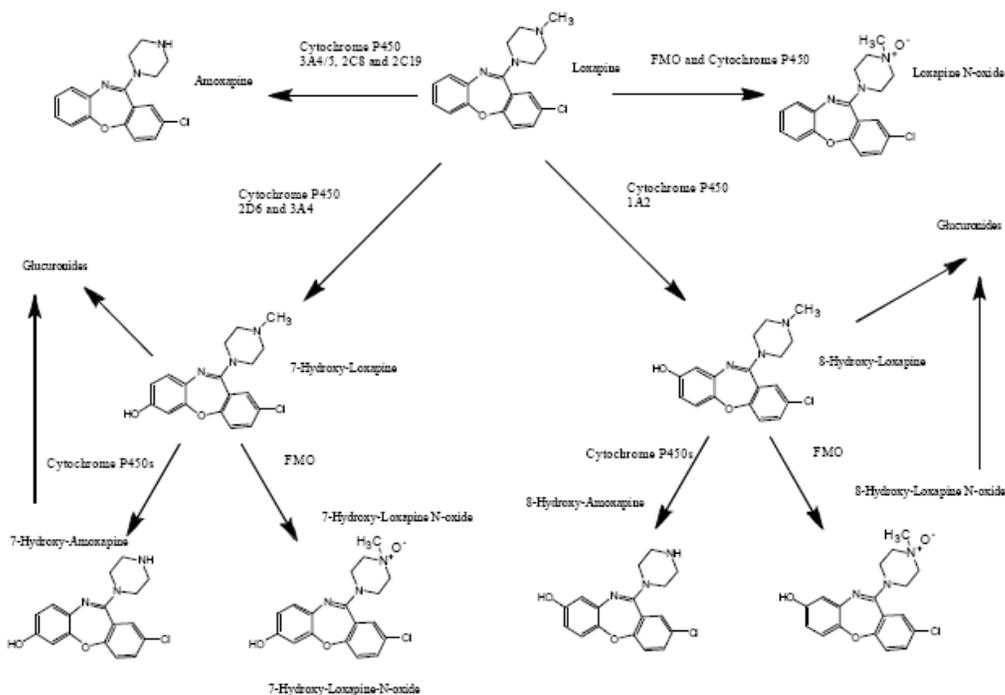
Figure 4. Mean Loxapine Concentration-Time Profiles in Smokers and Nonsmokers, 0 to 24 Hours after Dosing, Semi-Log Scale.



The pharmacokinetics for smokers and nonsmokers were the same for Staccato Loxapine.

#### WHICH ENZYMES SYSTEMS HAVE BEEN SHOWN TO BE INVOLVED IN THE METABOLISM OF LOXAPINE?

Proposed Loxapine Metabolism in Humans based upon in vitro studies with human liver microsomes.



The major metabolites are amoxapine, 7-hydroxy loxapine, 8 hydroxyloxapine and the loxapine N-oxide. CYP enzymes are involved in the pathways for 7-hydroxy loxapine are 2D6 and 3A4 while 1A2 is responsible for 8-hydroxy loxapine formation. Amoxapine is formed by 3A4/5, 2C8 and 2C9. Loxapine N-oxide is formed by flavanoid monamine oxidases.

Exposure ratios based upon AUCinf are 10% for 7-hydroxy loxapine, 10% for loxapine, N-oxide, 5% for amoxapine, and 50% for 8 hydroxy loxapine.

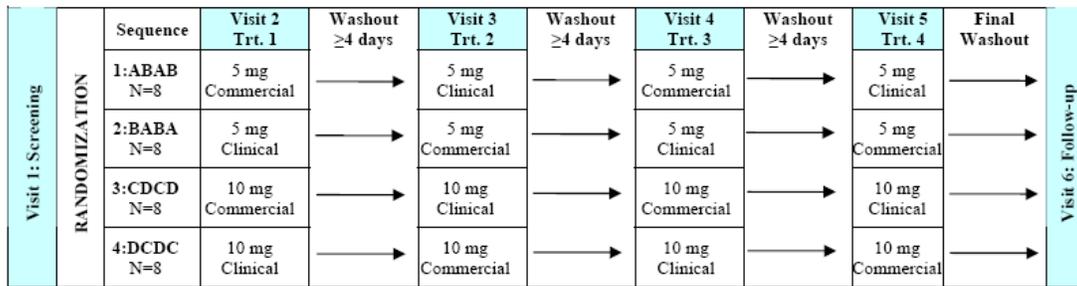
#### IS THE TRANSPORT OF LOXAPINE ACROSS CELL MEMBRANES INFLUENCED BY PGP TRANSPORTERS?

Loxapine transport Basal(B) to Apical(A) is not impacted by ketoconazole (Pgp inhibitor) and A to B transport is slightly increased in the presence of the P-gp inhibitor, ketoconazole.

#### WERE THERE ANY POTENTIAL DESIGN ISSUES RELATED TO THE CONDUCT OF THE PIVOTAL BE STUDY 103?

The pivotal BE study 103 was done as a 4 way replicate design between the 5 mg commercial, 5 mg clinical, 10 mg commercial and 10 mg clinical formulations

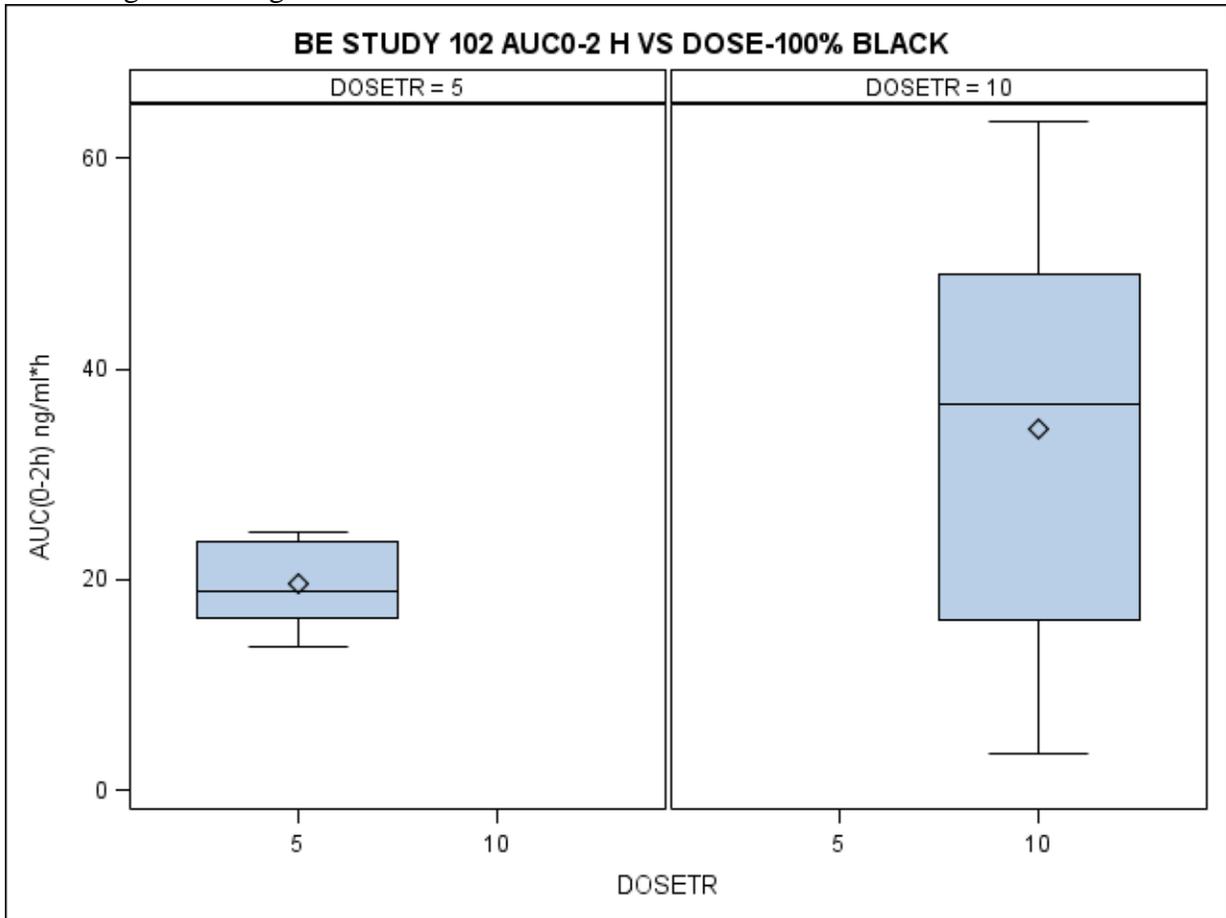
Figure 5 . Study Schematic



A=5-mg *Staccato* Loxapine commercial; B=5-mg *Staccato* Loxapine clinical; C=10-mg *Staccato* Loxapine commercial; D=10-mg *Staccato* Loxapine clinical

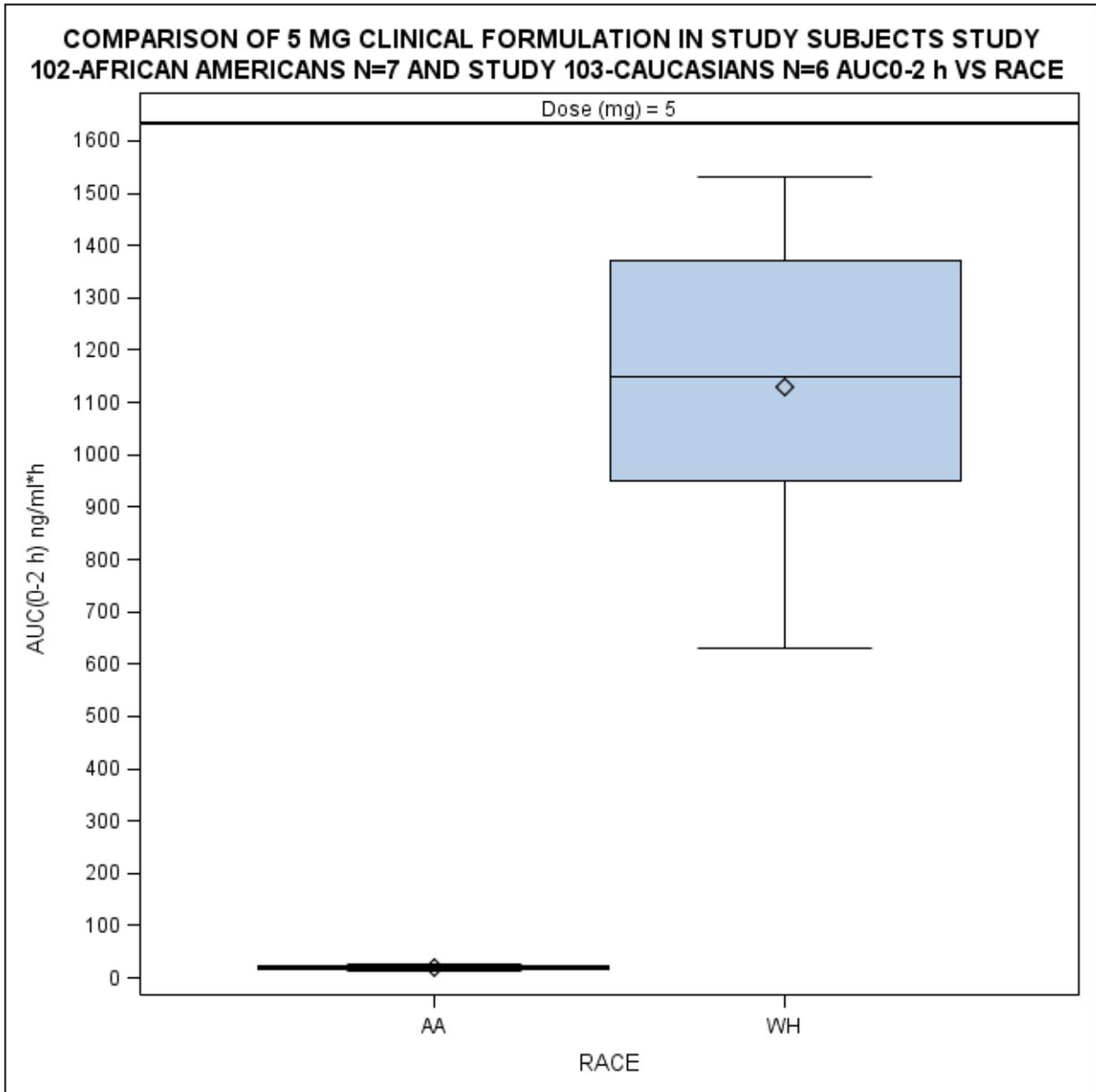
Each subject was randomly assigned (1:1:1:1) to 1 of 4 different *Staccato* Loxapine dosing sequences, 8 subjects per sequence (Figure 5). The study was done in a 90% Caucasian population. Therefore one needs to assure that Caucasian exposure was representative of other ethnic groups for the pivotal metric AUC(0-2hr). Subsequently, AUC(0-2hr) for study 103 was compared to study 102 where 100% of the subjects were African-Americans (non-African Americans removed).

Figure 6. Plot of AUC (0-2 h) for study 102 where the predominant racial group was African-Americans. Subjects 8 and 12 were deleted since they were not African-Americans. Values are only from period 1 with the 10 mg treatments i.e., 20 mg dose and 30 mg dose being combined.



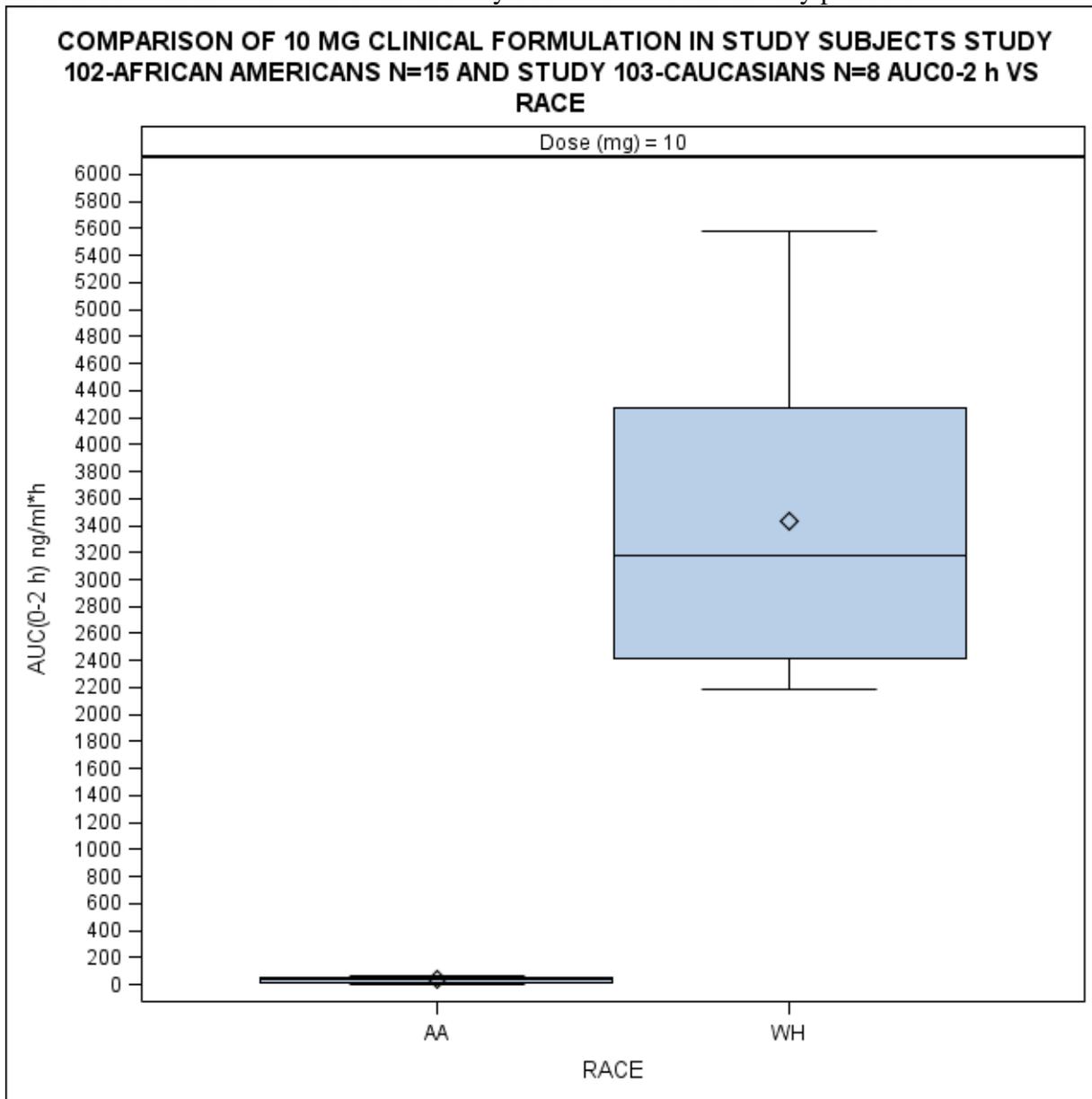
Dose=15 mg (5mg) N=7; Dose=20mg (10mg)N=7 , Dose=30 mg (10mg) N=7

Figure 7. Plot of AUC (0-2 h) vs. race, 5 mg dose, for studies 102 and 103 for the Clinical formulation 2. All non-African Americans were deleted from study 102 while all non-Caucasians were deleted from study 103. Values are from only period 1.



The median values at 5 mg were 60 fold higher for study 103 with Caucasians (~1200 ng/mlxh) compared to study 102 with African-Americans (~20 ng/mlxh).

Figure 8. Plot of AUC (0-2 h) vs. race, 10 mg dose, for studies 102 and 103 for the Clinical formulation 2. All non-African Americans were deleted from study 102 while all non-Caucasians were deleted from study 103. Values are from only period 1.



The median values at 10 mg were 80 fold higher for study 103 with Caucasians (~3200 ng/mlxh) compared to study 102 with African-Americans (~40 ng/mlxh).

Although loxapine exposure in Caucasians was greater than for African-Americans, equivalent exposure would be expected between formulations to be the same/similar in African-Americans at each dose. This would be true if they were analyzed alone or combined with Caucasians. The lower variability for AUC(0-2h) in African-Americans is unlikely to result in an increase in the width of the 90% CI.

ARE THERE ANY ISSUES RELATED TO THE DETERMINATION OF EQUIVALENT EXPOSURE BY COMBINING THE 5 MG AND 10 MG DOSES?

Loxapine exhibits linear pharmacokinetics therefore, for traditional BE the doses could be combined with C<sub>max</sub> and AUC<sub>inf</sub> being evaluated. However, C<sub>max</sub> was not expected to be Bioequivalent since it is a discrete variable that occurs within 2 min of drug administration, which makes it difficult to accurately measure. It was considered a secondary measure. AUC(0-2h) which is not a conventional metric was used as the primary metric and is related to early exposure. In addition, there was sufficient data to analyze each dose independently. Therefore, it was decided by OCP not to combine the doses and alternatively to evaluate the 5 mg and 10 mg doses separately.

WERE THERE ANY SUBJECT RELATED RESPONSE ISSUES IN THE BE STUDY?

Yes, there was a female subject #8 who obtained AUC(0-2hr) values on the Reference product (Clinical Version 2) that were well below the range of AUC(0-2h) values seen in the other 15 subjects in the 10 mg dose group. The Clinical Version 2 will not exist in the marketplace, therefore there would be no issues related to switchability.

There is no scientific basis for removing subject 8 from the analysis since these are replicated observed values that were consistently lower than those for the population. With subject #8 included the 90% CI for AUC(0-2h) are 1.095-1.535 with a point estimate of 1.29. Although the upper limit of 1.535 exceeds the established limit for conventional equivalence, it does not present a safety concern. An oral capsule formulation of loxapine is administered at doses of 60-100mg/day which is much higher than the 10 mg dose for Staccato loxapine.

WAS EQUIVALENT EXPOSURE ESTABLISHED BETWEEN THE CLINICAL AND MARKETED FORMULATIONS FOR STACCATO LOXAPINE AT EACH TO-BE-MARKETED DOSE?

In this “bioequivalence” (BE) study, the sponsor used a replicated crossover design - each subject received a version of the Test product (Commercial Version 1) twice and a version of the Reference product (Clinical Version 2) twice, either in the sequence T R T R or else in the sequence R T R T. Half of the subjects received a 5 mg dose of each product and the other half received a 10 mg dose of each product.

The results for the statistical analysis are presented in Table 3.

Table 3. Results from analysis of study 103 for the 5 mg dose and the 10 mg dose as separate doses.

Treatment	AUC(0-2h) 90% CI	Cmax
5 mg dose only#	0.9992,1.257	-----
5 mg dose only#^	0.9997,1.238	-----
10 mg dose only*	1.095, 1.535	-----
10 mg dose only**	1.093, 1.287	-----

\* with subject 8

\*\* without subject 8

# based upon Satterthwaite" option denominator degrees of freedom in Proc Mixed

#^based upon Kenward-Roger" option denominator degrees of freedom in Proc Mixed

See statistical report in the Appendix

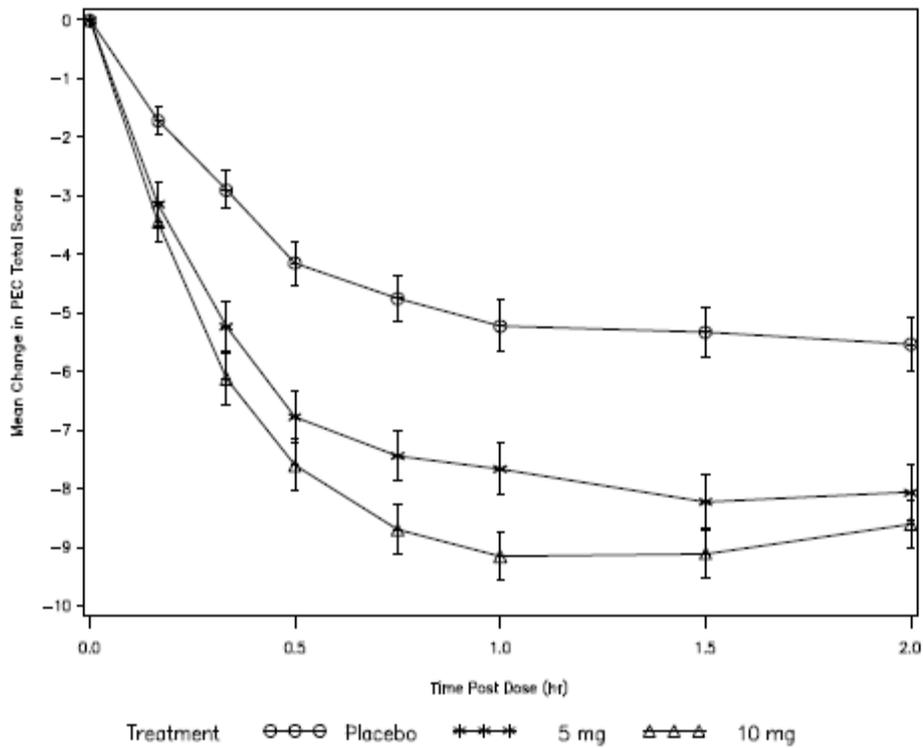
Exposure Equivalence for AUC(0-2h) was observed only for the 5 mg dose using the "Kenward-Roger" option denominator degrees of freedom in Proc Mixed (please see attached statistical review for explanation).

Exposure Equivalence for AUC(0-2h) was not observed for the 10 mg dose ( 90% CI 1.095-1.535, point estimate 1.29) but this is not a safety issue as previously discussed.

**DID THE PRIMARY CLINICAL ENPOINT PEC (POSITIVE AND NEGATIVE SYMPTOM SCALE EXCITED COMPONENT) SHOW A DOSE RESPONSE IN SCHIZOPHRENIC SUBJECTS?**

The primary efficacy endpoint was the change in the PEC score from baseline to 2 hours after Dose 1 (active versus placebo). The clinical study was done in N=115 placebo subjects, N=116 (5 mg dose), and N=112 (10 mg dose) subjects.

Figure 9. Mean Change from Baseline in PEC Score through 2 Hours after Dose 1 (ITT Population with LOCF)-Schizophrenia



There was a dose response relative to placebo; however, any separation in response for the 5 mg and 10 mg doses was only evident from 0.5h to 1.5 h and was not proportional to dose.

FOR THE MAJOR ADVERSE EVENTS WAS THERE EVIDENCE OF A DOSE RESPONSE IN SCHIZOPHRENIC PATIENTS?

Adverse Events in More than 1 Patient in Any Treatment Group (Safety Population)

System Organ Class Adverse Event, n (%)	<i>Staccato</i> Placebo (N=115)	<i>Staccato</i> Loxapine 5 mg (N=116)	<i>Staccato</i> Loxapine 10 mg (N=113)
Fatigue	1 (0.9%)	2 (1.7%)	0
Nervous system disorders			
Dizziness	11 (9.6%)	6 (5.2%)	12 (10.6%)
Headache	16 (13.9%)	3 (2.6%)	3 (2.7%)
Sedation	11 (9.6%)	15 (12.9%)	12 (10.6%)
Somnolence	3 (2.6%)	3 (2.6%)	3 (2.7%)

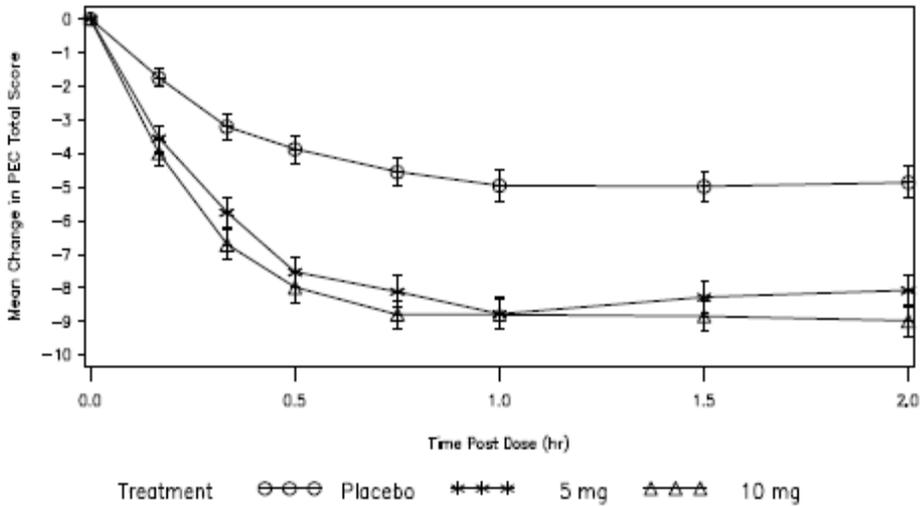
Hypotension was reported as an AE in 1 loxapine-treated patient and 1 placebo-treated

patient. There was no evidence of a dose response since the placebo in some cases gave a response comparable to the high dose (e.g. , dizziness).

**DID THE PRIMARY CLINICAL ENPOINT PEC –POSITIVE AND NEGATIVE SYMPTOM SCALE , EXCITED COMPONENT SHOW A DOSE RESPONSE IN PATIENTS WITH BIPOLAR I DISORDER**

The primary efficacy endpoint was the change in the PEC score from baseline to 2 hours after Dose 1 (active versus placebo). The clinical study was done in N=105- placebo subjects, N=104-5 mg dose, and N=105-10 mg dose subjects.

Figure 10. Mean Change from Baseline in PEC Score through 2 Hours after Dose 1 (ITT Population with LOCF) for patients with bipolar I disorder



There was a response which was greater than placebo but there was no separation in response between the doses.

**FOR THE MAJOR ADVERSE EVENTS IN THE BIPOLAR PATIENTS WAS THERE EVIDENCE OF A DOSE RESPONSE IN BIPOLAR I PATIENTS**

Safety population was 314 subjects N=105 placebo, N=104 5 mg and N=105 10 mg.

System Organ Class Adverse Event	Staccato Placebo (N=105)	Staccato Loxapine 5 mg (N=104)	Staccato Loxapine 10 mg (N=105)

Fatigue	3 (2.9%)	4 (3.8%)	3 (2.9%)
Nervous system disorders			
Dizziness	6 (5.7%)	6 (5.8%)	5 (4.8%)
Headache	7 (6.7%)	3 (2.9%)	0
Sedation	3 (2.9%)	7 (6.7%)	6 (5.7%)

There were small decreases in the mean systolic and diastolic blood pressure at scheduled assessments in the hours after administration of *Staccato* Loxapine, and the effect was larger in the 10-mg group than the 5-mg group:

Figure 11. Mean Change from Baseline in Systolic Blood Pressure (Safety Population)

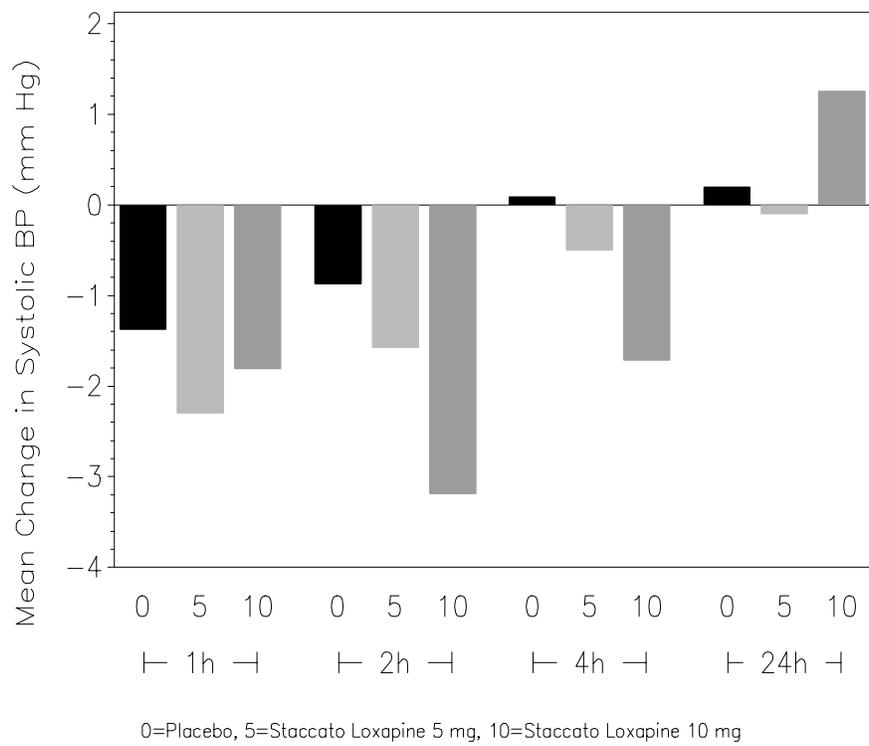
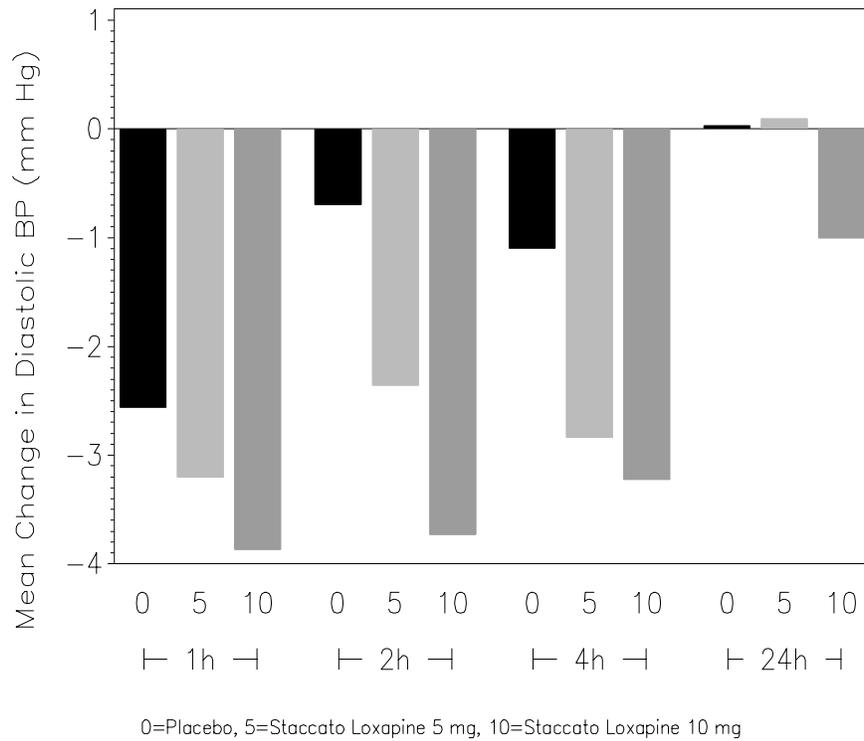


Figure 12. Mean Change from Baseline in Diastolic Blood Pressure (Safety Population)



**WERE THERE ANY MAJOR SAFETY CONCERNS FOR STACATTO LOXAPINE?**

The major safety issue was pulmonary toxicity observed at the 10 mg dose.

**ARE THERE ANY ISSUES RELATED TO FORMULATION THAT ARE NOT DIRECTLY ADDRESSED BY THE BIOEQUIVALENCE STUDY COMPARING THE CLINICAL VERSION 2 (USED FOR PHASE III TRIALS) AND THE COMMERCIAL VERSION 1.**

The commercial version 1 which was used for the pivotal BE study has had several minor changes since the study was done which include:

(b) (4)

ONDQA is currently investigating the product quality implications of these changes to the product.

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

**APPENDIX I****ASSAY VALIDATION****ANALYTICAL**

<b>Parameter</b>	Loxapine	Amoxapine	7-OH Loxapine	8-OH Loxapine
Method	LC\ Mass Spectrometric \ Mass Spectrometric Detection			
Number of Freeze-	3 Cycles QC's 0.15 ng/ml	3 Cycles QC's 0.15 ng/ml	3 Cycles QC's 0.15 g/ml	3 Cycles QC's 0.15ng/ml

thaw	40 ng/ml	40 ng/ml	40 ng/ml	40 ng/ml
Benchtop extract stability at RT	45hrs	45hrs	45hrs	45hrs
Bench top	6 h	6 h	6 h	6 h
Long term at -20° C	244 days	244 days	244 days	244 days
Extraction Recovery			87% @ 0.15 ng/ml	95% @ 0.15 ng/ml
Low	84.6% @ 0.15 ng/ml	79% @ 0.15 ng/ml	87% @ 5 ng/ml	94% @ 5 ng/ml
Med		92% @ 5 ng/ml	77% @ 40 ng/ml	82% @ 40 ng/ml
High	88% @ 5 ng/ml 75.7% @ 40 ng/ml	80% @ 40 ng/ml		

### Description of Staccato Loxapine

*Staccato* Loxapine is a hand-held drug-device product using Alexza’s proprietary *Staccato* delivery system that produces a thermally generated aerosol of the dopamine-blocking agent, loxapine, for rapid delivery to the systemic circulation via the lungs.

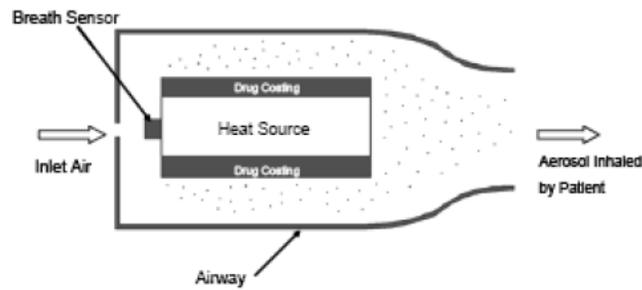
(b) (4)

Oral inhalation through the device initiates the controlled rapid heating of a thin film of excipient-free loxapine to form a highly pure drug vapor. The vapor condenses into aerosol particles with a particle size distribution appropriate for efficient delivery to the deep lung. The rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration. *Staccato* Loxapine is designed to be a single-use product.

The principal components of the single-dose drug product, which are shown schematically in Figure 1, are as follows:

- Heat source (“heat package”) consisting of a battery-activated, hermetically sealed package, with a stainless steel substrate on 1 side
- Thin coating of pure loxapine on the stainless steel substrate
- Surrounding airway with airflow inlets
- Breath-activated mechanism for initiating the heating, and thus, aerosol generation

**Figure 1. Schematic Side-View of *Staccato* Loxapine**



The interior surface of the stainless steel substrate of the sealed heat package is coated with a (b) (4) capable of undergoing a controlled, oxidation-reduction (redox) gasless reaction that liberates heat. The exterior surface of the stainless steel substrate is coated with the drug dose (5 mg or 10 mg). Embedded in the heat package is a starter that is used to initiate the redox reaction.

Inhalation through the product is detected by the breath sensor, which generates an electrical signal that activates the starter. This leads to heat package reaction initiation and rapid heating of the exterior surface of the sealed heat package to approximately  $400^{\circ}\text{C} \pm 50^{\circ}\text{C}$ . Heat then transfers into the loxapine coated as a thin film on the heat package exterior. Because the thin film of loxapine has a high surface area, vaporization of the loxapine is very rapid, occurring in  $<1$  second, therefore limiting thermal decomposition. Once vaporized, the loxapine cools in the airflow generated by subject inhalation and condenses to form aerosol particles. These particles then coalesce into an aerosol characterized by a mass median aerodynamic diameter in the range of 1.0 to 3.5  $\mu\text{m}$ .

## STUDY PROTOCOL AMDC-004-101

### STUDY OBJECTIVES

The objective of this study was to assess the safety, tolerability and pharmacokinetics of a single inhaled dose (administered in 1 or 2 puffs) of *Staccato* Loxapine in healthy volunteers.

### Overall Study Design and Plan

This was a single-center, randomized, double-blind, placebo-controlled, dose escalation study of the safety, tolerability, and pharmacokinetics of single doses of *Staccato* Loxapine. The doses to be studied were 0.625 mg, 1.25 mg, 2.5 mg, 5.0 mg, and 10 mg. These were the total doses of drug coated on the heat package for vaporization. The doses of 0.625 mg, 2.5 mg, and 5 mg were administered as 1 single puff, whereas the doses of 1.25 mg and 10 mg were administered as 2 puffs of either 0.625 mg or 5 mg of *Staccato* Loxapine. Safety and tolerability were assessed for each dose group by the Principal Investigator and Alexza Medical Monitor before advancing to the next scheduled dose group. This design was used to allow subjects to achieve a maximally tolerated dose.

### Treatment Received Population

As specified in the Statistical Analysis Plan the failure of the chemical heat pack activation mechanism was anticipated for some of the devices. Following the evaluation of returned study devices, any heat packs which failed to activate (no drug

delivered) were determined. In this case the actual treatment delivered (Treatment Received) was determined for each subject. Since this is a Phase 1 trial, the primary safety and pharmacokinetic analyses were based on Treatment Received.

**Table 1 Loxapine Doses Administered**

Cohort	Treatment	No. of Devices per Treatment, and Device Strength
A	Inhaled loxapine 0.625 mg or placebo (8:2)	1 x 0.625 mg
B	Inhaled loxapine 1.25 mg or placebo (8:2)	2 x 0.625 mg
C	Inhaled loxapine 2.5 mg or placebo (8:2)	1 x 2.5 mg
D	Inhaled loxapine 5 mg or placebo (8:2)	1 x 5 mg
E	Inhaled loxapine 10 mg or placebo (8:2)	2 x 5 mg

Immediately following each inhalation and breath hold, the subject exhaled through the supplied exhalation filter to collect the exhaled aerosol. If 2 devices were used to deliver the dose (e.g., Cohorts B and E), an attempt was made to have the subject inhale through the second device within 1 minute of the first device, and exhale through a second exhalation filter.

Lot information for study AMDC-004-101 is provided in Table 2. The devices used in this study were Clinical Version 1 (please refer to NDA 022549, [Sequence 0001](#), [Response to Information Request, Section 2.3](#) for a description of device versions).

**Table 2 Lot Information for Study AMDC-004-101**

Clinical Study	Device Version	Manufact -urer	Doses (mg)	Lot Numbers	Date of Manufacture
004-101: Phase 1 single-dose PK study	Clinical 1	Alexza	0.625 mg <sup>a</sup>	M0203	04-SEP-2005
			2.5 mg	M0206	19-SEP-2005
			5 mg <sup>a</sup>	M0207	20-SEP-2005
			Placebo	M0204	19-SEP-2005

<sup>a</sup> The 1.25-mg dose regimen used in Study 004-101 consisted of using 2 drug products of 0.625 mg each. Similarly, the 10-mg dose regimen consisted of 2 drug products of 5mg each

Source: NDA 022549, [Sequence 0000](#), [Response to Information Request, Table 1](#).

### Safety Measurements Assessed

Safety was evaluated by the incidence of adverse events, and the assessment of clinical laboratory testing (blood chemistry, hematology, and urinalysis), vital signs, postural blood pressure and pulse, physical examination, 12-lead electrocardiogram, continuous

12-lead Holter monitoring, pulmonary function test, pulse oximetry, sedation assessment and akathisia assessment.

### **Data Sets Analyzed**

All subjects enrolled, (N=50), were included in the safety assessment. Of the 40 subjects randomly assigned to active drug, 4 subjects (1 assigned to 0.625 mg, 2 to 2.5 mg, and 1 to the 5 mg dose group) used devices in which the device failed to heat (subject received no drug). Safety and pharmacokinetic analyses by dose group were based on Treatment Received. Thus 36 subjects were exposed to active loxapine rather than the 40 subjects assigned.

### **Demography (Safety Population)**

The *Staccato* Loxapine active treatment groups consisted of 19 (53%) females and 17 (47%) males with a mean age of 29.4 years. The majority of subjects were Caucasian (97%). The placebo population consisted of 8 (57%) females and 6 (43%) males with a mean age of 37.8 years, and the majority of subjects were Caucasian (79%).

### ***Description of Pharmacokinetic Variables***

The maximum concentration ( $C_{max}$ ) and the time to  $C_{max}$  ( $T_{max}$ ) were the observed values. 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  $C_{last}$  and  $k_e$  are the last measurable plasma concentration and the terminal rate constant, respectively. The half-life was calculated as  $\ln(2)/k_e$ . In addition, individual  $C_{max}$  and  $T_{max}$  values were recorded after each administered dose.

### **ANALYTICAL**

Study Dates: September 2005-November 2005  
Sample received: October 25, 2005  
Analysis Completed: December 7, 2005  
Total Storage Time: 90 days

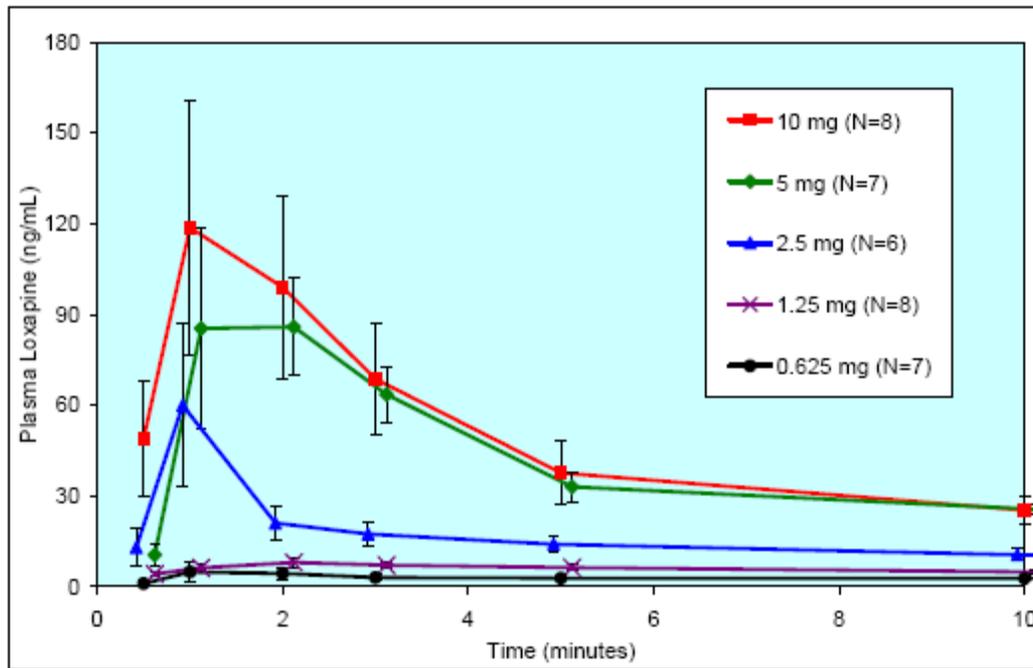
Stability of QC samples after frozen storage for up to 244 days at storage temperatures of  $-20^{\circ}\text{C}$  was established during method validation. The duration of frozen stability covers that for the sample storage for this study.

The firm had an amended report since the original analysis had some problems. The revised values reported were within 1% of the original values.

Parameter	Loxapine	Amoxapine	7-OH loxapine	8-OH loxapine
Method	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
Sensitivity/LOQ	0.05 ng/mL	0.05 ng/mL	0.05 ng/mL	0.05 ng/mL
Linearity (Standard curve samples)	0.048, 0.159, 0.78, 5.23, 37, and 46 ng/ml	0.048, 0.159, 0.78, 5.23, 37, and 46 ng/ml	0.048, 0.159, 0.78, 5.23, 37, and 46 ng/ml	0.048, 0.159, 0.78, 5.23, 37, and 46 ng/ml
Quality Control (QC) Samples	0.015, 5, 40 ng/mL			
Precision of Standards (%CV)	5.3% @0.05ng/ml 4.65 @ 50 ng/ml	6.1% @0.05ng/ml 6.3 @ 50 ng/ml	7.3% @0.05ng/ml 4.1 @ 50 ng/ml	8.9% @0.05ng/ml 2.9 @ 50 ng/ml
Precision of QC Samples (%CV)	<u>3.9% @ 0.15ng/ml</u> 3.4% @ 40 ng/ml	4.6% @ 0.15 ng/ml 3.3% @ 40 ng/ml	3.5% @ 0.15 ng/ml 2.3% @ 40 ng/ml	4.7% @ 0.15 ng/ml 3.3% @ 40 ng/ml
Accuracy of Standards (%)	99% @0.05ng/ml 95% @ 47.3 ng/ml	99% @0.05ng/ml 95% @ 47.3 ng/ml	98% @0.05ng/ml 95% @ 47.3 ng/ml	99% @0.05ng/ml 95% @ 47.3 ng/ml
Accuracy of QC Samples (%)	104% @ 0.15 ng/ml 97.2% @ 40 ng/ml	102% @ 0.15 ng/ml 97.2% @ 40 ng/ml	102% @ 0.15 ng/ml 97.2% @ 40 ng/ml	106% @ 0.15 ng/ml 97.2% @ 40 ng/ml

## RESULTS

**Figure 1. Plasma Concentrations of Loxapine by Dose Group, First 10 min.**  
All PK Subjects (N=36), Mean  $\pm$  1 SEM



**Table 3 Pharmacokinetic Parameters for Loxapine by Dose**  
All Dose Groups (N=36 subjects), Mean  $\pm$  SD

Parameter	0.625 mg (N=7)	1.25 mg (N=8)	2.5 mg (N=6)	5 mg (N=7)	10 mg (N=8)
$t_{max}$ (min)	12.6 $\pm$ 21.3	2.15 $\pm$ 1.31	2.87 $\pm$ 3.62	2.13 $\pm$ 0.687	5.25 $\pm$ 10.0
Half-life (hr)	5.20 $\pm$ 1.30	6.56 $\pm$ 1.44	6.92 $\pm$ 1.93	6.20 $\pm$ 1.14	6.14 $\pm$ 2.16
$k_e$ (/hr)	0.143 $\pm$ 0.047	0.111 $\pm$ 0.026	0.108 $\pm$ 0.033	0.115 $\pm$ 0.020	0.122 $\pm$ 0.032
CL/F (L/hr)	56.2 $\pm$ 14.1	55.9 $\pm$ 13.7	61.1 $\pm$ 18.8	53.8 $\pm$ 9.74	78.0 $\pm$ 25.8

Mean=arithmetic mean, SD=standard deviation  
Data Source: Table 14.3.10.1 & Listing 16.3.14

### Loxapine Metabolite Concentrations

Plasma concentrations of the metabolites were not consistently measurable following loxapine doses less than 5 mg.

Figure 2. Plasma Loxapine & 7-OH Loxapine Concentrations, 10 mg Dose, 24 hrs  
All PK Subjects Received 10 mg (N=8), Mean  $\pm$  2 SEM

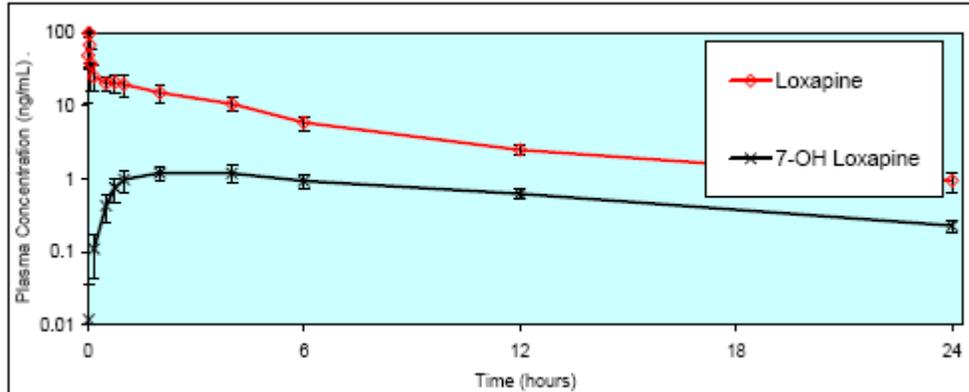


Table 4. AUC and C<sub>max</sub> by Dose Group for Loxapine and 7-OH Loxapine  
All PK Subjects (N=36), Mean  $\pm$  SD (N)

	0.625 mg	1.25 mg	2.5 mg	5 mg	10 mg
<b>Loxapine</b>					
AUC <sub>inf</sub> (hr*ug/L)	11.9 $\pm$ 3.70 (N=7)	23.4 $\pm$ 4.87 (N=8)	44.6 $\pm$ 14.7 (N=6)	95.5 $\pm$ 16.6 (N=7)	140.6 $\pm$ 44.6 (N=8)
AUC <sub>last</sub> (hr*ug/L)	11.1 $\pm$ 3.41 (N=7)	21.9 $\pm$ 4.53 (N=8)	41.5 $\pm$ 13.9 (N=6)	89.7 $\pm$ 15.2 (N=7)	132.2 $\pm$ 44.2 (N=8)
C <sub>max</sub> (ug/L)	6.5 $\pm$ 8.79 (N=7)	9.7 $\pm$ 3.49 (N=8)	62.9 $\pm$ 63.0 (N=6)	105.0 $\pm$ 80.6 (N=7)	134.6 $\pm$ 118.8 (N=8)
<b>7-OH Loxapine</b>					
AUC <sub>inf</sub> (hr*ug/L)	(N=0)	(N=0)	4.9 $\pm$ 0.81 (N=3)	11.5 $\pm$ 1.94 (N=7)	19.9 $\pm$ 3.75 (N=7)
AUC <sub>last</sub> (hr*ug/L)	0.70 $\pm$ 0.43 (N=6)	1.34 $\pm$ 0.34 (N=8)	3.11 $\pm$ 1.27 (N=6)	9.64 $\pm$ 1.61 (N=7)	15.95 $\pm$ 3.76 (N=8)
C <sub>max</sub> (ug/L)	0.12 $\pm$ 0.05 (N=6)	0.18 $\pm$ 0.06 (N=8)	0.33 $\pm$ 0.13 (N=6)	0.82 $\pm$ 0.14 (N=7)	1.29 $\pm$ 0.43 (N=8)

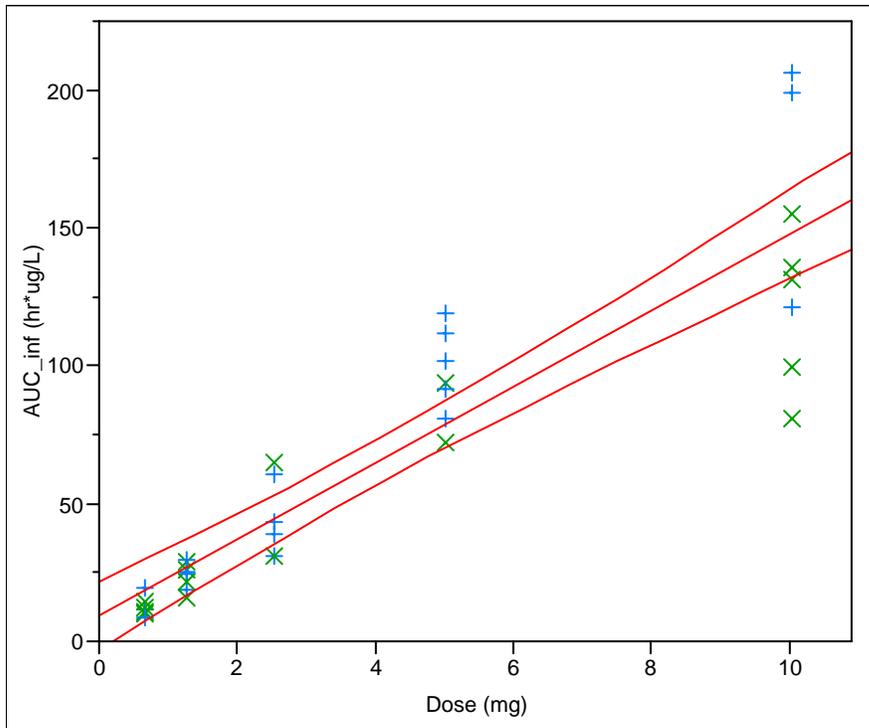
### Loxapine Dose Proportionality

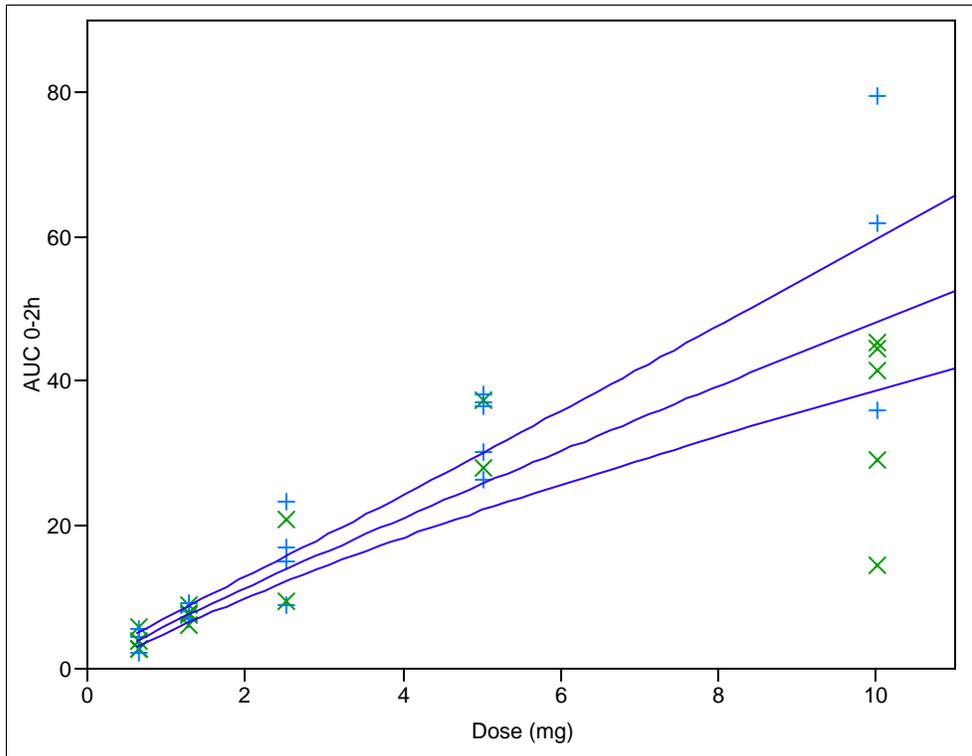
The exposure parameters (AUC<sub>inf</sub>, AUC<sub>last</sub>, and C<sub>max</sub>) increased with dose. Table 4 shows the mean and SD of for each of these 3 measures by dose group for loxapine and 7-OH loxapine.

**Table 5. AUC(0-2h) values as a function of dose for study 101.**

Dose (mg)	Mean AUC(0-2h)	Standard Deviation (AUC 0-2h)
0.625	3.6865	1.4509
1.25	7.6342	0.9982
2.5	15.5379	5.9133
5	33.1804	5.0404
10	43.8288	19.9476

Figure 3 Dose Proportionality Based on AUC<sub>inf</sub> and AUC(0-2h) for all 5 Dose Groups All PK Subjects (N=36), Regression (95% CI), X = male, + = female





+ = Female, x = Male

#### Comments

1. The failure rate for the device in this study was 10% which seems high.
2. The reported 95% CI for slope was 0.832-0.987. Since this does not include 1 it indicates that loxapine AUC<sub>inf</sub> is a little less than dose proportional from 5 mg to 10 mg.
3. The active metabolite 7-OH may contribute to clinical effect.
4. The 10 mg dose is 2x the 5 mg dose but the exposure increase for AUC(0-2h) is only 1.32 which means that the 10 mg dose provides no real increase in exposure when administered as 2 puffs in this study.
5. CL increased with dose or F decreased.

#### **STUDY NUMBER: AMDC-004-102**

Title: Safety, Tolerability, and Pharmacokinetics of Multiple Doses of Staccato® Loxapine for Inhalation in Subjects on Chronic, Stable Antipsychotic Regimens

#### STUDY OBJECTIVES

The objective of this study was to assess the safety, tolerability, and pharmacokinetics of

multiple inhaled doses of *Staccato* Loxapine. The dosing frequency was intended to assess the appropriateness of repeat dosing every 4 hours in the Phase 3 studies. The placebo group served as a comparator for safety.

### **Description of Overall Study Design**

Eligible subjects were on stable, oral, chronic (more than 2 months) antipsychotic medication regimens and were able to tolerate the rapid oral dose taper and substitution regimen ( $\frac{1}{2}$  oral dose  $\times$  1 day, followed by  $\frac{1}{4}$  oral dose  $\times$  1 day, followed by loxapine or placebo  $\times$  1 day. Subjects were enrolled in 1 of 4 dose regimens. The total doses studied were 0 (placebo), 15, 20, and 30 mg.

This is a single-center, randomized, double-blind, multiple dose, placebo-controlled, safety and pharmacokinetic study of *Staccato*® Loxapine for Inhalation in subjects on a **chronic, stable antipsychotic regimens**. Adult subjects (18-65 years, inclusive) were randomized to 1 of the 4 parallel groups *Staccato* Loxapine 15, 20, or 30 mg (total daily dose) or *Staccato* 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 divided by 4 hours. The study enrolled 32 subjects, 8 per treatment group. Subjects were on stable, oral, chronic (more than 2 months) antipsychotic medication regimens. After eligibility was confirmed, each subject was enrolled in the study, randomized to 1 or 4 dose regimens, and Dose 1 of study medication was administered. Doses 2 and 3 were administered at 4 hr and at 8 hours.

### **Treatments Administered**

Subjects were randomized to 1 of 4 dose regimens (1:1:1:1, Table 3)

Table 1. Loxapine Doses Administered

<b>Dose Regimen</b>	<b>Period 1 (T=0 h)</b>	<b>Period 2 (T=4 h)</b>	<b>Period 3 (T=8 h)</b>	<b>Total Dose (mg)</b>
A	10 mg	10 mg	10 mg	30 mg
B	10 mg	5 mg	5 mg	20 mg
C	5 mg	5 mg	5 mg	15 mg
D	Placebo	Placebo	Placebo	0 mg

### **Identity of the Investigational Product**

Study drug was manufactured by Alexza Pharmaceuticals in the form of 5 mg, 10 mg, and placebo. Study drug was supplied from the following lots: *Staccato* Loxapine 5 mg Lot #M0410, *Staccato* Loxapine 10 mg Lot #M0427, and *Staccato* Placebo Lot #M0406.

Clinical Study	Device Version	Manufact -urer	Doses (mg)	Lot Numbers	Date of Manufacture
004-102: Phase 1 multi-dose PK study	Clinical 2	Alexza	5 mg	M0410	13-APR-2007
			10 mg	M0427	19-APR-2007
			Placebo	M0406	21-MAR-2007
			Placebo	M0630	21-FEB-2009

Table 2. Demographics and Baseline Characteristics (Safety Population)

Demographic or Baseline Characteristic	<i>Staccato</i> Placebo (N=8)	<i>Staccato</i> Loxapine 15 mg (N=8)	<i>Staccato</i> Loxapine 20 mg (N=8)	<i>Staccato</i> Loxapine 30 mg (N=8)	Overall Study Population (N=32)
Gender, n (%):					
Female	3 (37.5%)	2 (25.0%)	3 (37.5%)	2 (25.0%)	10 (31.3%)
Male	5 (62.5%)*	6 (75.0%)	5 (62.5%)	6 (75.0%)	22 (68.8%)
Age (years):					
Mean (SD)	40.4 (10.8)	42.5 (7.73)	44.3 (8.08)	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 (5.60)	164 (15.2)	173 (6.65)	175 (9.01)	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
Other <sup>b</sup>	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%)

### Device Complaints: Reported Malfunctions

Three devices were returned to Alexza via the Device Complaint System (Table 3). Upon receipt, these devices were inspected for obvious damage and for the physical changes

associated with actuation, and when relevant, loxapine delivery. In addition, their electrical and mechanical components were tested.

Table 3. Study Medication Returned via the Device Complaint System

Subject No.	Staccato System	No. of Units Returned	Batch No.
01-018	Staccato Placebo	1	M0406
01-027	Staccato Loxapine 5 mg	2	M0410

### **Description of Pharmacokinetic Variables**

The maximum concentration ( $C_{max}$ ) and the time to  $C_{max}$  ( $T_{max}$ ) were the observed values. 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  $C_{last}$  and  $k_e$  are the last measurable plasma concentration and the terminal rate constant, respectively. The half-life was calculated as  $\ln(2)/k_e$ . In addition, individual  $C_{max}$  and  $T_{max}$  values were recorded after each administered dose.

Dose proportionality for loxapine was examined across the dose groups using the power model (linear regression of the log  $AUC_{inf}$  against the log dose). Since the range of doses in this study was only 2-fold (15 to 30 mg), the data were combined with the  $AUC_{inf}$  from [AMDC-004-101](#) for dose proportionality analyses.

### **Sedation Assessment**

Sedation level was assessed at pre-specified time points throughout the study using a 100 mm visual analogue scale (VAS) between the verbal anchors extremely sleepy and wide awake. Observed values of each VAS sedation score and changes from baseline were summarized by treatment group at each time point. Baseline was defined as Visit 2 Day 0 (Pre-0). Confidence intervals (90%) were constructed for within-treatment group changes from baseline.

### **ANALYTICAL**

October 11, 2007 (first subject dosed)  
 December 21, 2007 (last subject visit)  
 Analysis completed: February 12, 2008  
 Total time = 120 days

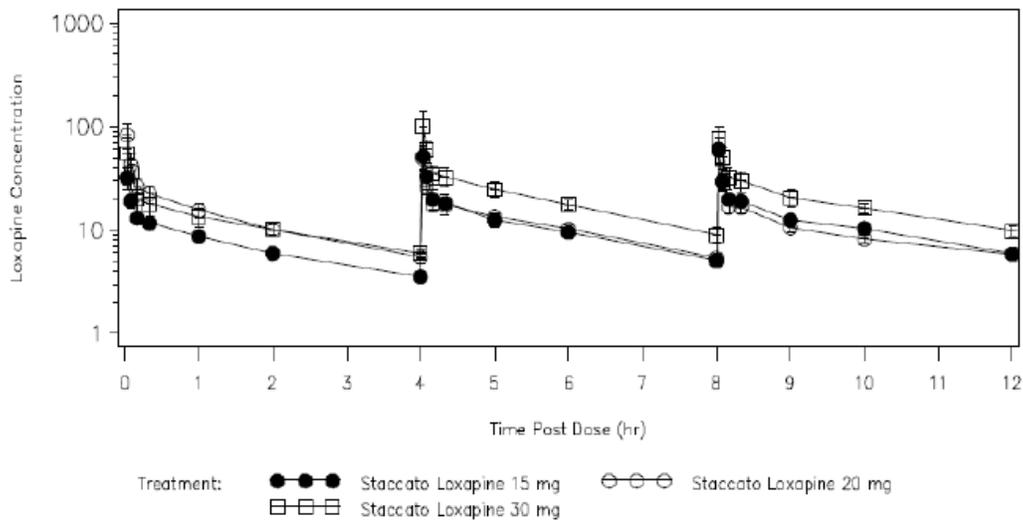
Parameter	Loxapine	Amoxapine	7-OH loxapine	8-OH loxapine
Method	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
Sensitivity/LOQ	0.05 ng/mL	0.05 ng/mL	0.05 ng/mL	0.05 ng/mL
Linearity (Standard curve samples)	0.048, 0.159, 0.78, 5.23, 37, and 46 ng/ml	0.048, 0.159, 0.78, 5.23, 37, and 46 ng/ml	0.048, 0.159, 0.78, 5.23, 37, and 46 ng/ml	0.048, 0.159, 0.78, 5.23, 37, and 46 ng/ml
Quality Control (QC) Samples	0.015, 5, 40 ng/mL			

Precision of Standards (%CV)	6.8% @0.05ng/ml 4.2% @ 50 ng/ml	6% @0.05ng/ml 4.5% @ 50 ng/ml	8.8% @0.05ng/ml 5.2% @ 50 ng/ml	7.4% @0.05ng/ml 5.0% @ 50 ng/ml
Precision of QC Samples (%CV)	<u>7.9% @ 0.15ng/m</u> 5.1% @ 40 ng/ml	8.8% @ 0.15 ng/ml 6% @ 40 ng/ml	6.8% @ 0.15 ng/m 5.7% @ 40 ng/ml	11% @ 0.15 ng/m 3.3% @ 40 ng/ml
Accuracy of Standards (%)	99% @0.05ng/ml 98% @ 47.3 ng/ml	99% @0.05ng/ml 99% @ 47.3 ng/ml	98% @0.05ng/ml 99% @ 47.3 ng/ml	99% @0.05ng/ml 99% @ 47.3 ng/ml
Accuracy of QC Samples (%)	91% @ 0.15 ng/m 94% @ 40 ng/ml	97% @ 0.15 ng/m 97.2% @ 40 ng/ml	92% @ 0.15 ng/m 92% @ 40 ng/ml	94% @ 0.15 ng/m 93% @ 40 ng/ml

## RESULTS

### Loxapine Concentrations

Figure 1. Plasma Concentrations of Loxapine by Dose, First 12 h  
All PK Subjects (N=24), Mean  $\pm$  1 SEM by Dose Group



Subject=17 TPD=4, subject=1 TPD=8, and subject=21 TPD=4 excluded due to timing uncertainties (concentration rising before dosing)

SAS Program Name: cpfigures3-3.sas    Date: 03MAR2009:10:57:49    Source Data: Table 14.8.1.1

Table 4. Pharmacokinetic Parameters of Loxapine by Dose Group  
All Dose Groups (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) – Dose 1	2 [2, 5] (8) <sup>a</sup>	2 [2, 60] (8)	10 [2, 120] (8)
– 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)	6.57 ± 2.04 (8) <sup>b</sup>	7.94 ± 2.28 (8)	6.75 ± 1.31 (8)
k <sub>e</sub> (/h)	0.116 ± 0.0383 (8)	0.0941 ± 0.0273 (8)	0.106 ± 0.0215 (8)
CL/F (L/h)	86.6 ± 22.6 (8)	101 ± 42.4 (8)	122 ± 75.8 (8)
AUC <sub>inf</sub> (ng•h/mL)	184 ± 49.6	226 ± 82.7	315 ± 145
AUC <sub>last</sub> (ng•h/mL)	167 ± 46.0	197 ± 71.8	284 ± 129
C <sub>max</sub> (ng/mL) – Dose 1	32.7 ± 19.1	84.8 ± 65.0	57.8 ± 61.7
– Dose 2	52.3 ± 40.6	48.8 ± 28.2	102 ± 102
– Dose 3	62.2 ± 48.9	59.4 ± 49.0	78.4 ± 63.5
– All	49.1 ± 36.5	64.4 ± 50.0	79.4 ± 76.9
Doses			

a. Median [Min, Max] (N).

b. Mean ± SD (N).

Mean=arithmetic mean, SD-standard deviation

Table 5 . AUC values for the 15 mg, 20 mg and 30 mg Multiple Dose treatment regimens

	Staccato Loxapine 5mg+5mg+5mg	Staccato Loxapine 10mg+5mg+5mg	Staccato Loxapine 10mg+10mg+10mg
AUC(0-4) ng*hr/ml	34.3	63.9	50.3
AUC(4-8) ng*hr/ml	47.6	48.6	95.1
AUC(8-12) ng*hr/ml	48.1	41.6	76.7
Accumulation Dose2/Dose1	1.38	-----	1.89
Accumulation Dose3/Dose1	1.40	-----	1.52

COMMENTS:

1.The dose proportionality results for study 004-102 are difficult to interpret since they combined the data from study 004-101 to increase the number of subjects. In addition the

study designs were different. Doses of 1.25 mg and 10 mg from study 101 were administered by giving 2 puffs which seems to impact the kinetics of loxapine.

2. Based upon C<sub>max</sub> there appeared to be an increase in the value with dose and also between dose 1 and dose 2, except at the 20 mg dose which decreased. The increase in exposure for a 2 fold increase in dose for AUC<sub>inf</sub> was 1.7 which is larger than that observed between the 5 mg and 10 mg doses following single dose administration in study 004-101 (used 1 puff for 5 mg dose and 2 puffs for the 10 mg dose).
3. All of the subjects used in this study were African American.

**STUDY NUMBER: AMDC-004-106**

**Study Title:** Pharmacokinetics of Staccato® Loxapine for Inhalation in Smokers Compared to Nonsmokers

**STUDY OBJECTIVES**

The objective of this study was to assess the pharmacokinetics of a single dose of 10 mg *Staccato* Loxapine administered to smokers compared to nonsmokers.

**Overall Study Design**

The study was designed as a Phase 1, single-center, open label, 2-group study which assessed the pharmacokinetics of a single dose of *Staccato* Loxapine 10 mg administered to smokers compared with nonsmokers.

There were 2 study visits. Screening took place at Visit 1. During Visit 2 (Day 0), subjects were administered treatment (*Staccato* Loxapine 10 mg). The study was targeted to enroll approximately 36 adult male and female subjects: 18 active chronic smokers and 18 nonsmokers.

Figure 1. Design of Study AMDC-004-106

Visit 1	Visit 2		
Screening	Study Group	Treatment	Discharge
	Smokers Planned: n=18	<i>Staccato</i> Loxapine 10 mg	
	Nonsmokers Planned: n=18	<i>Staccato</i> Loxapine 10 mg	

***Smokers had to meet the following inclusion criteria:***

A history of smoking > 15 cigarettes/day currently and for at least the last 2 years.  
Urine cotinine ≥ 500 ng/mL.

***Nonsmokers had to meet the following inclusion criteria:***

A history of never smoking > 5 cigarettes/day and not smoking at all for at least the last

2 years prior to Visit 1.  
 Urine cotinine  $\leq$  40 ng/mL.

### Demographics and Baseline Characteristics (Safety Population)

Demographic or Baseline Characteristic	<i>Staccato</i> Loxapine 10 mg Nonsmoker (N=18)	<i>Staccato</i> Loxapine 10 mg Smoker (N=17)	Total (N=35)
Gender, n (%):			
Female	9 (50.0%)	7 (41.2%)	16 (45.7%)
Male	9 (50.0%)	10 (58.8%)	19 (54.3%)
Age (years):			
Mean (SD)	25.7 (7.05)	31.5 (8.26)	28.5 (8.10)
Median	23	31	24
Minimum, maximum	20, 45	20, 45	20, 45
Race, n (%):			
Caucasian	13 (72.2%)	14 (82.4%)	27 (77.1%)
Black	3 (16.7%)	3 (17.6%)	6 (17.1%)
Hispanic	1 (5.6%)	0	1 (2.9%)
Other <sup>a</sup>	1 (5.6%)	0	1 (2.9%)
Height (cm):			
Mean (SD)	172.97 (9.623)	172.48 (8.206)	172.73 (8.834)
Median	173.9	170.7	171.2
Minimum, maximum	151.9, 190.5	161.3, 187.0	151.9, 190.5
Weight (kg):			
Mean (SD)	74.58 (11.053)	74.70 (9.003)	74.64 (9.961)
Median	73.2	74.9	74.9
Minimum, maximum	56.1, 96.3	55.8, 90.0	55.8, 96.3
Smoking history, n (%):			
Never smoked	15 (83.3%)	0	15 (42.9%)
Current smoker	0	17 (100.0%)	17 (48.6%)
Ex-smoker	3 (16.7%)	0	3 (8.6%)
Method of smoking, n (%):			
Cigarettes	3 (100.0%)	17 (100.0%)	20 (100.0%)

Dosage Administration  
 Each subject received *Staccato* Loxapine 10 mg.

Table 1. Lot Numbers and Manufacturer Information for Investigational Product

		<b>Staccato Loxapine 10 mg</b>			
Lot No.		M0624-A			
Manufacturer or supplier		Alexza Pharmaceuticals, Inc. 2091 Stierlin Court Mountain View, CA 94043			

Clinical Study	Device Version	Manufact -urer	Doses (mg)	Lot Numbers	Date of Manufacture
004-106: PK in smokers	Commercial	Alexza	10 mg	M0624-A	09-FEB-2009

***Selection and Timing of Dose for Each Subject***

Each subject received *Staccato* Loxapine 10 mg. Dosing was conducted between 07:00 and 10:00. Subjects were seated during dosing and were required not to stand up for at least 1.5 hours after dosing. Subjects were trained on how to use the *Staccato* system at screening (Visit 1) and on treatment day (Visit 2).

***Sample Collection***

PK blood samples were collected for evaluating pharmacokinetic parameters at predose and at 30 seconds; 1, 2, 3, 10, 30, and 60 minutes; and 2, 6, 12, and 24 hours after dosing. Blood samples (4 mL each) were collected into evacuated tubes from each subject.

**ANALYTICAL**

Study Start Date: April 2009  
 Study Completion Date: July 2009  
 Analysis completed: July 2009  
 Total time =120 days

Parameter	Loxapine	Amoxapine	7-OH loxapine	8-OH loxapine
Method	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
Sensitivity/LOQ	0.05 ng/mL	0.05 ng/mL	0.05 ng/mL	0.05 ng/mL
Linearity (Standard curve samples)	0.05-50 ng/ml	0.05-50 ng/ml	0.05-50 ng/ml	0.05-50 ng/ml
Quality Control (QC) Samples	0.015, 5, 40 ng/mL	0.015, 5, 40 ng/mL	0.015, 5, 40 ng/mL	0.015, 5, 40 ng/mL
Precision of Standards (%CV)	9.8% @0.05ng/ml 5.4% @ 50 ng/ml	8% @0.05ng/ml 4.2% @ 50 ng/ml	5.1% @0.05ng/ml 4.9% @ 50 ng/ml	6.4% @0.05ng/ml 8.1% @ 50 ng/ml
Precision of QC Samples (%CV)	<u>11% @ 0.15ng/ml</u> 10% @ 40 ng/ml	8.8% @ 0.15 ng/ml 6% @ 40 ng/ml	9.3% @ 0.15 ng/ml 4.4% @ 40 ng/ml	10% @ 0.15 ng/ml 7.4% @ 40 ng/ml

Accuracy of Standards (%)	99% @0.05ng/ml 96% @ 50 ng/ml	99% @0.05ng/ml 99% @ 47.3 ng/ml	98% @0.05ng/ml 92% @ 47.3 ng/ml	99% @0.05ng/ml 95% @ 47.3 ng/ml
Accuracy of QC Samples (%)	98% @ 0.15 ng/m 100% @ 40 ng/ml	99% @ 0.15 ng/ml 99% @ 40 ng/ml	102% @ 0.15 ng/ml 95% @ 40 ng/ml	99% @ 0.15 ng/m 93% @ 40 ng/ml

*Pharmacokinetic Variables*

Plasma concentrations of loxapine and metabolites were used to estimate the following PK parameters: area under the plasma concentration-time curve from Time 0 extrapolated to infinity ( $AUC_{inf}$ ); AUC from 0 to 2 hours ( $AUC_{0-2h}$ ); AUC from Time 0 to the time of the last quantifiable concentration ( $AUC_{last}$ ); maximum observed plasma concentration ( $C_{max}$ ); observed time of  $C_{max}$  ( $T_{max}$ ); terminal rate constant ( $k_e$ ); terminal half-life calculated from  $k_e$  ( $T_{1/2}$ ); and  $T_{half-max}$ , the time from  $T_{max}$  to time when concentration falls to half peak level,  $C_{max}/2$ . In addition,  $CL/F$  (clearance uncorrected for bioavailability) was estimated for loxapine only.

RESULTS

Figure 2. Mean Loxapine Concentration-Time Profiles in Smokers and Nonsmokers, 0 to 2 Hours after Dosing, Semi-Log Scale.

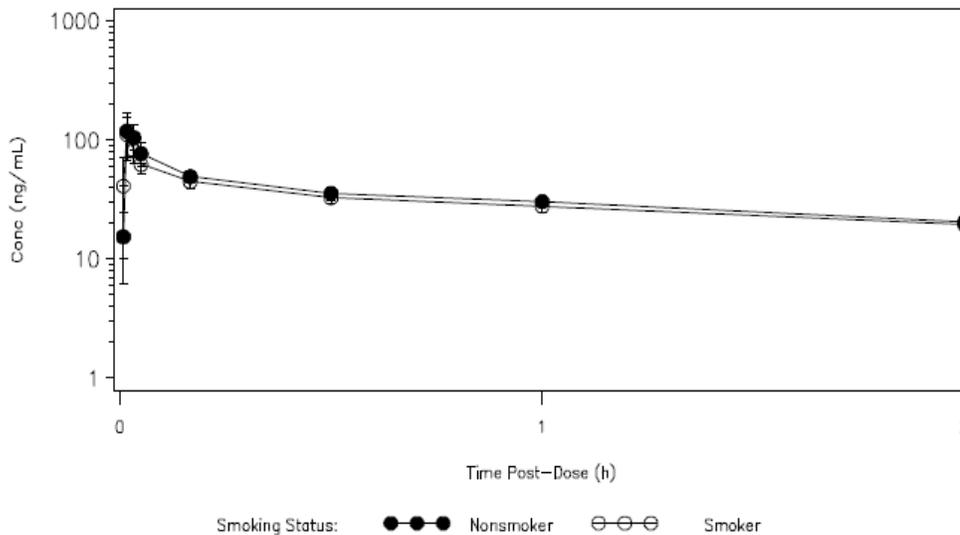


Figure 3. Mean 7-OH-Loxapine Concentration-Time Profiles in Smokers and Nonsmokers, Semi-Log Scale.

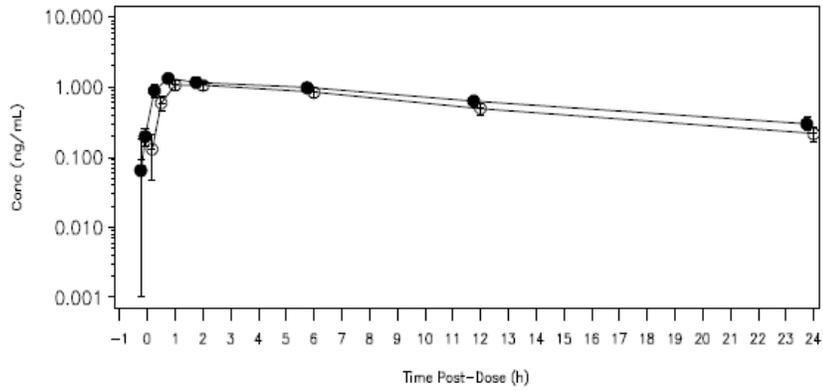


Figure 4. Mean 8-OH-Loxapine Concentration-Time Profiles in Smokers and Nonsmokers, Semi-Log Scale.

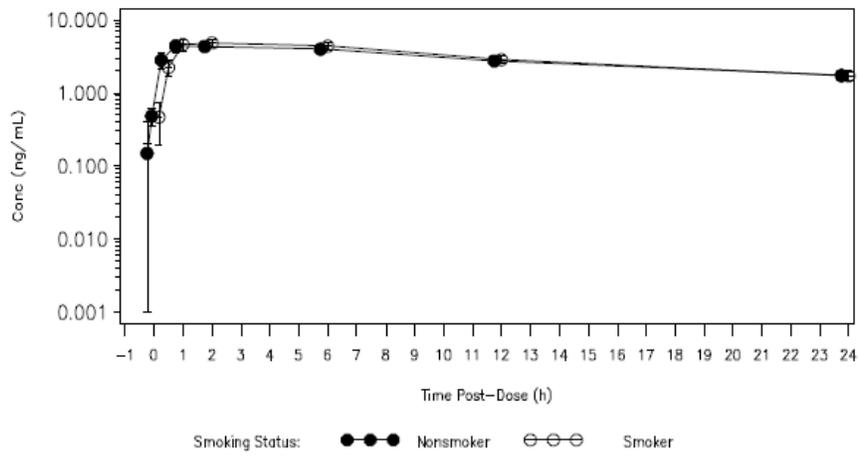


Figure 5. Mean Amoxapine Concentration-Time Profiles in Smokers and Nonsmokers, Semi-Log Scale.

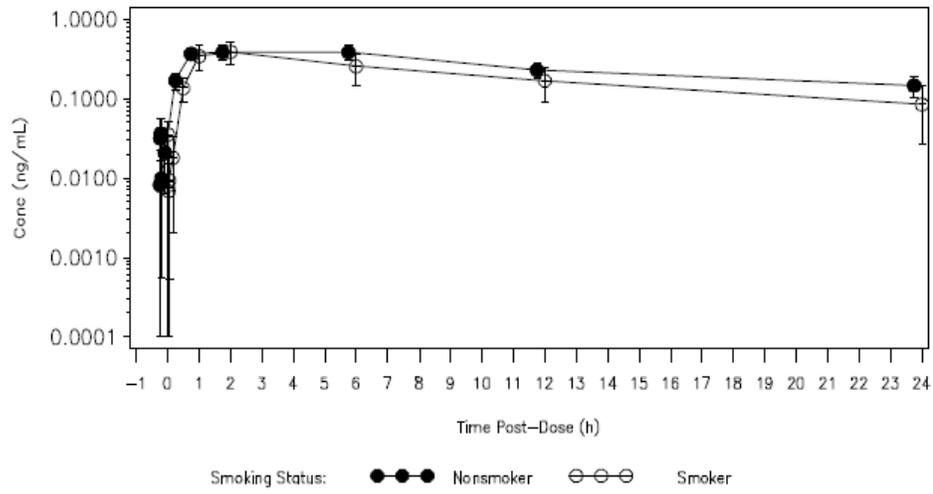


Table 2. Pharmacokinetic Parameters for Loxapine in Smokers and Nonsmokers (PK Population)

Parameter	<i>Staccato</i> Loxapine 10 mg Nonsmoker (N=18)	<i>Staccato</i> Loxapine 10 mg Smoker (N=17)	Total (N=35)	Ratio (Smoker- Nonsmoker) (90% CI)
				Ratio (CI difference) <sup>a</sup>
T <sub>max</sub> (min) <sup>c</sup>	1.88 [0.864, 30.0]	1.01 [0.636, 9.95]	1.57 [0.636, 30.0]	70.3% (-4.41, 1.95)
T <sub>half-max</sub> (min) <sup>c</sup>	6.05 [0.852, 108]	4.85 [0.960, 79.5]	5.80 [0.852, 108]	95.4% (-21.3, 18.6)
k <sub>e</sub> (h) <sup>d</sup>	0.101 (0.0268)	0.116 (0.0340)	0.108 (0.0310)	115% (-0.00250, 0.0324)
T <sub>½</sub> (h) <sup>d</sup>	7.30 (1.78)	6.52 (2.01)	6.92 (1.91)	89.3% (-1.86, 0.305)
CL/F (L/h) <sup>d</sup>	48.4 (8.28)	57.1 (11.1)	52.6 (10.5)	118% (3.08, 14.2) <sup>e</sup>
				GMR (CI ratio) <sup>b</sup>
C <sub>max</sub> (ng/mL) <sup>d</sup>	136 (109)	132 (91.0)	134 (99.3)	99.0% (64.8%, 151%)
AUC <sub>0-2h</sub> (ng·h/mL) <sup>d</sup>	67.5 (16.1)	61.8 (15.1)	64.7 (15.6)	91.6% (80.1%, 105%)
AUC <sub>inf</sub> (ng·h/mL) <sup>d</sup>	213 (39.0)	183 (42.9)	198 (43.1)	85.3% (76.4%, 95.3%) <sup>e</sup>
AUC <sub>last</sub> (ng·h/mL) <sup>d</sup>	194 (37.0)	169 (39.7)	182 (39.8)	86.7% (77.5%, 97.1%) <sup>e</sup>

SD=standard deviation; GMR=geometric mean ratio

- Disposition parameters (T<sub>max</sub>, T<sub>half-max</sub>, k<sub>e</sub>, T<sub>½</sub>, and CL/F) were not transformed. The LS Mean was equivalent to the arithmetic mean for this model. The ratio and the difference of LS means and the 90% CI for the difference were calculated.
- Exposure parameters (C<sub>max</sub>, AUC<sub>0-2h</sub>, AUC<sub>inf</sub>, and AUC<sub>last</sub>) were natural-log-transformed. The LS Mean was equivalent to the geometric mean for this model. GMR and 90% CI were calculated (exponentiated).
- T<sub>max</sub> and T<sub>half-max</sub> presented as median (min, max)
- Data presented as mean (SD)
- CI does not include zero (non-exponentiated) or 100 (exponentiated).

Source: Section 11.1, Table 2.6, Table 2.13; Appendix 12.2, Listing 2.2

Table 3. Exposure Ratios of Loxapine Metabolites to Loxapine in Smokers and Nonsmokers by Gender (PK Population)

Parameter	Gender	Metabolite/Loxapine Ratio Mean (SD)		
		Nonsmokers (N=18)	Smokers (N=17)	Overall (N=35)
<b>7-OH-loxapine</b>				
AUC <sub>inf</sub> ratio	Female	0.109 (0.0266)	0.0840 (0.0500)	0.0978 (0.0392)
	Male	0.0916 (0.0254)	0.0999 (0.0283)	0.0960 (0.0265)
AUC <sub>0-2h</sub> ratio	Female	0.0286 (0.00714)	0.0225 (0.00660)	0.0259 (0.00738)
	Male	0.0321 (0.0108)	0.0300 (0.0142)	0.0310 (0.0124)
<b>8-OH-loxapine</b>				
AUC <sub>inf</sub> ratio	Female	0.500 (0.173)	0.646 (0.131)	0.564 (0.168)
	Male	0.566 (0.166)	0.601 (0.218)	0.584 (0.191)
AUC <sub>0-2h</sub> ratio	Female	0.0825 (0.0311)	0.120 (0.0341)	0.0988 (0.0367)
	Male	0.123 (0.0394)	0.113 (0.0557)	0.118 (0.0476)
<b>Amoxapine</b>				
AUC <sub>inf</sub> ratio	Female	0.0555 (0.0188) <sup>a</sup>	0.0456 (0.0229) <sup>b</sup>	0.0517 (0.0202) <sup>c</sup>
	Male	0.0517 (0.0268) <sup>d</sup>	0.0400 (0.0287)	0.0449 (0.0277) <sup>e</sup>
AUC <sub>0-2h</sub> ratio	Female	0.00697 (0.00284)	0.00755 (0.00342)	0.00722 (0.00301)
	Male	0.00967 (0.00408)	0.00791 (0.00460)	0.00874 (0.00434)
<b>Loxapine N-oxide</b>				
AUC <sub>inf</sub> ratio	Female	0.112 (0.0340)	0.139 (0.0242)	0.124 (0.0323)
	Male	0.112 (0.0212)	0.148 (0.0460)	0.131 (0.0400)
AUC <sub>0-2h</sub> ratio	Female	0.0531 (0.0121)	0.0715 (0.0159)	0.0611 (0.0164)
	Male	0.0631 (0.0113)	0.0795 (0.0234)	0.0717 (0.0200)

Nonsmokers comprised 9 female subjects and 9 male subjects, and smokers comprised 7 female subjects and 10 male subjects, except as noted.

Mean value is average of each subject's metabolite-to-parent-drug ratio.

## Comments

1. There were no differences observed between smokers and non-smokers related to the disposition of Loxapine.
2. These ratios were similar for male smokers and nonsmokers. For female subjects, almost all exposure ratios were similar for smokers and nonsmokers (exceptions were the AUC<sub>0-2h</sub> exposure ratio for 8-OH-loxapine and the AUC<sub>inf</sub> ratio for 7-OH-loxapine).
3. 80% of the subjects in this study were Caucasian.

## PROTOCOL NUMBER: AMDC-004-103

**Protocol Title:** Bioequivalence of the Commercial Product Design (CPD) and the Current Clinical Version (CCV) of *Staccato*® Loxapine for Inhalation in Healthy Volunteers

### STUDY OBJECTIVES

The objectives of this study were as follows:

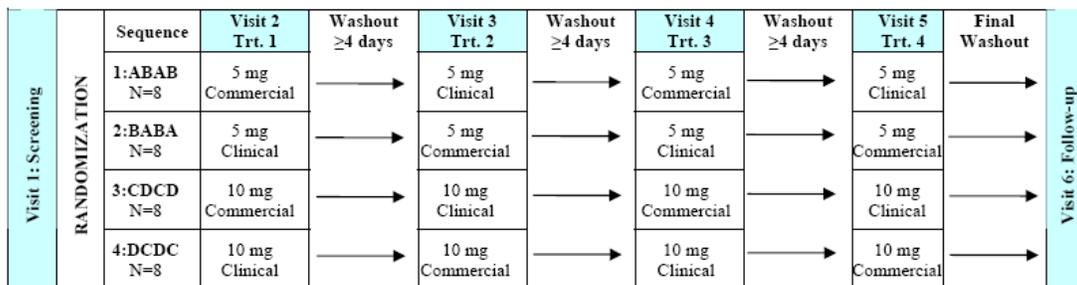
- To assess the pharmacokinetics of 5 mg and 10 mg Commercial Product Design of *Staccato* Loxapine
- To assess the single-dose bioequivalence of Commercial Product Design vs. Current Clinical Version
- To assess the safety and tolerability of 5 mg and 10 mg of *Staccato* Loxapine delivered via Commercial Product Design

### Description of Overall Study Design

Study AMDC-004-103 was a Phase 1, randomized, single-center, 2-treatment, 4-period, dose-stratified, replicate-design study to assess the safety, pharmacokinetics, and bioequivalence of the commercial and clinical versions of *Staccato* Loxapine in healthy volunteers. Study 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. Note that subjects received only 1 dose level, either 5 mg or 10 mg, and were not crossed over between dose levels.

The study evaluation period started with the administration of Dose 1 (Time 0) and continued for 24 hours.

**Figure 1. Study 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

Each subject was randomly assigned (1:1:1:1) to 1 of 4 different *Staccato* Loxapine dosing sequences, 8 subjects per sequence (Figure 1).

*Changes Incorporated into the Commercial Version of Staccato Loxapine*

Prior to Study AMDC-004-103, *in vitro* comparability testing was conducted (Alexza Pharmaceuticals; data on file). The commercial and clinical versions were shown to have comparable aerosol performance properties (mean emitted dose, emitted dose content uniformity, aerosol particle size distribution, and aerosol impurities) and key user interface characteristics (inhalation resistance of the drug-device combination product, performance of the breath actuation mechanism).

Table 1. Lot Numbers and Manufacturer Information for Investigational Product

	<i>Staccato</i> Loxapine 5 mg Commercial	<i>Staccato</i> Loxapine 10 mg Commercial	<i>Staccato</i> Loxapine 5 mg Clinical	<i>Staccato</i> Loxapine 10 mg Clinical
<b>Lot No.</b>	M0583	M0584	M0531	M0537
<b>Manufacturer or Supplier</b>	Alexza Pharmaceuticals, Inc 2091 Stierlin Court, Mountain View, CA 94043			

<b>Clinical Study</b>	<b>Device Version</b>	<b>Manufact -urer</b>	<b>Doses (mg)</b>	<b>Lot Numbers</b>	<b>Date of Manufacture</b>
<b>004-103: Bioequivalence</b>	<b>Clinical 2</b>	<b>Alexza</b>	<b>5 mg</b>	<b>M0531</b>	<b>14-NOV-2007</b>
			<b>10 mg</b>	<b>M0537</b>	<b>26-NOV-2007</b>
	<b>Commercial</b>	<b>Alexza</b>	<b>5 mg</b>	<b>M0583</b>	<b>26-JUN-2008</b>
			<b>10 mg</b>	<b>M0584</b>	<b>30-JUN-2008</b>

## DEMOGRAPHICS

Table 2. Demographics and Baseline Characteristics

Demographic or Baseline Characteristic	Safety Population (N=32)	BE Population* (N=30)
Age (y)		
Mean (SD)	25.8 ± 7.69	25.9 ± 7.93
Minimum, maximum	20, 52	20, 52
Gender, n (%):		
Female	19 (59.4%)	17 (56.7%)
Male	13 (40.6%)	13 (43.3%)
Race, n (%):		
Caucasian	26 (81.3%)	25 (83.3%)
Hispanic	1 (3.1%)	0
Asian	4 (12.5%)	4 (13.3%)
Other	1 (3.1%)	1 (3.3%)
Weight (kg)		
Mean (SD)	72.30 ± 13.991	73.41 ± 13.737
Minimum, maximum	52.3, 102	52.3, 102
Height (cm)		
Mean (SD)	170.7 ± 10.77	171.6 ± 10.48
Minimum, maximum	153, 192	153, 192
Smoking history, n (%):		
Never smoked	25 (78.1%)	NC
Ex-smoker	7 (21.9%)	NC

NC=not calculated

a. BE population without Subject 008

***Selection and Timing of Dose for Each Subject***

Subjects were randomized to *Staccato* Loxapine 5 or 10 mg. Administration of Dose 1 occurred at “Time 0.” Subjects were trained in the use of the *Staccato* system during screening and again during baseline assessments.

Subjects were required to fast from 23:00 the night before dosing. Breakfast was served just before the first dosing. Subjects were instructed to remain properly hydrated. Meals were served to the subjects at times that did not interfere with scheduled doses or assessments.

## ANALYTICAL

August 11, 2008 (first subject dosed)

Analysis completed: September 16, 2008

Total time =30 days

Parameter	Loxapine	Amoxapine	7-OH loxapine	8-OH loxapine
Method	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
Sensitivity/LOQ	0.05 ng/mL	0.05 ng/mL	0.05 ng/mL	0.05 ng/mL
Linearity (Standard curve samples)	0.048, 0.159, 0.78, 5.23, 37, and 46 ng/ml	0.048, 0.159, 0.78, 5.23, 37, and 46 ng/ml	0.048, 0.159, 0.78, 5.23, 37, and 46 ng/ml	0.048, 0.159, 0.78, 5.23, 37, and 46 ng/ml
Quality Control (QC) Samples	0.015, 5, 40 ng/mL			
Precision of Standards (%CV)	6.8% @0.05ng/ml 4.2% @ 50 ng/ml	6% @0.05ng/ml 4.5% @ 50 ng/ml	8.8% @0.05ng/ml 5.2% @ 50 ng/ml	7.4% @0.05ng/ml 5.0% @ 50 ng/ml
Precision of QC Samples (%CV)	<u>7.9% @ 0.15ng/ml</u> 5.1% @ 40 ng/ml	8.8% @ 0.15 ng/ml 6% @ 40 ng/ml	6.8% @ 0.15 ng/ml 5.7% @ 40 ng/ml	11% @ 0.15 ng/ml 3.3% @ 40 ng/ml
Accuracy of Standards (%)	99% @0.05ng/ml 98% @ 47.3 ng/ml	99% @0.05ng/ml 99% @ 47.3 ng/ml	98% @0.05ng/ml 99% @ 47.3 ng/ml	99% @0.05ng/ml 99% @ 47.3 ng/ml
Accuracy of QC Samples (%)	91% @ 0.15 ng/ml 94% @ 40 ng/ml	97% @ 0.15 ng/ml 97.2% @ 40 ng/ml	92% @ 0.15 ng/ml 92% @ 40 ng/ml	94% @ 0.15 ng/ml 93% @ 40 ng/ml

### *Appropriateness of Measurements*

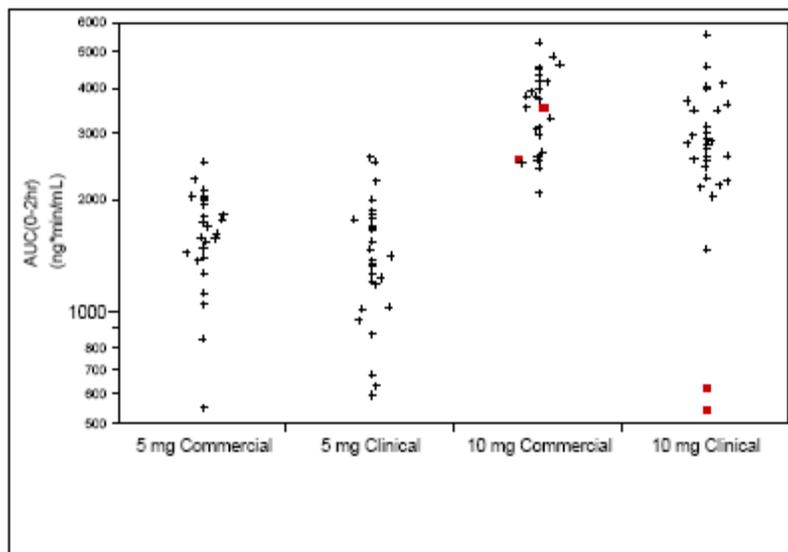
The intensive sampling for the loxapine concentrations (30 seconds, and 1, 2, 3, 5, 10, and 30 minutes, and 1, 2, 4, 6, 12, and 24 hours after dosing) was necessary to adequately characterize the  $C_{max}$ .

### *Pharmacokinetic Methods*

Plasma samples for pharmacokinetic analysis were collected beginning at Time 0 (immediately before dosing), and at 0.5, 1, 2, 3, 5, 10, and 30 minutes, and 1, 2, 4, 6, 12, and 24 hours after dosing. Plasma concentrations of loxapine and the 2 major metabolites of loxapine (7-OH-loxapine and 8-OH-loxapine) were examined over time for individual subjects and treatment groups, and used to estimate the following PK parameters: area under the plasma concentration-time curve from Time 0 extrapolated to infinity ( $AUC_{inf}$ ), AUC from 0 to 2 hours ( $AUC_{0-2h}$ ), AUC from Time 0 to the time of the last quantifiable concentration ( $AUC_{last}$ ), maximum observed plasma concentration ( $C_{max}$ ), observed time of  $C_{max}$  ( $T_{max}$ ), terminal rate constant ( $k_e$ ), terminal half-life calculated from  $k_e$  ( $t_{1/2}$ ), clearance, and the concentration at 2 hours ( $C_{2h}$ ).

### Results

**b) AUC<sub>0-2h</sub>**



Subject 008 represented by a red box [■]; all other subjects represented by black crosses (+)  
Source: Section 11.2, [Figure 2.42](#); Appendix 12.2, [Listing 2.3](#)

Table 3. Pharmacokinetic Parameters for Loxapine and Loxapine Metabolites by Treatment (PK Population, without Subject 008)

Parameter	5 mg Commercial (N=15)	5 mg Clinical (N=15)	10 mg Commercial (N=16)	10 mg Clinical (N=16)
<b>Loxapine</b>				
AUC <sub>inf</sub> (ng*min/mL), mean ± SD	4332 ± 950	4068 ± 1201	9748 ± 1920	8911 ± 1920
AUC <sub>0-2h</sub> (ng*min/mL), mean ± SD	1620 ± 386	1450 ± 487	3610 ± 806	3065 ± 792
C <sub>max</sub> (ng/mL), mean ± SD	116 ± 73.9	115 ± 98.3	363 ± 255	265 ± 256
C <sub>2h</sub> (ng/mL), mean ± SD	6.75 ± 1.36	6.28 ± 1.59	14.82 ± 3.91	13.07 ± 3.26
T <sub>max</sub> (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 <sub>1/2</sub> (min), mean ± SD	452 ± 126	465 ± 144	458 ± 100	492 ± 70.3
k <sub>e</sub> (/min), mean ± SD	0.00166 ± 0.000440	0.00162 ± 0.000364	0.00160 ± 0.000328	0.00147 ± 0.000194
CL/F (L/min), mean ± SD	1.23 ± 0.358	1.34 ± 0.414	1.07 ± 0.249	1.19 ± 0.279
<b>Loxapine Metabolites</b>				
C <sub>max</sub> 7-OH-loxapine (ng/mL), mean ± SD	0.824 ± 0.263	0.743 ± 0.269	1.44 ± 0.634	1.19 ± 0.312
C <sub>max</sub> 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

#### COMMENTS:

1. The conclusion from the statistical analysis was that when using the "Kenward-Roger" option for the *denominator degrees-of-freedom method* (DDFM) in Proc Mixed the 5 mg dose is BE between the Test product (Commercial Version 1) and Reference product (Clinical Version 2), 90% CI=[0.997-1.238].

2. The statistical analysis completed by Don Schuirmann is appended to this review.

#### ADDENDUM REPORT ON PHARMACOKINETICS AND RACE

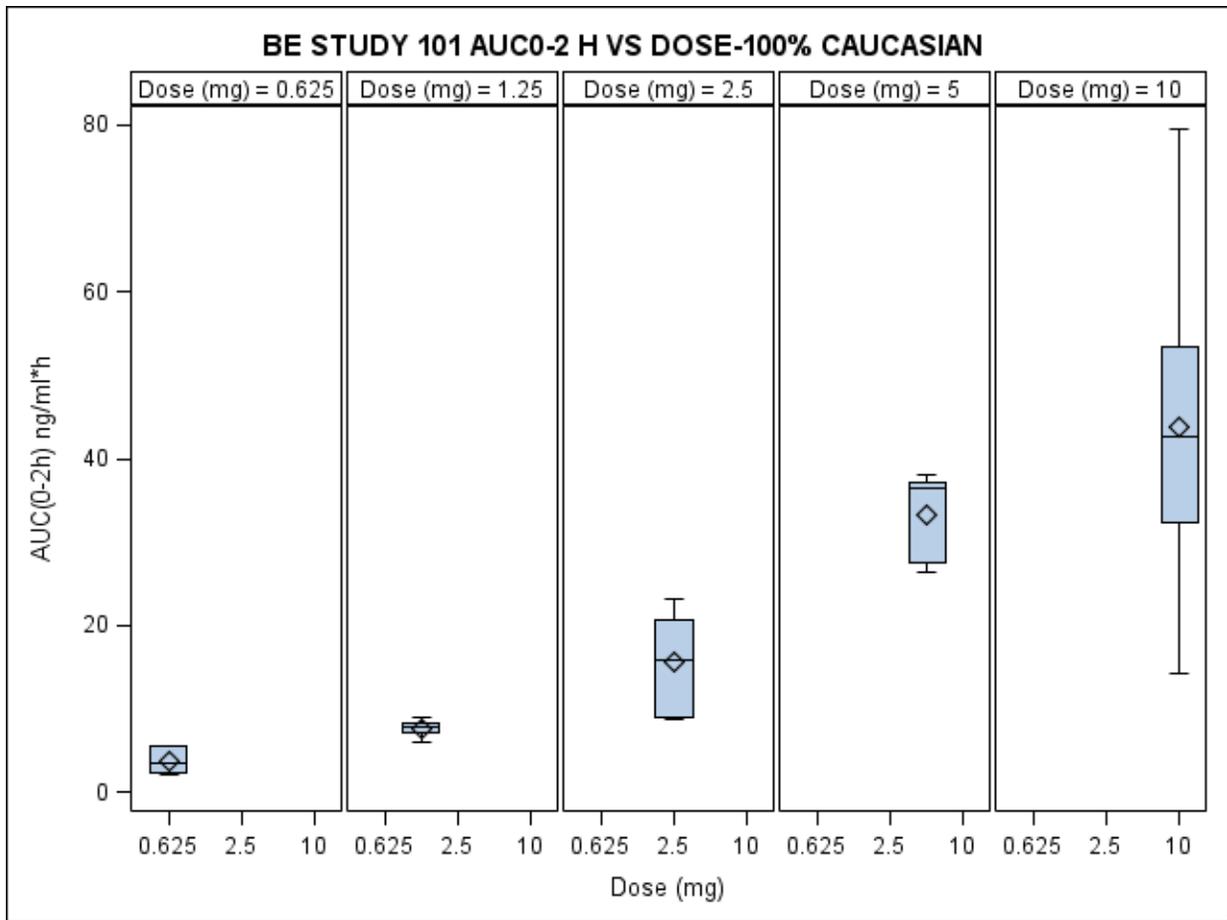
The studies submitted by the firm were analyzed for the BE metric AUC(0-2hr) to determine if there were any exposure differences between the different ethnic populations used in the study since Studies 102 had ( 94% Black) and pivotal BE study 103 had ( 83% Caucasian). Due to the differences there was a concern that the point estimate may be different for the two races and thus not adequately represented in the pivotal BE study 103.

## Methods

A subset of each submitted study (i.e., 101, 102, 103 and 106) was constructed to contain only Blacks or Caucasians, dependent upon which group was the dominant group in the study. The AUC(0-2h) was calculated for each study and box plots constructed. Only period 1 subjects were compared since the studies were designed with single dosing (101, and 106) and with multiple doses (102, and 103).

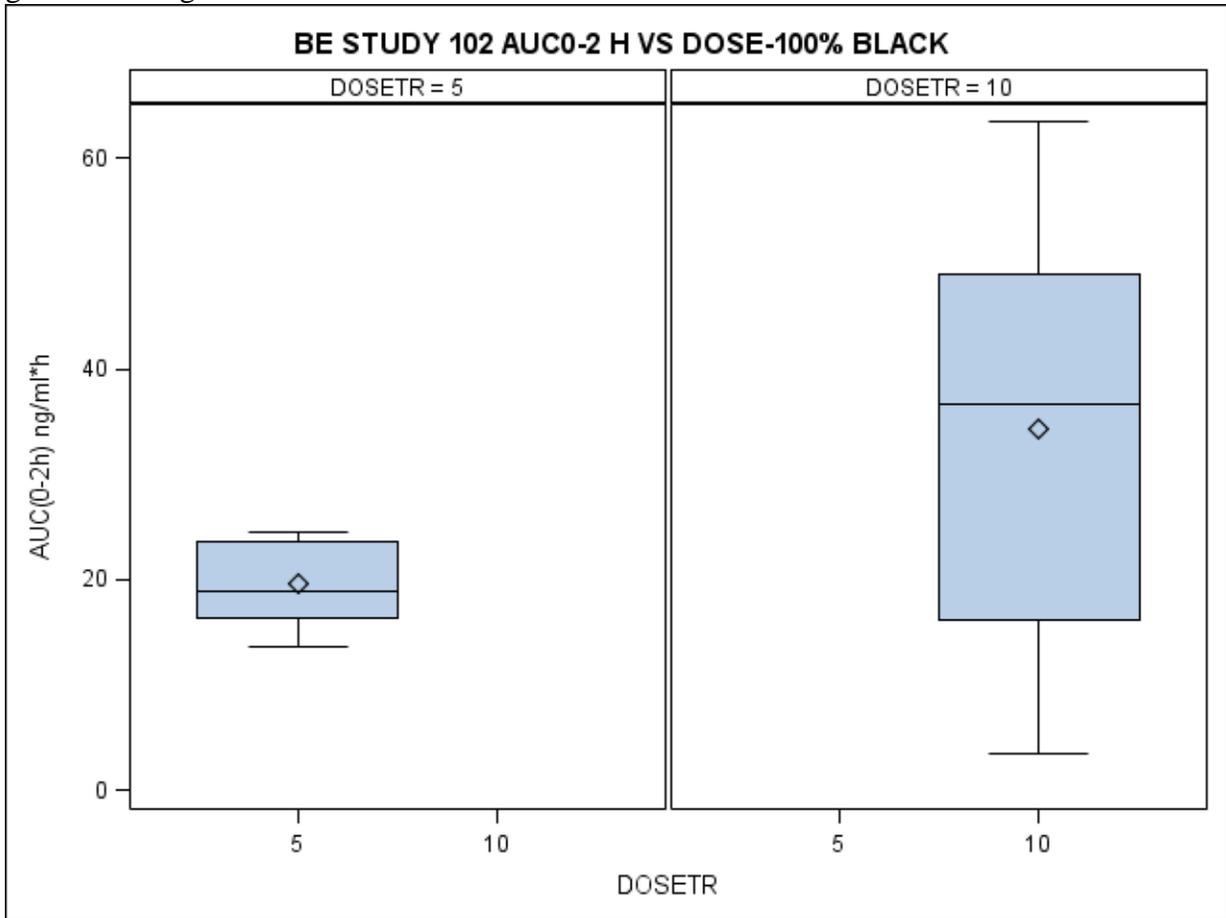
## Results

Figure 1 . Plot of AUC (0-2 h) for study 101 for the predominant racial group i.e. Caucasians. Subjects 8, 18, 21, and 36 were deleted since they were non Caucasian.



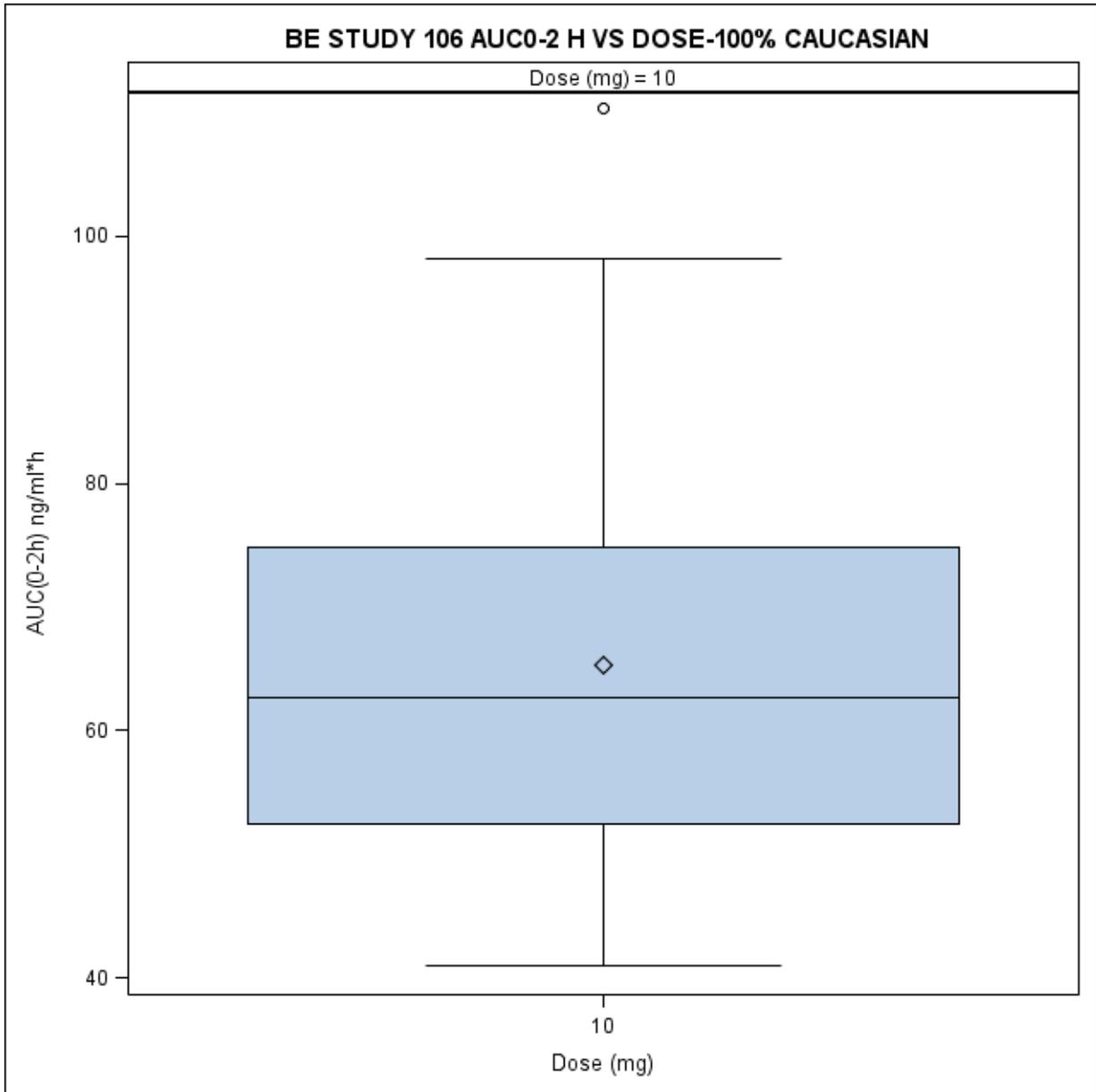
Dose= 0.625 mg N=6; Dose=1.25mg N=8; Dose=2.5mg N=6; Dose=5mg N=7;  
Dose=10mg N=8

Figure 2. Plot of AUC (0-2 h) for study 102 for the predominant racial group i.e. Blacks. Subjects 8 and 12 were deleted since they were not African-American. Values are from only period 1. The 10 mg doses from the 20 mg and 30 mg doses have been combined to give the 10 mg dose.



Dose=15 (5mg) N=7; Dose=20(10 mg) N=7; Dose=30(10 mg) N=7

Figure 3. Plot of AUC (0-2 h) for study 106 for the predominant racial group i.e. Caucasians. Subjects 9 ,11,12,16, 28, 30, and 35 were deleted since they were not Caucasian.



Dose=10mg N=28

Figure 4. Plot of AUC (0-2 h) at the 5 mg dose for study 103 for the predominant racial group i.e. Caucasians. Subjects 4, 6 and 22 were deleted from study 103 since they were not Caucasian. Subjects 8 and 12 were deleted from study 102 since they were not African Americans. Values are from only period 1.

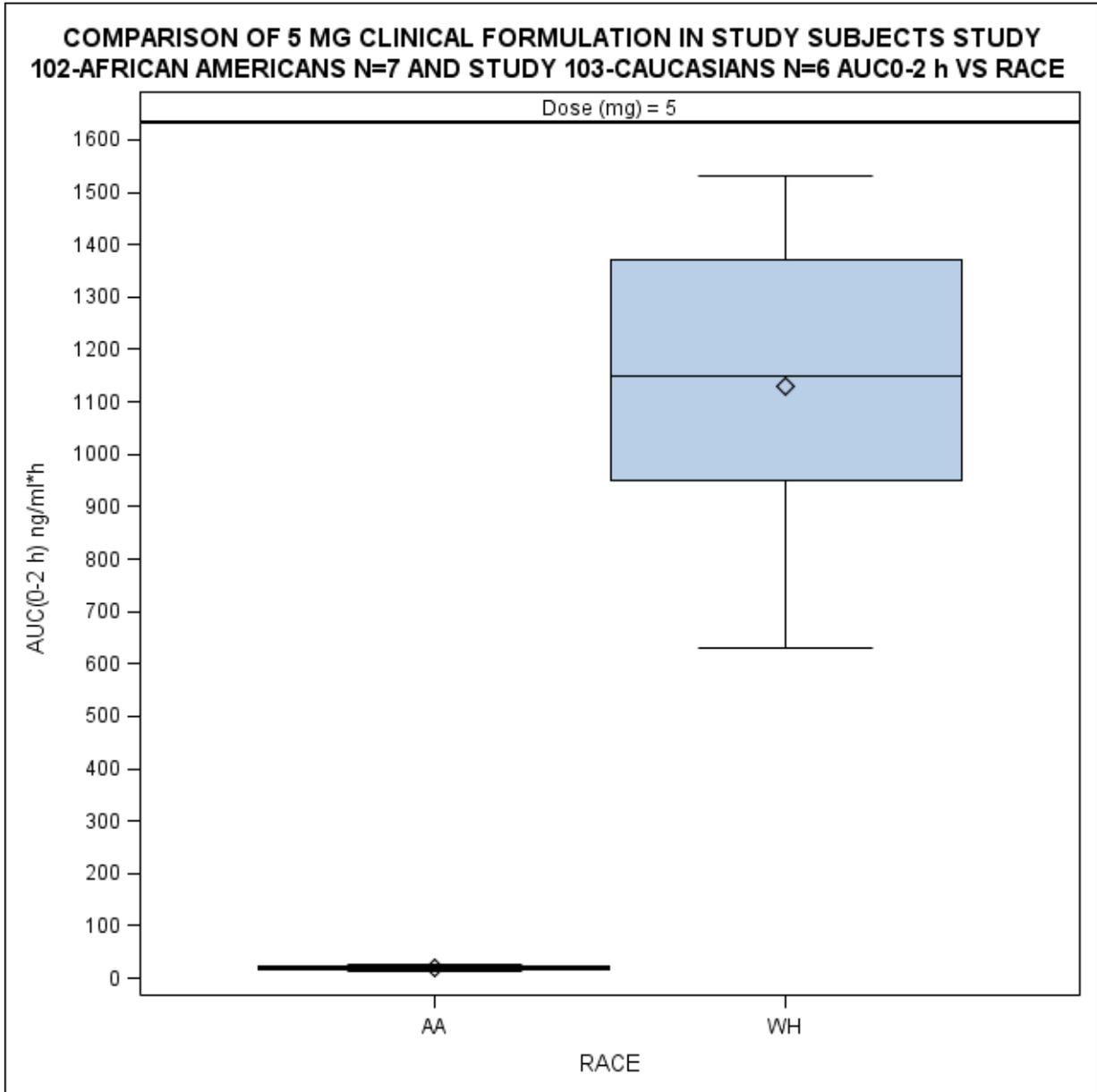


Figure 5. Plot of AUC (0-2 h) at the 10 mg dose for study 103 for the predominant racial group i.e. Caucasians. Subjects 4, 6 and 22 were deleted from study 103 since they were not Caucasian. Subjects 8 and 12 were deleted from study 102 since they were not African American. Values are from only period 1.

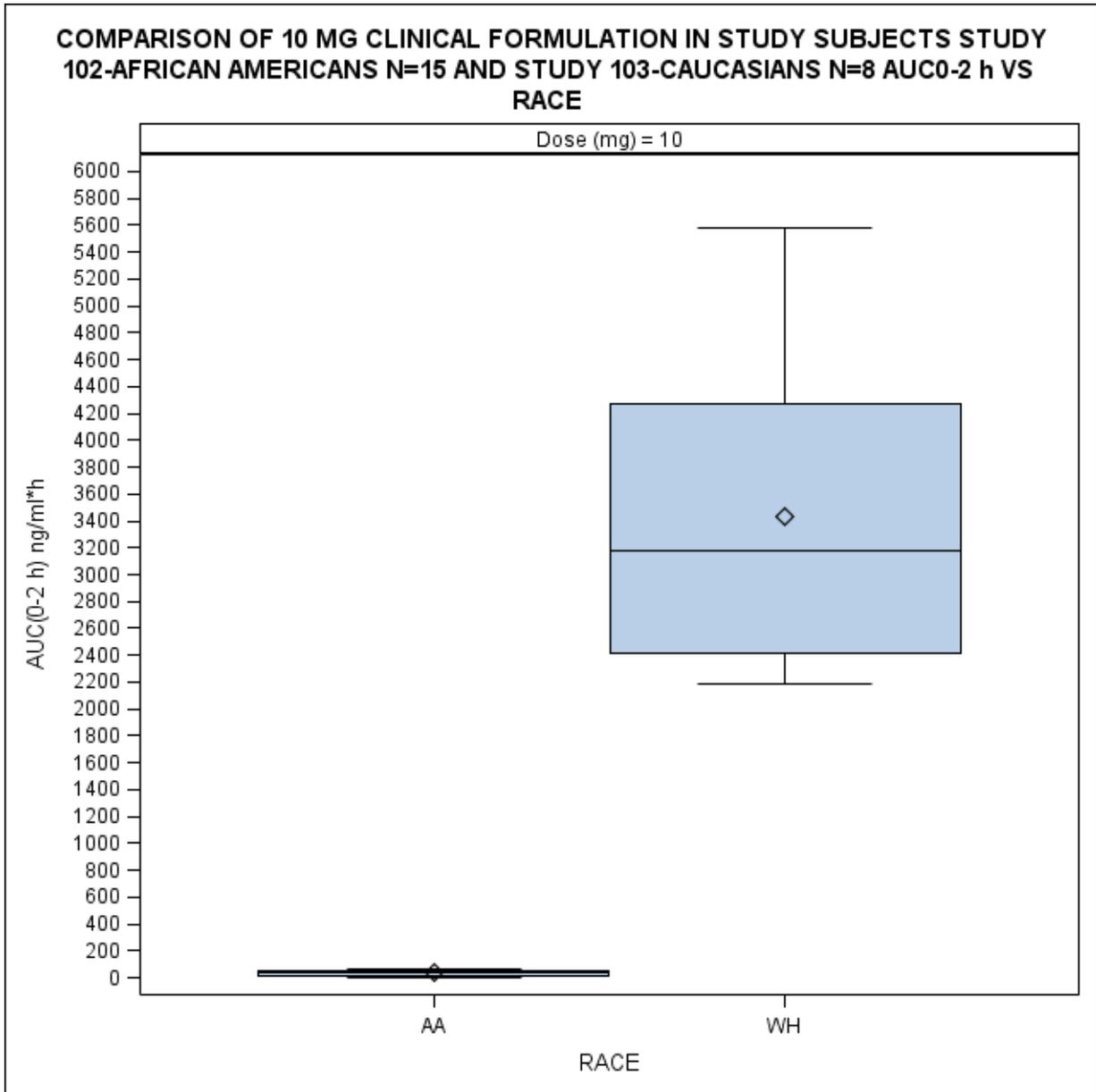


Table 1. Calculated AUC(0-2h ) values for the 10 mg dose

Dose (mg)	Subject	RACE	_TYPE_	_FREQ_	AUC0_2
10	1	AA	0	7	34.26
10	6	AA	0	7	28.65
10	7	AA	0	7	10.36
10	10	AA	0	7	3.53
10	12	AA	0	7	12.67
10	13	AA	0	7	20.13
10	15	AA	0	7	36.7
10	17	AA	0	7	51.71
10	20	AA	0	7	45.48
10	23	AA	0	7	43.76
10	24	AA	0	7	16.11
10	26	AA	0	7	41.58
10	28	AA	0	7	63.54
10	30	AA	0	7	49.02
10	32	AA	0	7	55.8
10	3	WH	0	10	2184.37
10	7	WH	0	10	4560.53
10	10	WH	0	10	3641.85
10	14	WH	0	10	5584.3
10	17	WH	0	10	2600.15
10	21	WH	0	10	2724.42
10	25	WH	0	10	3982.18
10	31	WH	0	10	2223.85

Table 2 . Ratio of metabolites/loxapine ratio for each Clinical Pharmacology study. All values are arithmetic means of the ratios.

STUDY AUCinf	STUDY 101			STUDY 102			STUDY 106		STUDY 103	
	2.5 mg	5 mg	10 mg	15 mg	20 mg	30 mg	10 mgS	10 mgNS	5 mg	10 mg
7OH loxapine/loxapine	0.089	0.12	0.13	0.128	0.158	0.162	0.09	0.1	0.15	0.12
8OH loxapine/loxapine	0.74	0.80	0.82	1.01	1.2	0.86	0.61	0.53	0.75	0.72
Amoxapine/loxapine	---	---	0.05	0.04	0.08	0.05	0.04	0.05	---	---

s-smokers ns-nonsmokers

In the pivotal BE study 103, Caucasian AUC(0-2) ng/mlxhr median values were 60 to 80 fold higher in Caucasians than African Americans in study 102. However due to the higher variability in Caucasians, which gives higher sensitivity, the conduct of study 103 is acceptable to OCP with respect to ethnic composition.

**SIGNATURES**

Andre Jackson \_\_\_\_\_  
Reviewer, Psychiatry Drug Products, DCP I  
Office of Clinical Pharmacology

RD/FTinitialized by Raman Baweja,  
Ph.D. \_\_\_\_\_  
Team Leader, Psychiatry Drug Products, DCP I  
Office of Clinical Pharmacology

cc: NDA 22549, HFD-860(Mehta, Baweja, Jackson)

**APPENDIX II**

**REVIEW OF IN VITRO STUDIES SUBMITTED BY FIRM**

METHODS  
PLASMA PROTEIN BINDING  
*Spiked Ultrafiltrate Standards*



*Plasma Protein Binding Samples*



Analytical methods were acceptable to OCP.

#### ***Concentration of Unbound Drug***

The concentration of unbound drug was determined by comparing the plasma ultrafiltrate levels for the samples against the standard curve (STDs). This was calculated as follows:  
Concentration of unbound drug = (Peak area of plasma sample x Slope) + y-intercept

#### ***Percent Plasma Protein Binding***

The percent protein binding was determined by subtracting the percent unbound from 100%:

% plasma protein binding = 100 - [Concentration of unbound drug / Total concentration of plasma sample\*] x 100%

\*plasma sample concentration = 50, 100 or 500 ng/mL

Results:

The extent of protein binding of loxapine in human plasma is 96.6%.

However there was poor recovery which raises a question related to bias of the value.

The extent of protein binding of amoxapine in human plasma was 77.8%. Recovery was low 26-61%. The average extent of protein binding of 7-OH-loxapine in human plasma was 93.4% while for 8-OH-loxapine it was 92.3%.

### **RED CELL PARTIONING METHODS**

#### **Incubation Conditions**

(b) (4)

Analytical methods were acceptable to OCP.

The Partitioning Ratio was calculated using the following equation:

Partitioning Ratio =  $C_b / C_p$

where:

$C_b$  was the concentration in whole blood

$C_p$  was the concentration in spiked plasma

**Table 1 Loxapine <sup>(b) (4)</sup> Partitioning Results**

Loxapine Concentration (ng/mL)	Concentration of Loxapine in Whole Blood (ng/mL)	Concentration of Loxapine in Plasma (ng/mL)	Partitioning Ratio
10	8.99	10.38	0.87
100	102.78	92.58	1.11

The ratios at the two plasma concentrations were 0.87 to 1.11, indicating no red blood cell specific distribution at loxapine concentrations between 10 and 100 ng/mL.

## **DRUG METABOLISM REPORT**

### **CYP ENZYMES**

#### **Objective**

To determine from three experiments the cytochrome P450 (CYP) isoforms that metabolize loxapine to 7-OH-loxapine, 8-OH-loxapine and amoxapine in humans.

#### **Methods**

Loxapine (10  $\mu$ M) was incubated with pooled male, human liver microsomes at microsomal protein concentrations of 0.05, 0.1 or 0.2 mg/ml with an NADPH regeneration system. At time points of 0, 15, 30, and 60 minutes, aliquots were analyzed by LC/MS/MS to quantify each metabolite of interest.

For a CYP450 reaction, the substrate concentration was selected based on the Michaelis-Menten constant ( $K_m$ ) associated with the enzyme activity for the metabolite involved in the greatest intrinsic clearance of the parent. In humans, this metabolite is 8-OH-loxapine. An experiment to determine the loxapine incubation concentration for the phenotyping experiments was conducted.  $V_{max}$  and  $K_m$  values were determined from the linear regression of the Lineweaver-Burke plot. A  $V_{max}$  of 44 nM/mg protein-min and a  $K_m$  of 4.4  $\mu$ M was obtained for 8-OH-loxapine. A substrate concentration chosen for the phenotyping experiments should be  $\leq K_m$ , thus a final incubation loxapine concentration of 1  $\mu$ g/mL (3  $\mu$ M) was selected as the loxapine incubation concentration for all experiments.

The first study was conducted using 13 CYP isozymes commercially purchased. Each isozyme was expressed from the corresponding human isozyme cDNA. The first experiment utilized individual CYP isozymes expressed from human isozyme complimentary DNA using a baculovirus expression system in the form of a Supersome™ (recombinant enzymes).

Incubations were conducted at 37°C. 100  $\mu$ L aliquots were taken at Time 0 (immediately following addition of substrate), 30 and 60 minutes post addition of substrate. Control samples were sampled at Time 0 and 60 minutes. The aliquots were quenched by adding

200  $\mu\text{L}$  of an internal standard solution containing loxapine-d8 prepared at a concentration of 500 ng/mL in acetonitrile.

The second experiment was conducted using a reaction phenotyping kit with microsomes from 16 donors, 9 of which were male, 7 female, 1 smoker, 1 Asian, 3 African-American, aged 4-79.

The third study was conducted using cryopreserved, human liver microsomes pooled purchased commercially. An aliquot (10  $\mu\text{L}$ ) of inhibitors in either methanol or acetonitrile were added to 0.5 mL cofactors and 0.5 mL microsome (final protein concentration = 0.1 mg/mL and inhibitor concentration = 2 x  $K_i$ ) and incubated at 37°C for 30 minutes. 8-OH-loxapine formation was inhibited by the use of the inhibitors for CYPs 1A2, 2B6, 2C8, and 2C19. 7-OH-loxapine formation was inhibited by the use of inhibitors of CYPs 2C8 and 2C19. Amoxapine formation was inhibited by the use of inhibitors for 2C8, 2C9 and 3A4/5.

### Chemical Inhibitor Incubations (Experiment 3)

Inhibitor	Specific CYP Inhibited	$K_i$ ( $\mu\text{M}$ ) <sup>a</sup>	Solvent	Incubation Concentration ( $\mu\text{M}$ )	% Inhibition		
					Amoxapine	7-OH-Loxapine	8-OH-Loxapine
Furafylline	1A2	0.73	50% Acetonitrile/ Methanol	1.46	32	60	94
Tranylcypromine	2A6	0.2	Methanol	0.4	36	44	57
Ticlopidine	2B6	0.2	Methanol	0.4	37	74	93
Quercetin	2C8	1.1	50% Acetonitrile/ Methanol	2.2	99	98	98
Sulfaphenazole	2C9	0.3	Acetonitrile	0.6	87	40	15
Ticlopidine	2C19	1.2	Methanol	2.4	69	88	97
Quinidine (hydrochloride, monohydrate)	2D6	0.4	Acetonitrile	0.8	43	57	6
Ketoconazole	3A4/5	0.18	Methanol	0.36	97	79	66

### Data Analysis Methods

#### Correlation Analysis

Reaction phenotyping experiments utilizing human microsomes are most relevant when a single CYP is responsible for the metabolism of the parent. A correlation with a participating CYP can become less obvious when the number of CYPs involved increases; as in the case with loxapine. Multiple regression analyses can be conducted, but a larger pool of microsomes from different donors is required. For the current studies only single regression analyses were conducted.

### Results

### CYP Isozyme Studies

In the studies with CYP isozymes from a vendor, positive responses (Area Ratio >0.0050) were seen for CYP1A2 (8-OH-loxapine, 7-OH-loxapine), 2C19 (amoxapine), 2D6 (7-OH-loxapine), and 3A4 (7-OH-loxapine, amoxapine).

The metabolism of loxapine to 8-OH-loxapine appears to be mediated primarily by CYP1A2 with the results from the correlation analysis, CYP isozyme studies and the chemical inhibition studies supporting this result.

### Reaction Phenotyping, CYP Isozyme and Chemical Inhibitor Results for 8-OH-loxapine

Isozyme	Experiment		
	CYP Isozyme (Area Ratio per pmol enzyme)	Correlation Analysis (R <sup>2</sup> )	Chemical Inhibition (% Inhibition)*
1A2	0.0067	0.706 (7-ethoxyresorufin O-dealkylation), 0.841 (Phenacetin O-deethylation)	94
1B1	0.0000	ND	NA
2A6	0.0001	0.000	57
2B6	0.0000	0.004, 0.017	93
2C8	0.0000	0.211	98
2C9	0.0001	0.147	15
2C18	0.0000	ND	NA
2C19	0.0000	0.001	97
2D6	0.0003	0.001	6
2E1	0.0000	0.165	NA
3A4/5	0.0008 (3A4), 0.0000 (3A5)	0.117 (testosterone 6β-hydroxylation), 0.203 (midazolam 1'-hydroxylation)	66
3A7	0.0000	ND	NA

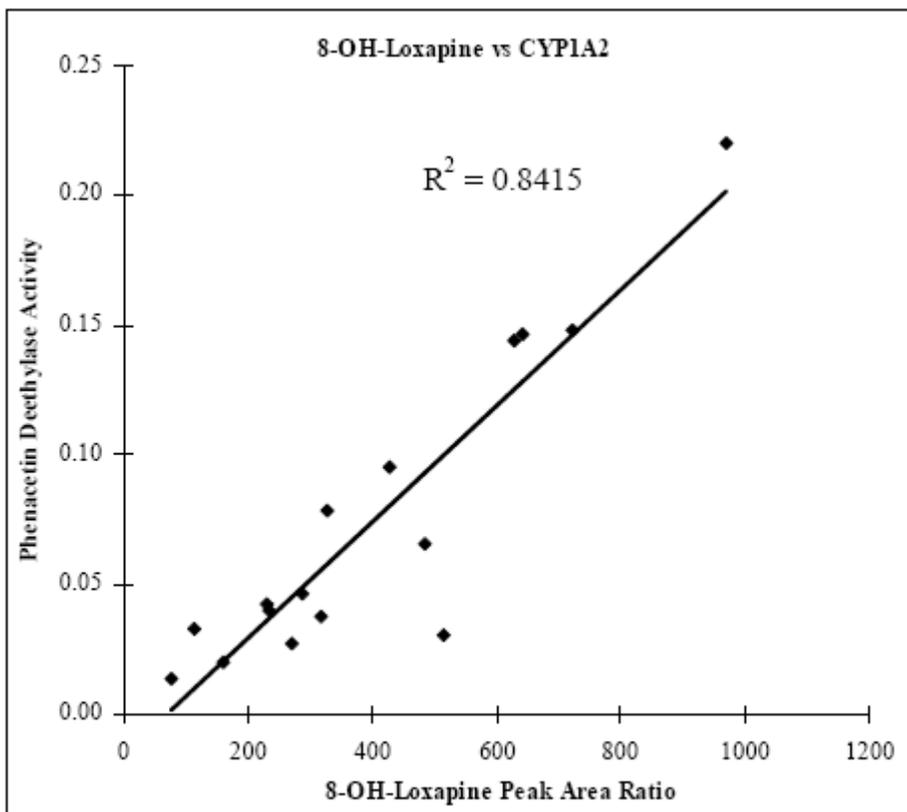
\* % Inhibition = 100% - % of control incubation

NA = Not analyzed

ND = No data from vendor

n=2 incubations per isozyme

### Correlation Plot for 8-OH-loxapine vs CYP1A2 (Phenacetin Deethylase Activity)



### 7-OH-loxapine Formation

In the CYP isozyme experiments, the area ratio per pmol of isozyme was highest for CYP2D6 (0.0206) and CYP3A4 (0.0117). In the correlation analysis experiments, the highest  $R^2$  values were for CYP2D6 (0.534), CYP3A4/5 testosterone  $6\beta$ -hydroxylation (0.397), and CYP3A4/5 midazolam 1'-hydroxylation (0.248).

**Reaction Phenotyping, CYP Isozyme and Chemical Inhibitor Results for 7-OH-loxapine**

Isozyme	Experiment		
	CYP Isozyme (Area Ratio per pmol enzyme)	Correlation Analysis (R <sup>2</sup> )	Chemical Inhibition (% Inhibition)*
1A2	0.0054	0.003 (7-ethoxyresorufin O-dealkylation), 0.000 (Phenacetin O-deethylation)	60
1B1	0.0001	ND	NA
2A6	0.0005	0.050	44
2B6	0.0020	0.097, 0.001	74
2C8	0.0006	0.045	98
2C9	0.0013	0.003	40
2C18	0.0006	ND	NA
2C19	0.0021	0.010	88
2D6	0.0206	0.534	57
2E1	0.0003	0.004	NA
3A4/5	0.0117 (3A4), 0.0033 (3A5)	0.397 (testosterone 6 $\beta$ -hydroxylation), 0.248 (midazolam 1'-hydroxylation)	79
3A7	0.0001	ND	NA

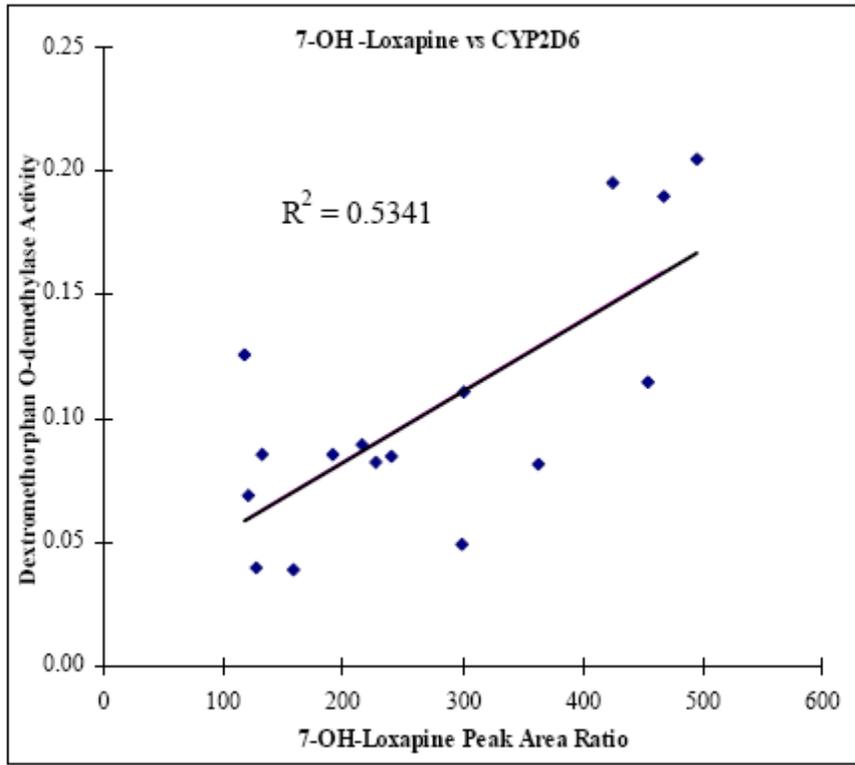
\* % Inhibition = 100% - % of control incubation

NA = Not analyzed

ND = No data from vendor

n=2 incubations per isozyme

**Correlation Plot for 7-OH-loxapine vs CYP2D6 (Dextromethorphan Odeethylase Activity)**



Overall, the metabolism of loxapine to amoxapine appeared to be mediated primarily by CYP3A4/5 with a potential minor contribution from CYP2C19 and 2C8

## Reaction Phenotyping, CYP Isozyme and Chemical Inhibitor Results for Amoxapine

Isozyme	Experiment		
	CYP Isozyme (Area Ratio per pmol enzyme)	Correlation Analysis (R <sup>2</sup> )	Chemical Inhibition (% Inhibition)*
1A2	0.0016	0.019 (7-ethoxyresorufin O-dealkylation), 0.009 (Phenacetin O-deethylation)	32
1B1	0.0018	ND	NA
2A6	0.0000	0.025	36
2B6	0.0009	0.002, 0.037	37
2C8	0.0028	0.013	99
2C9	0.0003	0.112	87
2C18	0.0013	ND	NA
2C19	0.0082	0.025	69
2D6	0.0001	0.041	43
2E1	0.0000	0.129	NA
3A4/5	0.0203 (3A4), 0.0023 (3A5)	0.003 (testosterone 6β-hydroxylation), 0.001 (midazolam 1'-hydroxylation)	97
3A7	0.0002	ND	NA

\* % Inhibition = 100% - % of control incubation

NA = Not analyzed

ND = No data from vendor

## CYP ENZYME INHIBITION

### Objective

The potential for loxapine, amoxapine, 7-OH-loxapine, 8-OH-loxapine, and loxapine N-oxide to inhibit cytochrome P450 catalytic activity was evaluated at (b) (4). Fluorescent probe substrates were incubated at or near the K<sub>m</sub> for the isoforms tested using recombinant cDNA expressed P450s in microsomes prepared from baculovirus infected insect cells. The fluorometric screening results for CYP 2D6 with loxapine, and CYP 3A4 with 8-OH-loxapine, were further investigated using pooled human liver microsomes (50 donors) with the model substrates dextromethorphan (CYP 2D6) and testosterone and midazolam (CYP 3A4) to determine if in vitro interaction exists between loxapine, its metabolites and CYP model substrates using pooled human liver microsomes.

### Procedures

Assays using fluorometric probe substrates and cDNA expressed enzyme were conducted with duplicate incubations in 96-well microtiter plates. A summary of the probe substrates and control inhibitors used in the fluorometric procedures is described in Table

1. The substrate concentrations were chosen at or near the apparent substrate  $K_m$  values. Assay parameters for the fluorometric assays are described in Table 2. Assays using the model substrates dextromethorphan, midazolam, and testosterone and pooled human liver microsomes were conducted with duplicate incubations. A summary of the model substrates and control inhibitors used with human liver microsomes is described in Table 3.

**Table 1 Probe Substrates Used for the Characterization of Cytochrome P450 Isoform Activities**

CYP P450 Isoform	Fluorometric Probe Substrates	Control Inhibitors
1A1	7-Benzylxyresorufin (Bz-Res)	Alpha-naphthoflavone
1A2	3-cyano-7-ethoxycoumarin (CEC)	Furafylline
2A6	Coumarin	Tranlycypromine
2B6	7-Ethoxy-4-trifluoromethylcoumarin (EFC)	Tranlycypromine
2C8	Dibenzylfluorescein (DBF)	Quercetin
2C9	7-methoxy-4-trifluoromethylcoumarin (MFC)	Sulfaphenazole
2C19	3-cyano-7-ethoxycoumarin (CEC)	Tranlycypromine
2D6	3-[2-(N,N diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin (AMMC)	Quimidine
2E1	7-methoxy-4-trifluoromethylcoumarin (MFC)	Diethyldithiocarbamate
3A4	Dibenzylfluorescein (DBF)	Ketoconazole
3A4	7-Benzylxy-4-trifluoromethyl-resorufin (BFC)	Ketoconazole

**Table 2 Assay Parameters for cDNA-expressed Enzymes**

CYP Enzyme Substrate	1A1 BzRes	1A2 CEC	2A6 Coumarin	2B6 EFC	2C8 DBF	2C9 MFC	2C19 CEC	2D6 AMMC	2E1 MFC	3A4 DBF	3A4 BFC
Substrate conc. ( $\mu$ M)	12.5	2.5	3	2.5	1	50	6	0.5	100	1	50
Incubation Time (min)	30	15	10	30	30	45	30	30	45	10	30
Protein Conc. (mg/mL)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
KPO4 buffer (mM)	100	100	0	100	50	25	50	100	100	200	200
Tris buffer (mM)	0	0	100	0	0	0	0	0	0	0	0
Excitation (nm)	530	410	390	410	485	410	410	390	410	485	410
Emission (nm)	590	460	460	530	538	530	460	460	530	538	530

Table 3. Model substrates and control inhibitors for CYP2D6 and CYP3A4 human liver microsome experiments.

CYP P450 Isoform	Model Substrates	Control Inhibitors
2D6	Dextromethorphan	Quimidine
3A4	Midazolam	Ketoconazole
3A4	Testosterone	Ketoconazole

**Summary Table 1 In vitro IC50 Determination of Loxapine and Metabolite CYP Inhibition**

Isoform	Loxapine IC50 (µM)	Amoxapine IC50 (µM)	7-OH-loxapine IC50 (µM)	8-OH-loxapine IC50 (µM)	Loxapine N-oxide IC50 (µM)
CYP 1A1	8.35	>10	2.60	8.70	>10
CYP 1A2	>10	>10	>10	>10	>10
CYP 2A6	>10	>10	>10	>10	>10
CYP 2B6	>10	>10	>10	>10	>10
CYP 2C8	>10	>10	>10	>10	>10
CYP 2C9	>10	>10	>10	>10	>10
CYP 2C19	8.30	>10	>10	9.00	>10
CYP 2D6	4.30	2.80	>10	>10	>10
CYP 2E1	9.90	9.05	8.60	9.10	7.60
CYP 3A4 (BFC)	>10	>10	9.50	0.980	>10
CYP 3A4 (DBF)	>10	>10	>10	7.70	>10

The fluorometric screening results for CYP 2D6 with loxapine and CYP 3A4 with 8-OH-loxapine were further investigated using pooled human liver microsomes with the model substrates, dextromethorphan (CYP 2D6) and testosterone and midazolam (CYP 3A4). The IC50 values for loxapine inhibition of CYP 2D6 and 8-OH-loxapine inhibition of CYP 3A4 were all > 10 µM.

The in vitro results showed no significant inhibition of any of the tested CYP isoforms by loxapine, amoxapine, 7-OH-loxapine, 8-OH-loxapine, or loxapine N-oxide.

## IC50 Determination for Inhibition of P-glycoprotein Transport by Loxapine in Caco-2 Cell Monolayers

### Objective:

To determine the permeability and transport properties of loxapine.

### Transport Studies

Prior to all experiments, trans-epithelial electrical resistance (TEER) measurements were conducted, with all monolayers needing to have a minimum TEER value greater than 200 ohm.cm<sup>2</sup>. Loxapine was assayed in triplicate at one concentration (1 µM, <sup>(b) (4)</sup>) equivalent) in the presence and absence of ketoconazole (25 µM). Permeability in both the apical (A) to basolateral (B) and B to A directions was determined during the course of 90-minutes. All permeability studies were performed at 37°C in a 24-well format. Propranolol (50 µM, [<sup>3</sup>H]-propranolol) and mannitol (50 µM, [<sup>14</sup>C]-mannitol) were used as permeability markers, and both were tested in triplicate. For the digoxin inhibition studies, 5 µM [<sup>3</sup>H]-digoxin was used. All concentrations of comparators and positive controls were measured by liquid scintillation counting, and loxapine concentrations were measured by LC/MS/MS. At the end of the studies, Lucifer Yellow (100 µM) was added to each well and the flux was measured using a fluorescent plate reader to determine that the cells had maintained their integrity.

$$\text{Efflux ratio} = P_{B/A} / P_{A/B}$$

## RESULTS AND DISCUSSION

All of the wells used in the studies had acceptable TEER values, indicating good monolayer integrity prior to the initiation of each study. All TEER values were in the range of 262-395 ohm.cm<sup>2</sup>, with mean TEER values of 351(31) and 368(22) ohm.cm<sup>2</sup> for the permeability and inhibition assays, respectively. The Lucifer Yellow P<sub>app</sub> values were low (mean values of <0.074% in both studies) for all the wells, with the exception of one well for mannitol, indicating monolayer integrity was intact during the testing duration.

The permeability coefficients for loxapine and control compounds across Caco-2 cell monolayers in the A to B and B to A directions are summarized in [Table 1](#). Both the efflux ratios reported in the testing facility report and the efflux ratios calculated from rounded data are listed in the table.

**Table 1 Apparent Permeability of Control Compounds and Loxapine Transport and Inhibition by Ketoconazole in Caco-2 Cell Monolayers (n=3)**

**Permeability Controls (50 µM)**

Compound	Permeability Coefficient (P <sub>app</sub> ) (nm/s)				Mass Balance % Recovery
	160	170	180	170(10.0)	
Propranolol	160	170	180	170(10.0)	66(5.0)
Mannitol	ND	2	2.3	2.15(NC)	91(5.0)

NC = not calculated

**Loxapine (1 µM)**

Compound	Permeability Coefficient (P <sub>app</sub> ) (nm/s)				Mass Balance % Recovery
	Well #1	Well #2	Well#3	Mean(SD)	
A to B	63	63	75	67(6.9)	29(2.5)
B to A	69	73	78	73(4.5)	55(NC) <sup>a</sup>

<sup>a</sup> n=2

Efflux Ratio Calculated: 1.1

Efflux Ratio Reported: 1.1

**Loxapine (1 µM) + Ketoconazole (25 µM)**

Compound	Permeability Coefficient (P <sub>app</sub> ) (nm/s)				Mass Balance % Recovery
	100	100	100	100(0.0)	
A to B	100	100	100	100(0.0)	41(2.9)
B to A	100	120	130	117(15.3)	64(5.6)

Efflux Ratio Calculated: 1.2

Efflux Ratio Reported: 1.1

The control compounds Propranolol, the high permeability control compound, and mannitol, the low permeability control compound displayed P<sub>app</sub> values of 170 (10.0) and 2.15 nm/s, which indicated that the system was working well. The low mass balance for propranolol raises a question related to data validity. Loxapine transport B to A is not impacted by ketoconazole and A to B transport is slightly increased in the presence of the P-gp inhibitor, ketoconazole.

The results from the digoxin inhibition study are shown in Table 2. Loxapine (50  $\mu\text{M}$ ) reduced the polarization ratio of digoxin from 4.5 to 1.3 (reported values); corresponding to 91% inhibition of P-gp.

**Table 2 Apparent Permeability of Control Compounds and Loxapine Inhibition of Digoxin Transport (n=3)**

Permeability Controls (50  $\mu\text{M}$ )

Compound	Permeability Coefficient ( $P_{app}$ ) (nm/s)				Mass Balance % Recovery
	150	160	160	157(5.8)	
Propranolol	150	160	160	157(5.8)	67(4.0)
Mannitol	6.7	1.7	1.7	3.4 (2.9)	91(0.0)

Digoxin(5  $\mu\text{M}$ )

Compound	Permeability Coefficient ( $P_{app}$ ) (nm/s)				Mass Balance % Recovery
	Well #1	Well #2	Well#3	Mean(SD)	
A to B	20	21	19	20(1)	99(6.7)
B to A	86	93	96	92(5)	91(2)

Efflux Ratio Calculated: 4.6

Efflux Ratio Reported: 4.5

Digoxin(1  $\mu\text{M}$ ) + Ketoconazole (25  $\mu\text{M}$ )

Compound	Permeability Coefficient ( $P_{app}$ ) (nm/s)				Mass Balance % Recovery
	A to B	B to A	Mean(SD)	Mass Balance % Recovery	
A to B	29	32	28	30(2)	95(4.9)
B to A	30	34	41	35(5.6)	95(7.5)

Efflux Ratio Calculated: 1.2

Efflux Ratio Reported: 1.2

**Table 3. Inhibition of digoxin transport by loxapine**

Test article ID	Conc. [ $\mu\text{M}$ ]	Time [min]	$P_{app}$ [cm/sec]						Efflux Ratio [B-A/A-B]	Mass balance [% recovery]					
			A to B			B to A				A to B		B to A			
digoxin	5.0	90	2.0E-06	2.1E-06	1.9E-06	8.6E-06	9.3E-06	9.6E-06	4.5	92%	101%	105%	80%	91%	93%
digoxin + 25 $\mu\text{M}$ ketoconazole	5.0	90	2.9E-06	3.2E-06	2.8E-06	3.0E-06	3.4E-06	4.1E-06	1.2	90%	99%	98%	87%	96%	102%
digoxin + 50 $\mu\text{M}$ loxapine	5.0	90	2.7E-06	2.6E-06	2.6E-06	3.2E-06	3.4E-06	3.9E-06	1.3	85%	100%	101%	96%	93%	104%
<b>Permeability Comparators</b>															
propranolol	50	90	1.5E-05	1.6E-05	1.6E-05	-	-	-	-	83%	88%	71%	-	-	-
mannitol	50	90	6.7E-07	1.7E-07	1.7E-07	-	-	-	-	91%	91%	91%	-	-	-

The A to B permeability of loxapine was consistent across all three wells, with a mean  $P_{app}$  of 67 nm/s, indicating that loxapine has moderate to high permeability. Mass balance for loxapine was low (29%), so the results may be somewhat inconclusive; however, loxapine is rapidly absorbed in vivo, thus it is likely to have high permeability. Loxapine was not subject to B to A transport as indicated by the polarization ratios of 1.1 in the presence and absence of the P-gp inhibitor, ketoconazole, respectively, Table 1.

***OCP COMMENTS-INSPECTION REPORT***

1. OCP has reviewed the data related to #14 having consumed alcohol. The firm followed their protocol and tested this subject for alcohol prior to his admission to

- the study and the test was negative. Therefore, the data from this subject should be included in the study.
2. The firm has conducted additional dilution studies for concentrations at 2000 ng/ml, 1000 ng/ml and 500 ng/ml each diluted 50 fold with the resulting diluted samples falling within the established range of their calibration curve. Since the dilution QCs met all acceptance criteria dilution linearity up to 2000 ng/mL was established which covers all reported sample concentrations. Since all study samples were diluted to be in the calibration range, and the dilution up to 2000 ng/mL has since been validated, no reanalysis of the study data for 004-103 is requested.

14 Pages Have Been Withheld As A Duplicate Copy Of The "Statistical Review" dated September 24, 2010 Which Is Located In The Statistical Reviews Section Of This NDA Approval Package.

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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.**

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/s/

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ANDRE J JACKSON  
09/30/2010

RAMAN K BAWEJA  
09/30/2010

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 22549**

**Applicant: Alexza  
Pharmaceuticals**

**Stamp Date:**

**December 11, 2009**

**Drug Name: Staccato Loxapine    NDA/BLA Type: Standard  
for Inhalation**

On initial overview of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(2): Reference drug is loxapine
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title:004-101 and 004-102 Sample Size: 50 and 32 Arms:0.625,1.25,2.5,5,10,15,20,30 mg Location in submission:m5 3.3.1 and 3.3.2	X			
<b>EFFICACY</b>					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?  Pivotal Study #1 004-301	X			

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Indication: Acute agitation in patients with schizophrenia  Pivotal Study #2 004-302  Indication: Acute agitation in patients with Bipolar I Disorder				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?				
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product ( <i>e.g.</i> , QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?				
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested	X			

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	by the Division)?				
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes X \_\_\_\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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Reviewing Medical Officer

Date

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Clinical Team Leader

Date

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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.**

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/s/

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FRANCIS E BECKER

09/30/2010

This is a late entry. This filing checklist was completed prior to the filing meeting for this NDA.

ROBERT L LEVIN

09/30/2010

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

*General Information About the Submission*

	Information		Information
NDA/BLA Number	22549	Brand Name	Staccato Loxapine
OCP Division (I, II, III, IV, V)	I	Generic Name	Loxapine
Medical Division	Psychiatry	Drug Class	Anti agitation
OCP Reviewer	Andre Jackson	Indication(s)	Agitation associated with schizophrenia/bipolar
OCP Team Leader	Raman Baweja	Dosage Form	Inhalation
Pharmacometrics Reviewer	Andre Jackson/Yaning Wang	Dosing Regimen	5 mg , 10 mg
Date of Submission	12/11/2009	Route of Administration	Nasal
Estimated Due Date of OCP Review	9/6/2010	Sponsor	Alexa Pharmaceuticals
Medical Division Due Date	9/20/2010	Priority Classification	IS
PDUFA Due Date	10/11/2010		

*Clin. Pharm. and Biopharm. Information*

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
<b>I. Clinical Pharmacology</b>				
Mass balance:				

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

<b>Isozyme characterization:</b>	x	3		<p><b>1.Study DM -002</b> The potential for loxapine, amoxapine, 7-OH-loxapine, 8-OH-loxapine, and loxapine N-oxide to inhibit cytochrome P450-mediated drug metabolism was examined in vitro using cDNA expressed enzyme systems.</p> <p><b>2.Study DM-003</b> In this study, the in vitro metabolism of loxapine was determined in fresh lung microsomes prepared from male or female Sprague-Dawley rats or cryopreserved lung microsomes from male beagle dogs and mixed gender humans.</p> <p><b>3.Study DM-004</b> The firm investigated the metabolism of loxapine by the use of human recombinant CYP enzymes, specific chemical inhibitors, and human liver microsomes.</p>
<b>Blood/plasma ratio:</b>	x	1		<p><b>Study DM 008</b> Study was done to determine the extent of human red blood cell partitioning of loxapine since it has not been reported.</p>
<b>Plasma protein binding:</b>	x	1		<p><b>Study DM 001</b> Determined the plasma protein binding of amoxapine, 7-OH-loxapine, 8-OH-loxapine and loxapine N-oxide to rat, dog and human plasmas.</p>
<b>Caco-2 Cell transport</b>	x	1		<p><b>Study DM 005</b> The permeability and transport properties of loxapine had not been reported in literature, and thus were investigated.</p>
<b>PGP Transport</b>	x	1		<p><b>Study DM 006</b> The IC50 value for loxapine P-gp inhibition was determined in this study.</p>
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<b>Healthy Volunteers-</b>				
single dose:	x	1		<p><b>Study AMDC 004-101</b> Randomized single-center, double-blind, placebo-controlled, dose escalation study of the safety, tolerability, and pharmacokinetics of single doses of <i>Staccato</i> Loxapine. The doses to be studied were 0.625 mg, 1.25 mg, 2.5 mg, 5.0 mg, and 10 mg. Safety measures were assessed.</p>

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

multiple dose:	<b>x</b>	<b>1</b>		<p><b>Study AMDC 004-102</b> Randomized, double-blind, multiple dose, placebo-controlled, safety and pharmacokinetic study of Staccato® Loxapine for Inhalation in subjects on a chronic, stable antipsychotic regimens. Doses <i>Staccato</i> Loxapine 15, 20, or 30 mg (total daily dose). 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 divided by 4 hours.</p>
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
Smokers:	<b>x</b>	<b>1</b>		<p><b>AMDC 004-106</b> Single-center, open label, 2-group study assessed the pharmacokinetics of a single dose of <i>Staccato</i> Loxapine 10 mg administered to smokers compared with nonsmokers. Samples were assayed for loxapine and its metabolites, 7-OH-loxapine, 8-OH-loxapine, amoxapine, and Loxapine N-oxide, in order to compare the pharmacokinetics of smokers and nonsmokers.</p>
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:	x	1		<b>Study AMDC 004-103</b> Randomized, single-center, 2-treatment, 4-period, dose-stratified, replicate-design Compares commercial product vs current clinical product. Analysis of parent and 2 metabolites.
<b>Food-drug interaction studies</b>				
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>				

On **initial** review of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission	X			

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	searchable, does it have appropriate hyperlinks and do the hyperlinks work?				
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?				I can't comment based upon the submitted data. The primary endpoint of positive and negative symptom scale, excited component will have to be investigated further to see if based upon this measure there was dose optimization. The other endpoint clinical global impression-severity scale will also require further investigation related to optimization.
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?				Whether exposure response will be applicable for a 2 hr effect window has to be determined by a discussion with Pharmacometrics
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?				Not sure if this is applicable
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?				See prior exposure response comments
<b>General</b>					

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**  
  Yes  

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

General Comment related to in vitro Studies- Only those study results which the firm has placed in the label will be reviewed.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Andre Jackson	1/ 25 /2010
Reviewing Clinical Pharmacologist	Date
<hr/>	
Raman Baweja	1/ 25 /2010
Team Leader/Supervisor	Date

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

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/s/

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ANDRE J JACKSON  
02/11/2010

RAMAN K BAWEJA  
02/12/2010