

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022549Orig1s000**

**STATISTICAL REVIEW(S)**

## STATISTICAL REVIEW

NDA: 22-549	Submission Date(s): 12/11/2009
Brand Name	Staccato® Loxapine for Inhalation
Generic Name	Loxapine
Primary Statistical Reviewer	Donald J. Schuirmann, M.S.
Statistics Division Director	Stella G. Machado, Ph.D.
OCP Division	Clinical Pharmacology - 1
OB Division	Division of Biometrics VI
OND division	OND/ODEI/Division of Psychiatry Products
Sponsor	Alexza Pharmaceuticals, Inc.
Formulation; Strength(s)	5 mg, 10 mg
Proposed Indication	Rapid Treatment of Agitation Associated with Schizophrenia or Bipolar Disorder in Adults

Input for this review was provided by the CDER review team, in particular Andre J. Jackson, Ph.D. of the CDER Office of Clinical Pharmacology (OCP).

### 1 Executive Summary

The sponsor carried out an open label replicated-crossover bioequivalence (BE) study in healthy non-smoking volunteers, comparing the then proposed commercial formulation (commercial version 1) of Staccato Loxapine with the current clinical formulation (clinical version 2), studying both 5 mg and 10 mg doses.

Each subject was to receive a total of 4 doses of Staccato Loxapine (2 doses of the commercial version, and 2 doses of the clinical version) at 1 of 2 dose levels, either 5 mg or 10 mg. Each dose was administered in a separate treatment period with a washout period of  $\geq 4$  days between treatment periods.

The BE study is unusual in that two different dose levels were included, and the sponsor intended to combine the two dose groups into one overall BE analysis. Whether combining the dose groups is valid is a review issue for OCP. If OCP believes that combining the dose groups is justified, the results of the study do not contradict this belief.

In the study dataset, one subject (subject number 8, in the 10 mg dose group) appears to be an "outlier". Using the commercial product (the Test treatment), this subject obtained blood-levels of Loxapine similar to the other 15 subjects in the 10 mg dose group. However, using the clinical product (the Reference treatment), she obtained notably lower blood-levels of Loxapine, compared to the other 15 subjects in the 10 mg dose

group. This happened on two different occasions (since it was a replicated-crossover design), indicating that this outcome seems to truly characterize this subject.

Analyzing the endpoint area under the plasma concentration-time curve from 0 to 2 hours (AUC<sub>0-2</sub>, identified by OCP as the metric of medical interest), if the two dose groups are combined, as the sponsor wishes to do, the treatments pass the usual bioequivalence test (i.e. the 90% confidence interval for the Geometric Mean Ratio in the population falls within the interval [0.80, 1.25]) if subject number 8 is excluded from the analysis, but do not pass if subject number 8 is included. If subject number 8 is excluded from the BE analysis, the resulting inference will not include any persons who are like subject number 8 in how they handle the two treatments. If Staccato Loxapine is eventually approved, the clinical version will not exist in the market, so there would be no issue of a person beginning therapy on the commercial version and then switching to the clinical version, or *vice versa*. That could possibly be a justification for excluding subject number 8 from the analysis. OCP will make their own judgment on this issue.

If the dose groups are analyzed separately, the 10 mg dose group treatments do not pass the usual BE test, regardless of whether subject number 8 is included or excluded. In the case of the 5 mg dose group, the results of the study are on the borderline. If the 5 mg dose group is analyzed with the approach recommended in the January 2001 CDER guidance, they do not pass the usual BE test, but just barely (upper limit of the 90% confidence interval = 1.2523.) If a similar analysis is used, but with a different denominator degrees-of-freedom method (DDFM, see below for discussion), they pass the usual BE test (upper limit of the 90% confidence interval = 1.2380.) Since this alternate DDFM (DDFM =  $kr$ ) has some support in the general statistical community, the sponsor may be able to make a case that their 5 mg dose group results pass the usual BE test.

Whether the two products need to pass the usual BE test, or what alternate requirements may apply to this BE study, will be determined by OCP, in consultation with the CDER review team.

## 1.1 Recommendation

The Office of Biostatistics has reviewed the bioequivalence study (protocol number AMDC-004-103) submitted in support of NDA 22-549 for Staccato® Loxapine for Inhalation and finds that its acceptability depends on judgments that are outside of the realm of statistics. Based on our review we defer any approval/nonapproval recommendation to the Office of Clinical Pharmacology.

## 2 Description of the Study

NDA 22-549 - Staccato® Loxapine for Inhalation, 5 mg and 10 mg

NAME OF COMPANY: Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court  
Mountain View, CA 94043

NAME OF FINISHED PRODUCT: Staccato® Loxapine for Inhalation

NAME OF ACTIVE INGREDIENT: Loxapine

INDICATION: Rapid Treatment of Agitation Associated with Schizophrenia or  
Bipolar Disorder in Adults

Protocol Number: AMDC-004-103

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

Principal Investigator: George Peter Hodsman, MD

Study Center: Centre for Clinical Studies, Melbourne, Victoria, Australia

Objectives as stated by the sponsor:

- 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

Methodology: This was a Phase 1, randomized, single-center, 2-treatment, 4-period, dose-stratified, replicated-crossover design study to assess the safety, pharmacokinetics, and bioequivalence of the Commercial Product Design version (commercial version 1) and the Current Clinical version (clinical version 2) of Staccato Loxapine in healthy volunteers. The commercial version of Staccato Loxapine incorporated changes to

(b) (4)

The fundamental operating principles are the same as the clinical version, with comparable performance attributes and user interface characteristics.

Each subject was to receive a total of 4 doses of Staccato Loxapine (2 doses of the commercial version, and 2 doses of the clinical version) at 1 of 2 dose levels, either 5 mg or 10 mg. Each dose was administered in a separate treatment period with a washout period of  $\geq 4$  days between treatment periods. Subjects were randomized (1:1:1:1) to 1 of the following treatment sequences:

- Sequence 1: commercial, clinical, commercial, clinical; 5 mg in each dose (designated ABAB)
- Sequence 2: clinical, commercial, clinical, commercial; 5 mg in each dose (designated BABA)
- Sequence 3: commercial, clinical, commercial, clinical; 10 mg in each dose (designated CDCD)
- Sequence 4: clinical, commercial, clinical, commercial; 10 mg in each dose (designated DCDC)

Note that subjects received only 1 dose level, either 5 mg or 10 mg, and were not crossed over between dose levels.

Diagnosis and Main Criteria for Inclusion: Male and female nonsmoker subjects (18-55 years, inclusive) in good general health

### Analysis Datasets

Thirty-two (32) subjects were randomized to treatment. All 32 randomized subjects had one or more measurable loxapine plasma concentrations and were eligible for inclusion in the pharmacokinetic (PK) population. The bioequivalence (BE) population included all subjects who received any study drug and provided 2 or more AUC<sub>0-2</sub>, C<sub>max</sub> or AUC<sub>inf</sub> values. One subject (#32, 5 mg dose group, sequence ABAB) failed to return for the second dose and was therefore excluded from the BE population.

The sponsor identified one subject (#8, 10 mg dose group, sequence CDCD) as a statistically significant outlier. The sponsor excluded the data for this subject from their main presentation of the pharmacokinetic and bioequivalence evaluations.

### Treatments

Test Products: Staccato Loxapine Commercial Product Design (CPD, commercial version 1), 5 or 10 mg doses, inhaled.

Reference Products: Staccato Loxapine Current Clinical Version (CCV, clinical version 2), 5 or 10 mg doses, inhaled.

Lot numbers are presented in the sponsor's Table 3:

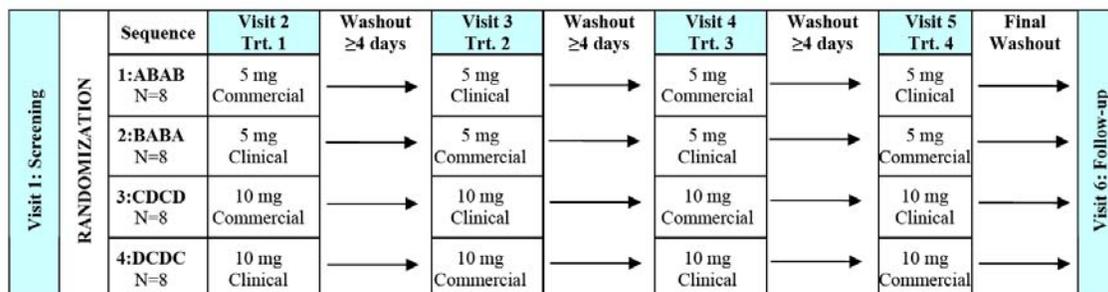
**Table 3. Lot Numbers and Manufacturer Information for Investigational Product**

	<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			

## Experimental Design

A schematic of the experimental design is presented in the sponsor's Figure 1:

**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

- study initiation date 11 August 2008 (first subject randomized)
- study completion date 06 October 2008 (end of protocol-mandated AE reporting period)

### blood sampling times:

Plasma samples for pharmacokinetic analysis were collected 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 each dose.

### Datasets submitted by the sponsor

This review utilized the SAS dataset ADPKPARAM submitted by the sponsor.

### Endpoints Considered in this Review

The Office of Clinical Pharmacology (OCP) identified the pharmacokinetic metric of medical interest as the area under the plasma concentration-time curve from 0 to 2 hours. Hereafter in this review, this endpoint will be called "AUC0-2".

At the direction of OCP, only the parent drug, Loxapine, was considered in this review.

### Statistical Methods

The pharmacokinetic (PK) endpoint AUC0-2 was statistically analyzed after log transformation, as is standard.

The sponsor reported using the following program statements in SAS PROC MIXED to do their analyses of this replicated-crossover study:

```
proc mixed;
class PERIOD SEQCD DEVICECD PATID;
model y = PERIOD SEQCD DEVICECD;
random PATID(SEQCD);
lsmeans DEVICECD/pdiff cl alpha=0.1;
run;
```

where  $y$  is the endpoint being analyzed,  $\log(\text{AUC}_{0-2})$  in this case.

PERIOD has 4 values, 1, 2, 3, and 4.

SEQCD has 4 values, ABAB and BABA for the 5 mg strength, CDCD and DCDC for the 10 mg strength.

DEVICECD has 2 values, CCV-ref (current device) and CPD-test (updated device)

PATID is the subject number (patient ID)

These SAS PROC MIXED are statements that might be used to analyze a *non-replicate* crossover study, provided one was willing to assume that the treatments have the same variance. The sponsor states

“... Compound symmetry was assumed. Thus, a common within-subject variance was assumed for both device types and a common between-subject variance types and a common between-subject variance was assumed for both device types. The effect of different variances for devices was investigated in a supportive analysis. ...”

This reviewer has not seen the sponsor’s “supportive analysis” investigating the effect of different variances in the protocol (004-103-protocol-final-amendment1.pdf), the final study report (004-103—csr.pdf), or the document titled “Replicate Statistical Model.pdf”. However, I note that in the protocol the sponsor cites the ability to separately estimate the within-subject variances of the two treatments as an advantage of a replicated-crossover design.

In this reviewer’s opinion, there is no basis for the assumption that both treatments have the same within-subject variance.

There is a more important issue regarding the sponsor’s SAS statements than the question of possibly unequal within-subject variances for the two treatments. The sponsor’s statistical model, as implemented by the sponsor’s SAS statements, does not allow for the possibility that the correlation, within a subject, between a Test and Reference observation may not be as high as the correlation, within a subject, between two Test observations or between two Reference observations. Such lower correlation between observations from different treatments, compared to the correlations between

observations from the same treatment, is an aspect of *subject-by-formulation interaction*. Any model used for the analysis of a replicated-crossover study should include aspects that allow for such interaction. The sponsor's model does not. That the possibility of subject-by-formulation interaction needs to be considered for the sponsor's bioequivalence study is illustrated dramatically by the results obtained for subject number 8 in the 10 mg dose group (to be discussed further later in this review.)

In the January 2001 CDER guidance document *Guidance for Industry: Statistical Approaches to Establishing Bioequivalence*, the following SAS PROC MIXED statements were recommended for analyzing replicated-crossover bioequivalence studies:

```
PROC MIXED;
CLASSES SEQ SUBJ PER TRT;
MODEL Y = SEQ PER TRT/ DDFM=SATTERTH;
RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;
REPEATED/GRP=TRT SUB=SUBJ;
ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.1;
RUN;
```

where Y is the endpoint being analyzed, log(AUC<sub>0-2</sub>) in this case  
 SEQ is the sequence of treatment administration (same as SEQCD in the sponsor's statements)  
 PER is the period of the design (same as PERIOD in the sponsor's statements)  
 TRT is the treatment  
 SUBJ is the subject number (same as PATID in the sponsor's statements)

The RANDOM statement in these guidance-recommended statements is a more general version of the sponsor's "random PATID(SEQCD);" statement – it allows for subject-by-formulation interaction. The REPEATED statement allows the within-subject variances for the two treatments to differ.

We used these guidance-recommended SAS statements for our analyses of individual dose group (5 mg group and 10 mg group) data. For combined dose group analyses, we used

```
PROC MIXED;
CLASSES SEQ PATID PERIOD TRT;
MODEL lauc2 = SEQ PERIOD TRT/ DDFM=satterth;
RANDOM TRT/TYPE=un SUB=patid G;
REPEATED/GRP=TRT SUB=patid;
ESTIMATE 'T vs. R' TRT 0.5 -0.5 0.5 -0.5/e CL ALPHA=0.1;
ESTIMATE 'interaction' TRT 1 -1 -1 1/e CL;
```

where lauc2 is log(AUC<sub>0-2</sub>).

Note that the “interaction” referred to in the second ESTIMATE statement is not subject-by-formulation interaction, but is instead a test comparing the Test–minus–Reference mean difference for the 5 mg group to the Test–minus–Reference mean difference for the 10 mg group.

One aspect of these guidance-recommended SAS statements is the *denominator degrees-of-freedom method* (DDFM). SAS PROC MIXED offers a number of different options for calculating the denominator degrees-of-freedom to be used in calculating p-values and confidence intervals. In the research and review leading up to the January 2001 guidance, the Quantitative Methods and Research Staff (QMR, which would later become the present Division of Biometrics VI) of the CDER Office of Biostatistics examined the different DDFM options available at the time, and decided that, in our opinion, DDFM = satterth (the “Satterthwaite” option) had the best properties for analyzing replicated-crossover bioequivalence studies.

Note that in the sponsor’s proposed SAS statements, DDFM is not specified. The sponsor’s analyses would therefore use the default DDFM option, which in this case is DDFM = contain (the “containment” option.)

Since the publication of the January 2001 guidance, SAS has produced two major upgrades. In the latest versions (e.g. the current version 9.1), an additional DDFM option is available that was not available when QMR did their review. This is DDFM = kr, the “Kenward-Roger” option. There is support in the literature and in the statistical community for using DDFM = kr. Two examples are a paper by Schaalje, McBride, and Fellingham (*Approximations to Distributions of Test Statistics in Complex Mixed Linear Models Using SAS® Proc MIXED*, SUGI Paper 262-26, available online at this link: <http://www2.sas.com/proceedings/sugi26/p262-26.pdf>) and the book *SAS for linear models* (fourth edition, 2002) by Ramón C. Littell, Walter Whitney Stroup, and Rudolf Jakob Freund. In the Schaalje *et al.* paper, they state “Even though it worked well in connection with the CS structure, there seems little reason to use the FC method now that the KR method is available. From the simulations, it appears that the KR method works as well as or better than the FC method in all situations.” [Note that in this quote, “FC” refers to the Fai-Cornelius method, which is in fact DDFM = satterth, and “CS” refers to Compound Symmetry, a type of covariance structure.] In the Littell *et al.* reference they advocate DDFM = kr for most PROC MIXED models, particularly those used for repeated measurements (crossover designs are a form of repeated measurement design.)

We at Division of Biometrics VI are not yet ready to change our recommendation from DDFM = satterth to DDFM = kr, until we study the two options further for the specific case of replicated-crossover studies. However, CDER guidance does not bind the industry, and a sponsor may use an alternate approach with justification. Because of the support for DDFM = kr, as exemplified in the citations given above, the sponsor may wish to argue for the use of DDFM = kr.

### Issues in the analysis of the bioequivalence study

There are two important issues regarding the analysis of this bioequivalence (BE) study:

1. Is it acceptable/legitimate to combine the data from the 5 and 10 mg dose groups into one analysis, thus comparing the mean of the means for the Test product to the mean of the means for the Reference product?
2. What shall we do about subject number 8?

I am not qualified by training to address issue 1. There could be a number of possible arguments in favor of combining the two dose groups, for example the assertion of dose proportionality. The sponsor's study report states "For the determination of bioequivalence in this study, the 5-mg and 10-mg doses were combined for the analyses of the primary outcome measures. The pooling of data across the 2 doses was justified since each subject received only 1 dose level, and all comparisons were within subject. Prior studies (AMDC-004-101 and AMDC-004-102) indicated that Staccato delivery was dose proportional across the dose range of 0.625 to 30 mg." We have not reviewed these prior studies. OCP will have to render a judgment about this issue. However, I can report that when a combined analysis is carried out, a test for interaction - i.e. a test of whether the geometric mean T/R ratio for the 5 mg dose group is the same as the geometric mean T/R ratio for the 10 mg group - provides no conclusive evidence of interaction. In an analysis of the BE population analysis dataset, using DDFM = satterth, the p value for interaction is  $p=0.2671$  in an analysis including subject number 8,  $p=0.5579$  in an analysis excluding subject number 8. Results for the PK population analysis dataset and/or using DDFM = kr produce similar p-values. While it is true that "absence of evidence is not evidence of absence", it is also true that if OCP feels that an analysis combining the two dose groups is justified, there is no evidence in the dataset itself to contradict that belief.

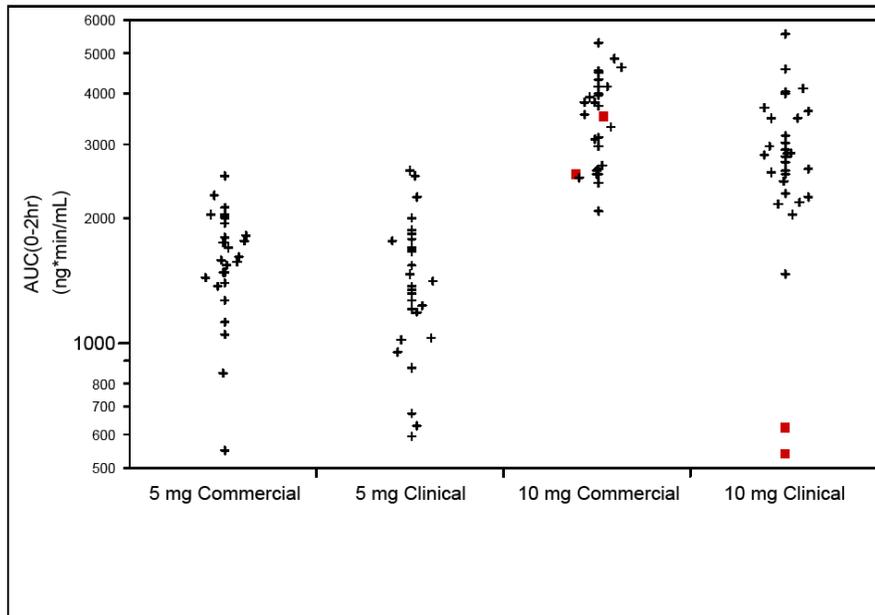
One other point that may be mentioned is that, traditionally, the doses of the Test product administered to subjects in a BE study are all the same *lot number*, and the doses of the Reference product administered to subjects in a BE study are all the same lot number. In this study, the 5 mg dose treatments and the 10 mg dose treatments are *different* lot numbers.

The other issue, issue 2, is subject number 8. This subject was in the 10 mg dose group, in the CDCD sequence. She received the Test product in study periods 1 and 3, and the Reference product in study periods 2 and 4. Her results may be summarized as follows:

		subject 8 values	all other subjects range
trt. 3 (Test)	AUC0-2	2523.14, 3479.06	2085.58 – 5268.93
	AUCLAST	6290.0933, 7495.4148	5494.85 – 12251.22
	CMAX	151, 423	31.4 – 1110.00
trt. 4 (Ref.)	AUC0-2	536.52, 618.45	1471.12 – 5576.66
	AUCLAST	2318.4545, 2477.028	4050.35 – 11499.49
	CMAX	5.94, 11	31.5 – 1780.00

These results are illustrated graphically for AUC0-2 in the sponsor’s study report (data for subject number 8 is illustrated by red boxes):

**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](#)

To summarize: this subject **consistently** obtained AUC0-2 values on the Test product (Commercial Version 1) that were within the range of AUC0-2 values seen in the other 15 subjects in the 10 mg dose group, and she **consistently** obtained AUC0-2 values on the Reference product (Clinical Version 2) that were well below the range of AUC0-2 values seen in the other 15 subjects in the 10 mg dose group. Similar results were seen for other pharmacokinetic parameters.

Because subject number 8 consistently obtained unusual AUC0-2 values on the Reference product, it is difficult to postulate a scenario under which her AUC0-2 values are considered an "irrelevant outlier" (e.g. "they mixed the wrong chemicals while assaying her samples".) We are left with the conclusion that this subject genuinely did respond differently to the two products.

It is clear that if the data for subject #8 are excluded from the analysis, the resulting inference will not be to the population that includes subjects who are like subject #8 - perhaps subject #8 is the only person in the world who responds to the two products in this way, or perhaps there are a number of such persons in the world. However, the characteristic that apparently describes subject #8, or subjects like her, is that they obtain low levels using the Reference product, Clinical Version 2. If Staccato Loxapine is eventually approved, Clinical Version 2 will not exist in the marketplace, so there is no issue of a subject beginning therapy on the Commercial product and then switching to Clinical Product 2, or *vice versa*, and so obtaining dangerously different blood levels after the switch. This may provide a justification for excluding the data from subject #8 in the analysis of this BE study. However, this is a review issue for OCP.

### Analysis Results

The point estimates and 90% confidence intervals (for the ratio of the Test product geometric mean AUC0-2 in the population over the Reference product geometric mean AUC0-2 in the population) from our analyses are presented here. All of the analyses used the BE population analysis dataset (i.e. with the single observation from subject #32 excluded.)

5 mg and 10 mg dose groups combined

	using DDFM = satterth	using DDFM = kr
including subject #8	1.2054 (1.0763, 1.3500)	1.2054 (1.0762, 1.3501)
excluding subject #8	1.1537 (1.0682, 1.2460)	1.1537 (1.0680, 1.2462)

10 mg dose group analyzed separately

	using DDFM = satterth	using DDFM = kr
including subject #8	1.2971 (1.0816, 1.5555)	1.2971 (1.0954, 1.5359)
excluding subject #8	1.1868 (1.0827, 1.3008)	1.1868 (1.0936, 1.2879)

5 mg dose group analyzed separately

using	using
DDFM = satterth	DDFM = kr
1.1125 (0.9824, 1.2523)	1.1125 (0.9997, 1.2380)

Summary: When the 5 and 10 mg dose groups are combined, the products pass the usual BE test (i.e. the 90% confidence interval falls within [0.80, 1.25]) if subject #8 is excluded from the analysis. If subject #8 is included, they do not pass the usual BE test.

If the 10 mg dose group is analyzed separately, the products do not pass the usual BE test, regardless of whether subject #8 is included or excluded.

If the 5 mg dose group is analyzed separately, we truly have a borderline case – the products do not pass the usual BE test using the DDFM = satterth option, as specified in the January 2001 guidance, but they do pass the usual BE test using the DDFM = kr option.

Note that OCP, possibly in consultation with the medical division, will make a determination as to whether it is necessary to pass the usual BE test for this clinical trial version vs. proposed commercial version BE study.

### Sponsor's Analyses

As noted earlier, the sponsor used a statistical model, as implemented by their choice of SAS PROC MIXED statements, more appropriate to the analysis of a non-replicate crossover study. However, their conclusion for the combined 5 and 10 mg dose group analysis is qualitatively the same as ours – they pass the usual BE test if subject #8 is excluded, they do not pass if subject #8 is included.

### Summary

1. It is not obvious that the 5 and 10 mg dose groups may be combined for the determination of bioequivalence. The Office of Clinical Pharmacology (OCP) will make a judgment on that question. If OCP believes that it is legitimate to combine the dose groups, there is no conclusive evidence in the dataset itself to contradict that belief.
2. The relative performance of the two treatments (Commercial Version 1, the Test treatment, and Clinical Version 2, the Reference treatment) for subject number 8 (in the 10 mg dose group, sequence CDCD) appears to be consistently different than for the other subjects in the 10 mg dose group. If this subject is excluded from the bioequivalence analysis, the resulting inference will not include any persons in the population who are similar to subject number 8. However, since

the property that characterizes subject number 8 is that she obtained unusually low blood levels of loxapine when using the Clinical Version, which will not be available if the product is eventually approved, there may be some basis for excluding the data for this subject. This is a review issue for OCP.

3. If the two dose groups are combined, the treatments pass the usual bioequivalence test (i.e. the 90% confidence interval for the Geometric Mean Ratio, Test/Reference, falls within [0.80, 1.25]) if subject number 8 is excluded from the analysis. If subject number 8 is included in the analysis, they do not pass.
4. If the 10 mg dose group is analyzed separately, the treatments do not pass the usual bioequivalence test, regardless of whether subject number 8 is excluded or included.
5. If the 5 mg dose group is analyzed separately, the result is truly borderline. If the SAS statements recommended in the January 2001 *Guidance for Industry: Statistical Approaches to Establishing Bioequivalence*, including the use of DDFM = satterth as the denominator degrees-of-freedom method, the treatments just barely fail to pass the usual bioequivalence test (upper limit of the 90% confidence interval = 1.2523) If the same SAS statements are used, but with the DDFM = kr denominator degrees-of-freedom method used instead of DDFM = satterth, the treatments do pass the usual bioequivalence test (upper limit of the 90% confidence interval = 1.2380.)
6. OCP, possibly in consultation with the medical division, will make a determination regarding the acceptability of this bioequivalence study, including the question of whether the two products need to pass the usual bioequivalence test.

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

**STATISTICAL REVIEW AND EVALUATION**  
Clinical Studies

NDA/Serial Number: 22-549 (S000)  
Drug Name: Staccato<sup>®</sup> (Loxapine for inhalation)  
Indication: Agitation  
Applicant: ZLEXZA  
Dates: Date of Document: 12/11/2009  
PDUFA Due Date: 10/11/2010  
Review Priority: Standard  
Biometrics Division: Biometrics I, HFD-710  
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# **1. EXECUTIVE SUMMARY**

## **1.1 CONCLUSIONS AND RECOMMENDATIONS**

The statistical reviewer confirmed the sponsor's efficacy analysis results for two phase-III studies (Studies CSR 004-301 and CSR 004-302). The data supported the efficacy of Staccato Loxapine for both 5 mg and 10 mg. However, besides at 2 hours, only the efficacy for 10 mg before an hour can be claimed in the labeling. Note that the testing for 5 mg at any time other than 2 hours and the testing for 10 mg beyond 45 minutes were not considered in the sponsor's per-specified testing procedure in terms of controlling the study-wise type I error rate.

## **1.2 BRIEF OVERVIEW OF CLINICAL STUDIES**

In this NDA application for Staccato Loxapine, the sponsor submitted three completed multicenter, double-blind, placebo-controlled studies to demonstrate the efficacy and safety of Staccato Loxapine at doses of 5 and 10 mg (i.e., Studies CSR 004-301, CSR 004-302 and CSR 004-201) for the treatment of agitation in patients with schizophrenia or bipolar disorder. The third study was a Phase IIA study. Since it had much fewer patients enrolled comparing to the other two studies and it studied patients not only with schizophrenia but also with schizophreniform disorder, or with schizoaffective disorder, only the first two pivotal Phase III studies were evaluated in detail in this statistical review. Based on the sponsor's analysis results, they concluded that the efficacy of both the 5- and 10-mg doses of Staccato Loxapine in the treatment of agitation in patients with schizophrenia or bipolar disorder was demonstrated.

## **1.3 STATISTICAL ISSUES AND FINDINGS**

For both pivotal Phase III studies, the statistical reviewer confirmed the sponsor's analysis results for the primary and secondary endpoints. For these two studies, even though the sponsor's prospectively-proposed statistical testing procedure does not completely control the overall study-wise type I error rate, due to the extremely small nominal p-values for almost all the comparisons between the drug and placebo at individual time points, the data indeed support the efficacy of Staccato Loxapine. However, statistically speaking, the treatment effect of Staccato Loxapine 5 mg at all individual time points except at 2 hours and the treatment effect of Staccato Loxapine 10 mg at time points beyond 45 minutes are not suitable to be described in the labeling since those tests were not prospectively planned in terms of controlling the study-wise type I error rate.

# **2. INTRODUCTION**

## **2.1 OVERVIEW**

Staccato® Loxapine for Inhalation (Staccato Loxapine) is a single-use, hand-held, drug device combination product that provides rapid systemic delivery by inhalation of a

thermally generated aerosol of loxapine. Staccato Loxapine represents a new dosage form for loxapine, an antipsychotic with dopamine D<sub>2</sub> blocking activity that has been available in the United States (US) since 1975. Oral loxapine is used in the treatment of schizophrenia. Although no longer marketed, an intramuscular (IM) formulation was previously approved for the management of acutely agitated patients. The pharmacological, pharmacokinetic, toxicological, and clinical safety and efficacy profiles of oral and IM formulations of loxapine have been previously established in the context of the NDAs for these approved formulations.

In this NDA application for Staccato Loxapine, the sponsor submitted three completed multicenter, double-blind, placebo-controlled studies to demonstrate the efficacy and safety of Staccato Loxapine at doses of 5 and 10 mg (i.e., Studies CSR 004-301, CSR 004-302 and CSR 004-201) for the treatment of agitation in patients with schizophrenia or bipolar disorder. Of the three studies, the first two were phase III studies designed to evaluate 1 to 3 doses of Staccato Loxapine in agitated patients with either schizophrenia or bipolar disorder. The third study was a phase IIA study, so the size of the study was much smaller than the other two. Since only the two Phase III studies showed statistically significant efficacy results for Staccato Loxapine, this review mainly focused on evaluating the efficacy analysis results for the two Phase III studies. The design and analysis results for the supportive Phase IIA study are described in the Appendix.

## 2.2 DATA SOURCES

The sponsor's submission including data and clinical study report were stored in CDER electronic document room (EDR) with the following link:

<\\CdseSub1\evsprod\NDA022549\0000>.

## 3. STATISTICAL EVALUATION

### 3.1 EVALUATION OF EFFICACY

#### 3.1.1 Description of Study AMDC-004-301 & Study AMDC-004-302

Study AMDC-004-301 was entitled 'A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Multi-Dose Efficacy and Safety Study of Staccato<sup>®</sup> Loxapine for Inhalation in Schizophrenic Patients with Agitation' and was conducted at 24 centers in the United States.

Study AMDC-004-302 was entitled 'A Multi-Center, Randomized, Double-Blind, Placebo Controlled, Multi-Dose Efficacy and Safety Study of Staccato<sup>®</sup> Loxapine for Inhalation in Patients with Bipolar I Disorder and Acute Agitation' and was conducted at 17 centers in the United States.

### 3.1.1.1 Study Objectives

The purposes of Study AMDC-004-301 [AMDC-004-302] were to confirm the safety and efficacy of Staccato Loxapine at 5- and 10-mg dose levels in the treatment of acute agitation in schizophrenic [in bipolar I disorder, either manic or mixed episodes] patients, and to confirm the tolerability of up to 3 doses administered in a 24-hour period.

### 3.1.1.2 Study Design

Study AMDC-004-301 [AMDC-004-302] was a Phase III, pivotal, in-patient, multicenter, randomized, double-blind, placebo controlled, parallel-group safety and efficacy study evaluating Staccato Loxapine for the treatment of agitation in patients with schizophrenia [bipolar I disorder]. Adult patients (18-65 years, inclusive) were randomized to Staccato Loxapine 5 or 10 mg or Staccato Placebo (1:1:1 randomization). Patients received 1 to 3 doses of study medication in the 24-hour study period, with Doses 2 and 3 administered only if needed.

The post-treatment evaluation period started with the administration of Dose 1 (Time 0) and continued for 24 hours. If required, a maximum of 3 doses of study medication were allowed during that 24-hour period, administered as follows. If agitation did not subside sufficiently after the first dose of study medication or if it recurred, a second dose could be given >2 hours after Dose 1 (after completion of the 2-hour efficacy assessments). If necessary, a third dose could be given  $\geq$  4 hours after Dose 2. Unless medically required, rescue medication was not to be used until after the 2-hour efficacy assessments had been completed, Dose 2 of study medication had been given, and at least 20 minutes had elapsed after administration of study medication.

### 3.1.1.3 Efficacy Endpoints and Analyses

#### Efficacy Endpoints:

The primary endpoint was the absolute change in Positive and Negative Symptom Scale, Excited Component (PEC) score from baseline to 2 hours following Dose 1 of Staccato Loxapine, compared with placebo.

One key secondary efficacy endpoint was the value of the CGI-I score 2 hours following Dose 1 of Staccato Loxapine, compared with placebo.

For the **10-mg** Staccato Loxapine-placebo comparison, the changes from baseline in PEC scores at 10, 20, 30, and 45 minutes were additional secondary endpoints. Even though the sponsor did not name them as key secondary endpoints, the testing of their significance was considered in controlling the overall study-wise type I error rate. Other tertiary efficacy endpoints included CGI-I responders (i.e., with CGI-I scores of 1 or 2) at 2 hours after Dose 1, Changes from baseline in PEC score at 1, 1.5, 4 and 24 hours after Dose 1 for 10-mg group only, Total number of patients per group who received 1, 2, or 3 doses of study medication with and without rescue medication by 4 hours and 24 hours after Dose

1, Time to rescue medication during the entire 24-hour post-treatment evaluation period, Time to Dose 2 (prn) of Staccato study medication during the 24-hour post-treatment evaluation period and ACES scores 2 hours after Dose 1.

#### Efficacy Analyses:

Again, the main efficacy analyses consisted of the following:

- The analysis of change from baseline in the PEC score at 2 hours after Dose 1
- The analysis of the CGI-I score at 2 hours after Dose 1
- The analysis of the change from baseline in the PEC score at 10, 20, 30, and 45 minutes after Dose 1 (only for the 10-mg/placebo comparison)

Note that the efficacy population, i.e., intent to treat population based on LOCF data, included all patients who received any study medication and had both baseline and at least one post-dose efficacy assessment or received rescue medication before 2 hours after dosing. The safety population included all patients who received any study medication.

#### Analysis of the Primary Efficacy Endpoint:

The primary efficacy endpoint was the absolute change from baseline in the PEC score at 2 hours after Dose 1. A “gatekeeper” analysis of covariance (ANCOVA) compared the changes among the 3 treatment groups for the primary efficacy endpoint using a global F-test with Dunnett’s t-tests for the 2 follow-up active/placebo pair-wise comparisons (adjusted for multiple comparisons). The 2 active/placebo comparisons adjusted for multiple comparisons based on Dunnett’s procedure were considered the primary analysis. Testing was 2-sided, with a family-wise  $\alpha = 0.05$ .

A main-effects ANCOVA model - including terms for baseline PEC score, treatment, and pseudocenter - was used to assess the overall treatment effect. Treatment and pseudocenter effects were considered statistically significant if  $p \leq 0.05$ . Dunnett’s t-tests were conducted within the framework of the ANCOVA model, which was based on least squares means (LS means) and the pooled standard deviation.

In addition, the treatment-by-pseudocenter interaction term was examined. This interaction term was not significant at  $\alpha = 0.05$ ; therefore, no further investigation was undertaken. (If it had been significant at  $\alpha = 0.05$ , further investigation was to be undertaken to determine if the treatment effects varied by pseudo-center in magnitude or direction. If necessary [i.e., direction of treatment effects varied by pseudo-center], further sensitivity analyses could have been undertaken to validate treatment efficacy.)

### Analysis of the Key Secondary Efficacy Endpoint:

One key secondary efficacy endpoint was the CGI-I score 2 hours after Dose 1. CGI-S (baseline assessment) and CGI-I (post-treatment assessment) scores of 0 (i.e., “not assessed”) were considered missing. The CGI-I data were provided in frequency tables by treatment group, along with standard descriptive statistics.

A “gatekeeper” analysis of variance (ANOVA) with terms for pseudo-center and treatment was used to compare the 3 treatment groups, with a global F-test and Dunnett’s t-tests for the 2 follow-up active/placebo pair-wise comparisons (adjusted for multiple comparisons). (If the parametric assumptions for ANOVA had not been met for these ordinal data, a nonparametric approach was to be substituted- e.g., a Kruskal-Wallis test to compare the 3 treatment groups, with Dunn’s Tests for the 2 follow-up active/placebo pair-wise comparisons.)

### Multiple Comparisons and Family-Wise $\alpha$ Level for the Main Efficacy Analyses:

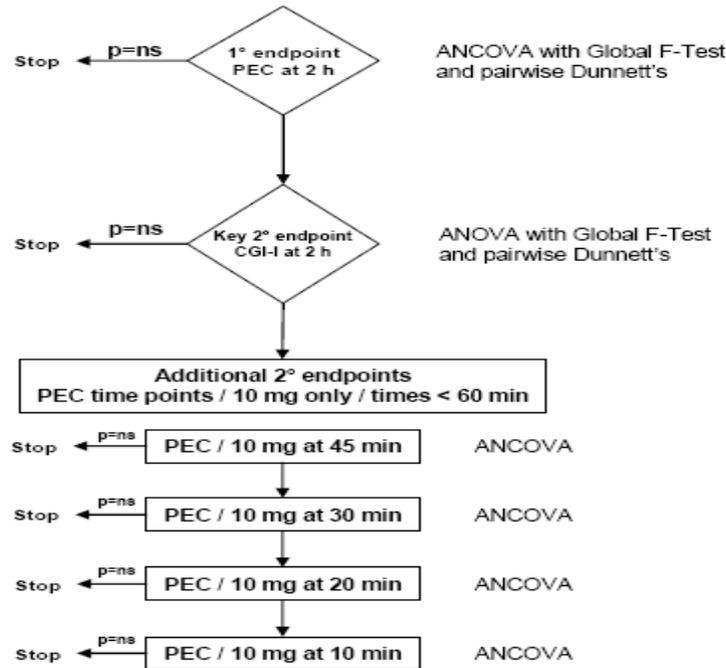
The sponsor claimed that the family-wise  $\alpha$ -level for the main efficacy analyses (i.e., the analysis of the primary, key secondary, and additional secondary endpoints for 10 mg before one hour) was maintained at 0.05 using the statistical methods described in this section. It was stated that these methods allowed evaluation of the overall treatment effect, as well as follow-up (adjusted) pair-wise 5-mg/placebo and 10-mg/placebo comparisons for the primary and key secondary efficacy endpoints, and the 10-mg/placebo pair-wise comparisons for the additional secondary endpoints. The statistical methodology, including the global “gatekeeper” tests with follow-up (adjusted) pair-wise testing, and closed-method hierarchical testing strategy, is summarized in the following Figure 1.

### **Statistical Reviewer’s Note:**

The sponsor’s testing procedure for dealing with multiplicity as mentioned above does not control the study-wise type I error rate. The Agency has pointed out the problem when the study protocols were submitted and reviewed. However, instead of revising the proposed procedure, the sponsor proposed three sensitivity analyses (i.e., the parallel gatekeeping procedure based on the Dunnett test (Dmitrienko et al,2006), the most basic parallel gatekeeping procedure based on the Bonferroni test (Dmitrienko and Tamhane, 2007) and a full Bonferroni adjustment that would permit simultaneous testing of all 8 inferential hypotheses).

Since the unadjusted p-values are extremely small for both study drug arms in both studies, the final conclusions for the efficacy analysis results were not affected based on different multiplicity procedures.

Figure 1. Statistical Testing Strategy for the Main Efficacy Analyses



### 3.1.2 Sponsor’s Efficacy Analysis Results for Study AMDC-004-301

#### 3.1.2.1 Disposition of Patients and Baseline Characteristics

Of the 374 patients who were screened for the study, 344 (92.0%) were randomized and received at least 1 dose of study medication, and 338 completed the study. Table 3.2.1 shows study patient disposition and reasons of premature discontinuation based on safety population. Table 3.2.2 shows patients’ demographic and other baseline characteristics. As shown in the table, the sponsor concluded that the groups were well matched for demographic and baseline characteristics, as well as baseline disease characteristics.

Table 3.2.1 Disposition of Patients and Reasons for Premature Discontinuation (Safety Population) for Study AMDC-004-301

Patient Disposition, n (%)	<i>Staccato</i> Placebo	<i>Staccato</i> Loxapine 5 mg	<i>Staccato</i> Loxapine 10 mg	Total
Randomized	115	116	113	344
Completed study	114 (99.1%)	114 (98.3%)	110 (97.3%)	338 (98.3%)
Discontinued prematurely	1 (0.9%)	2 (1.7%)	3 (2.7%)	6 (1.7%)
Reason for discontinuation:				
Adverse event	0	0	1 (0.9%)	1 (0.3%)
Patient withdrew consent	1 (0.9%)	1 (0.9%)	1 (0.9%)	3 (0.9%)
Investigator decision	0	0	1 (0.9%)	1 (0.3%)
Other	0	1 (0.9%) <sup>a</sup>	0	1 (0.3%)

a. “Other” reason: Patient 19-408 was withdrawn when it was discovered that she had previously completed the study at another center (as Patient 18-423). As Patient 19-408, she received 1 dose and was withdrawn before the 45-minute efficacy assessments.

Source: Sponsor’s Table 5 of CSR.

Table 3.2.2 Demographic and Baseline Characteristics (Safety Population) for Study AMDC-004-301

Demographic or Baseline Characteristic	Staccato Placebo (N=115)	Staccato Loxapine 5 mg (N=116)	Staccato Loxapine 10 mg (N=113)
Gender, n (%)			
Female	35 (30.4%)	29 (25.0%)	27 (23.9%)
Male	80 (69.6%)	87 (75.0%)	86 (76.1%)
Age (years):			
Mean (SD)	43.9 (9.45)	43.2 (10.24)	42.2 (9.82)
Race, n (%)			
Caucasian	32 (27.8%)	48 (41.4%)	36 (31.9%)
Black	70 (60.9%)	61 (52.6%)	67 (59.3%)
Hispanic	9 (7.8%)	6 (5.2%)	8 (7.1%)
Asian	4 (3.5%)	1 (0.9%)	1 (0.9%)
Other	0	0	1 (0.9%)
PEC score at baseline			
Mean (SD)	17.4 (1.80)	17.8 (2.34)	17.6 (2.06)
CGI-S score at baseline			
Mean (SD)	3.9 (0.53)	4.0 (0.56)	4.1 (0.60)
Time since diagnosis (years)			
Mean (SD)	18.8 (10.34)	16.5 (10.80)	18.2 (10.03)
No. of previous hospitalizations			
Mean (SD)	9.6 (8.96)	9.2 (12.22)	9.7 (11.26)

Source: Sponsor's Tables 8 and 9 of CSR.

### 3.1.2.2 Sponsor's Efficacy Analysis Results

The primary efficacy endpoint was the change in the PEC score from baseline to 2 hours after Dose 1 (active versus placebo). Both the 5- and 10-mg doses met this efficacy endpoint, with the tests for the overall treatment effect and the 2 follow-up active/placebo comparisons being highly statistically significant (overall treatment effect,  $p < 0.0001$ ; 5-mg/placebo,  $p = 0.0004$ ; 10-mg/placebo,  $p < 0.0001$ ). The detailed sponsor's analysis results for the baseline PEC score and the change from baseline to 2 hours are summarized by treatment group in Table 3.2.3. For the change from baseline to each time point in PEC scores are presented in Table 3.2.4.

Table 3.2.3 Sponsor's Analysis Results for Primary Efficacy Endpoint: Change in the PEC Score at 2 Hours After Dose 1 (ITT Population with LOCF) for Study AMDC-004-301

PEC Score	Staccato Placebo (N=115)	Staccato Loxapine 5 mg (N=116)	Staccato Loxapine 10 mg (N=112)
Baseline PEC score			
Mean (SD)	17.4 (1.8)	17.8 (2.34)	17.6 (2.06)
Change in PEC score from baseline to 2 hours after Dose 1			
Mean (SD)	-5.5 (4.92)	-8.1 (5.17)	-8.6 (4.37)
LS mean <sup>a</sup>	-5.8	-8.0	-8.7
p-value for active/placebo comparisons <sup>b</sup>		$P = 0.0004$	$P < 0.0001$
p-value for overall treatment effect	$P < 0.0001$		

<sup>a</sup> LS man was used in the primary efficacy analysis and the ANCOVA model was with terms for baseline PEC total score, pseudo-center, and treatment <sup>b</sup> Dunnett's t-test

Source: Sponsor's Table 12 of CSR

Table 3.2.4 Sponsor's Results for Change in the PEC Score at Assessment through 24 Hours after Dose 1 (ITT Population with LOCF) for Study AMDC-004-301

PEC Score (mean change)	Staccato Placebo (N=115)	Staccato Loxapine 5 mg (N=116)	Staccato Loxapine 10 mg (N=112)
+10 minutes	-1.7	-3.1	-3.4
p-value		NA	p<0.0001
+20 minutes	-2.9	-5.2	-6.1
p-value		NA	p<0.0001
+30 minutes	-4.1	-6.8	-7.6
p-value		NA	p<0.0001
+45 minutes	-4.8	-7.4	-8.7
p-value		NA	p<0.0001
+1 hour	-5.2	-7.7	-9.2
p-value		NA	p<0.0001
+1.5 hours	-5.3	-8.2	-9.1
p-value		NA	p<0.0001
+4 hours	-6.3	-8.2	-9.5
p-value		NA	p<0.0001
+24 hours	-4.4	-6.2	-6.9
p-value		NA	p<0.0001

Source: Sponsor's Table 13 of CSR.

The key secondary efficacy endpoint in the study was the value of the CGI-I score at 2 hours after the first dose of study medication (active versus placebo). At 2 hours after the first dose, the CGI-I scores in each Staccato Loxapine group was statistically significantly lower than those of the placebo group, indicating decreased agitation (overall treatment effect, p<0.0001; 5-mg/placebo, p=0.0015; 10-mg/placebo, p<0.0001). The sponsor's detailed results are shown in Table 3.2.5. The sponsor's analysis results for the tertiary endpoints are shown in Table 3.2.6. Based on the table, we noted that Staccato Loxapine 10 mg did better than 5 mg for all tertiary endpoints. The 5 mg had nominal p-value less than 0.05 only for the time to the first use of rescue medication but the 10 mg showed all nominal p-value less than 0.05 for all tertiary endpoints in comparison with placebo.

Table 3.2.5 Sponsor's Analysis Results for Key Secondary Efficacy Endpoint: CGI-I Score 2 Hours after Dose 1 (ITT Population with LOCF) for Study AMDC-004-301

CGI-S or CGI-I Score	Staccato Placebo (N=115)	Staccato Loxapine 5 mg (N=116)	Staccato Loxapine 10 mg (N=112)
Baseline (CGI-S score)			
Mean (SD)	3.9 (0.53)	4.0 (0.55)	4.1 (0.60)
2 hours (CGI-I score)			
Mean (SD)	2.8 (1.11)	2.3 (1.24)	2.1 (1.00)
p-value for active/placebo comparisons		p=0.0015	p<0.0001
p-value for overall treatment effect <sup>a</sup>	p<0.0001		

<sup>a</sup> ANOVA with term for pseudo-center and treatment

Source: Sponsor's Table 14 of CSR

Table 3.2.6 Sponsor’s Analysis Results for Tertiary Efficacy Endpoints for Study AMDC-004-301

Tertiary Efficacy Endpoints	Staccato Placebo (N=115)	Staccato Loxapine 5 mg (N=116)	Staccato Loxapine 10 mg (N=112)
CGI-I Responders 2 Hours after Dose 1	35.7%	57.4%	67.0%
ACES Score* 2 Hours after Dose 1, Mean (SD)	3.9 (1.76)	4.7 (2.09)	4.9 (2.03)
Use of Study Rescue Medication by 4 Hours			
1 dose study medication/no rescue medication	64 (55.7%)	78 (68.4%)	84 (75.0%)
2 doses study medication/no rescue medication	50 (43.5%)	35 (30.7%)	27 (24.1%)
2 doses study medication/with rescue medication	1 (0.9%)	1 (0.9%)	1 (0.9%)
p-value (active vs. placebo, Fisher’s Exact Test)		p = 0.0850	p = 0.0039
Use of Study Rescue Medication by 24 Hours			
1 dose study medication/no rescue medication	53 (46.1%)	62 (54.4%)	67 (60.9%)
2 doses study medication/no rescue medication	34 (29.6%)	35 (30.7%)	29 (26.4%)
3 doses study medication/no rescue medication	10 (8.7%)	10 (8.8%)	8 (7.3%)
1 dose study medication/with rescue medication	0	1 (0.9%)	1 (0.9%)
2 doses study medication/with rescue medication	12 (10.4%)	4 (3.5%)	3 (2.7%)
3 doses study medication/with rescue medication	6 (5.2%)	2 (1.8%)	2 (1.8%)
p-value (active vs. placebo, Fisher’s Exact Test)		p = 0.1548	p = 0.0485
Time to the First Use of Rescue Medication, rate	16%	6%	5%
p-value by Log Rank Test (active vs. placebo)		p = 0.0195	p = 0.0126
Time to the Use of Dose 2 of Study Medication, rate	54%	45%	38%
p-value by Log Rank Test (active vs. placebo)		p = 0.1155	p = 0.0076

\* ACES=Agitation-Calmness Evaluation Scale. 1=marked agitation, 2=moderate agitation, 3=mild agitation, 4=normal, 5=mild calmness, 6=moderate calmness, 7=marked calmness, 8=deep sleep, 9=unarousable

### 3.1.3 Sponsor’s Efficacy Analysis Results for Study AMDC-004-302

#### 3.1.3.1 Disposition of Patients and Baseline Characteristics

Of the 356 patients who were screened for the study, 314 (88.2%) were randomized and received at least 1 dose of study medication, and 312 completed the study. Two patients discontinued prematurely both because of an AE of moderate anxiety that resolved with medication. Table 3.3.1 shows the disposition of patients and patients’ reason of discontinuation and Table 3.3.2 shows patients’ baseline characteristics. As shown in the tables, the sponsor concluded that the groups were well matched for demographic and baseline characteristics, as well as baseline disease characteristics.

Table 3.3.1 Disposition of Patients and Reasons for Premature Discontinuation (Safety Population) for Study AMDC-004-302

Patient Disposition, n (%)	Staccato Placebo	Staccato Loxapine 5 mg	Staccato Loxapine 10 mg	Total
Randomized	105	104	105	314
Completed study	105 (100%)	104 (100%)	103 (98.1%)	312 (99.4%)
Discontinued prematurely	0	0	2 (1.9%)	2 (0.6%)
Reason for discontinuation:				
Adverse event	0	0	2 (1.9%)	2 (0.6%)

Source: Sponsor’s Table 5 of CSR

Table 3.3.2 Demographic and Baseline Characteristics (Safety Population) for Study AMDC-004-302

Demographic or Baseline Characteristic	Staccato Placebo (N=105)	Staccato Loxapine 5 mg (N=104)	Staccato Loxapine 10 mg (N=105)
Gender, n (%)			
Female	49 (46.7%)	57 (54.8%)	52 (49.5%)
Male	56 (53.3%)	47 (45.2%)	53 (50.5%)
Age (years):			
Mean (SD)	40.6 (9.82)	41.2 (9.63)	40.5 (9.80)
Race, n (%)			
Caucasian	33 (31.4%)	58 (55.8%)	47 (44.8%)
Black	54 (51.4%)	38 (36.5%)	47 (44.8%)
Hispanic	14 (13.3%)	8 (7.7%)	7 (6.7%)
Asian	0	0	1 (1.0%)
Native American	1 (1.0%)	0	1 (1.0%)
Other	3 (2.9%)	0	2 (1.9%)
PEC score at baseline			
Mean (SD)	17.7 (2.80)	17.4 (2.23)	17.3 (2.25)
CGI-S score at baseline			
Mean (SD)	4.1 (0.57)	4.0 (0.53)	4.0 (0.49)
Time since diagnosis (years)			
Mean (SD)	18.8 (10.34)	16.5 (10.80)	18.2 (10.03)
No. of previous hospitalizations			
Mean (SD)	5.9 (6.57)	5.5 (6.55)	5.1 (6.41)

Source: Sponsor's Tables 8 and 9 of CSR.

### 3.1.3.2 Sponsor's Efficacy Analysis Results

Same as Study AMDC-004-302, the primary efficacy endpoint was the change in the PEC score from baseline to 2 hours after Dose 1. Both the 5- and 10-mg doses were superior to placebo on this endpoint, with the tests for the overall treatment effect and the 2 follow-up active/placebo comparisons being highly statistically significant ( $p < 0.0001$  for the overall treatment effect and both active/placebo comparisons). The baseline PEC score and the change from baseline to 2 hours are summarized by treatment group in Table 3.3.3. The sponsor's analysis results for the change from baseline to each time point in PEC scores are presented in Table 3.3.4. As shown in the table, all nominal p-values were very small.

Table 3.3.3 Sponsor's Primary Efficacy Endpoint: Change in the PEC Score 2 Hours After Dose 1 based on ITT Population with LOCF Data for Study AMDC-004-302

PEC Score	Staccato Placebo (N=105)	Staccato Loxapine 5 mg (N=104)	Staccato Loxapine 10 mg (N=105)
Baseline PEC score			
Mean (SD)	17.7 (2.80)	17.4 (2.23)	17.3 (2.25)
Change in PEC score from baseline to 2 hours after Dose 1			
Mean (SD)	-4.9 (4.77)	-8.1 (4.90)	-9.0 (4.67)
LS mean <sup>a</sup>	-4.7	-8.2	-9.2
p-value for active/placebo comparisons <sup>b</sup>		$p = 0.0001$	$p < 0.0001$
p-value for overall treatment effect	$p < 0.0001$		

<sup>a</sup> LS mean was used in the primary efficacy analysis and the ANCOVA model was with terms for baseline PEC total score, pseudo-center, and treatment <sup>b</sup> Dunnett's t-test

Source: Sponsor's Table 12 of CSR

Table 3.3.4 Sponsor's Results for Change in the PEC Score at Assessment through 24 Hours after Dose 1 (ITT Population with LOCF) for Study AMDC-004-302

PEC Score (mean change)	Staccato Placebo (N=105)	Staccato Loxapine 5 mg (N=104)	Staccato Loxapine 10 mg (N=105)
+10 minutes	-1.8	-3.6	-4.0
p-value		NA	p<0.0001
+20 minutes	-3.2	-5.8	-6.7
p-value		NA	p<0.0001
+30 minutes	-3.9	-7.5	-8.0
p-value		NA	p<0.0001
+45 minutes	-4.6	-8.1	-8.8
p-value		NA	p<0.0001
+1 hour	-5.0	-8.8	-8.8
p-value		NA	p<0.0001
+1.5 hours	-5.0	-8.3	-8.8
p-value		NA	p<0.0001
+4 hours	-6.1	-8.3	-9.3
p-value		NA	p<0.0001
+24 hours	-4.5	-6.1	-6.0
p-value		NA	p<0.0011

Source: Sponsor's Table 13 of CSR.

The key secondary efficacy endpoint in the study was the value of the CGI-I score at 2 hours after the first dose of study medication (active versus placebo). Both the 5- and 10-mg beat placebo, with the tests for the overall treatment effect and the 2 follow-up active/placebo comparisons being highly statistically significant. At 2 hours after the first dose, the CGI-I scores in each Staccato Loxapine group were statistically significantly lower than those of the placebo group, indicating decreased agitation (p<0.0001 for the overall treatment effect and both active/placebo comparisons). The sponsor's analysis results for CGI-I score at 2 hours are shown in Table 3.3.5. For the tertiary efficacy endpoints, the sponsor's analysis results are summarized in the following Table 3.3.6. As shown on the table, we noted that all of the nominal p-values were less than 0.05.

Table 3.3.5 Sponsor's Analysis Results for Key Secondary Efficacy Endpoint: CGI-I Score 2 Hours after Dose 1 (ITT Population with LOCF) for Study AMDC-004-302

CGI-S or CGI-I Score	Staccato Placebo (N=105)	Staccato Loxapine 5 mg (N=104)	Staccato Loxapine 10 mg (N=105)
Baseline (CGI-S score)			
Mean (SD)	4.1 (0.57)	4.0 (0.53)	4.0 (0.49)
2 hours (CGI-I score)			
Mean (SD)	3.0 (0.99)	2.1 (1.10)	1.9 (1.14)
p-value for active/placebo comparisons		p < 0.0001	p < 0.0001
p-value for overall treatment effect <sup>a</sup>	p < 0.0001		

<sup>a</sup> ANOVA with term for pseudo-center and treatment

Source: Sponsor's Table 15 of CSR

Table 3.3.6 Sponsor’s Analysis Results for Tertiary Efficacy Endpoints for Study AMDC-004-302

Tertiary Efficacy Endpoints	Staccato Placebo (N=105)	Staccato Loxapine 5 mg (N=104)	Staccato Loxapine 10 mg (N=105)
CGI-I Responders 2 Hours after Dose 1	27.6%	66.3%	74.3%
ACES Score* 2 Hours after Dose 1, Mean (SD)	3.3 (1.68)	4.7 (1.98)	5.1 (2.06)
Use of Study Rescue Medication by 4 Hours			
1 dose study medication/no rescue medication	38 (36.2%)	62 (59.6%)	79 (76.0%)
2 doses study medication/no rescue medication	61 (58.1%)	40 (38.5%)	23 (22.1%)
2 doses study medication/with rescue medication	6 (5.7%)	2 (1.9%)	2 (1.9%)
p-value (active vs. placebo, Fisher’s Exact Test)		p=0.0019	p<0.0001
Use of Study Rescue Medication by 24 Hours			
1 dose study medication/no rescue medication	28 (26.7%)	43 (41.3%)	64 (61.5%)
2 doses study medication/no rescue medication	43 (41.0%)	46 (44.2%)	27 (26.0%)
3 doses study medication/no rescue medication	12 (11.4%)	6 (5.8%)	4 (3.8%)
1 dose study medication/with rescue medication	0	0	0
2 doses study medication/with rescue medication	15 (14.3%)	7 (6.7%)	7 (6.7%)
3 doses study medication/with rescue medication	7 (6.7%)	2 (1.9%)	2 (1.9%)
p-value (active vs. placebo, Fisher’s Exact Test)		p = 0.0280	p < 0.0001
Time to the First Use of Rescue Medication	21%	9%	9%
p-value by Log Rank Test (active vs. placebo)		p = 0.0122	p = 0.0103
Time to the Use of Dose 2 of Study Medication,	73%	59%	38%
p-value by Log Rank Test (active vs. placebo)		p = 0.0058	p < 0.0001

\* ACES=Agitation-Calmness Evaluation Scale. 1=marked agitation, 2=moderate agitation, 3=mild agitation, 4=normal, 5=mild calmness, 6=moderate calmness, 7=marked calmness, 8=deep sleep, 9=unarousable

### 3.1.4 Statistical Reviewer’s Findings and Comments

1. For both Studies 301 and 302, the statistical reviewer confirmed the sponsor’s efficacy analysis results for the primary endpoint and the key secondary endpoint.
2. For both Studies 301 and 302, even though the sponsor-proposed procedure for dealing with multiplicity resulting from multiple doses and the multiple efficacy endpoints can not completely control the study-wise type I error rate, the efficacy of Staccato Loxapine’s effect was indeed demonstrated. The above conclusion was made based on extremely small nominal p-values for the individual tests on the primary and secondary endpoints and supported by some sensitivity analyses.
3. The statistical reviewer noted that in the sponsor proposed labeling, both Staccato Loxapine 5 mg and 10 mg’s efficacy based on PEC score was claimed at each individual testing time point through 24 hours. According to the study protocols for both Studies 301 and 302, except at 2 hours, only the tests between Staccato Loxapine 10 mg and placebo at time points 45 , 30, 20 and 10 minutes were prospectively planned to be tested in terms of controlling the overall study-wise type I error rate. Statistically speaking, the efficacy finding of Staccato Loxapine 5 mg at individual time points other than 2 hours and the description of the efficacy of Staccato Loxapine 10 mg beyond 45 minutes cannot be described in the labeling.

4. The following Figures 2 and 3 show the empirical cumulative distribution functions for Study 301 and Study 302 based on PEC score at 2 hours, respectively. Note that since it occurred only about 1% early dropout patients for both studies, the differences that we observed between each of Staccato Loxapine 5 mg and 10 mg and placebo should be reliable. In addition to the clear separation between either Staccato Loxapine 5 mg and the placebo, or Staccato Loxapine 10 mg and the placebo, it is interesting to note that for Study 301, Staccato Loxapine 10 mg had higher percentage of patients who had at least minor or any moderate improvement than Staccato Loxapine 5 mg. For patients who had at least about 12 points improvement (i.e., mean change  $\leq -12$ ) on PEC score, Staccato Loxapine 5 mg group showed higher percentage than Staccato Loxapine 10 mg group did.

Figure 2. Empirical Cumulative Distribution Function Plot for Study 301

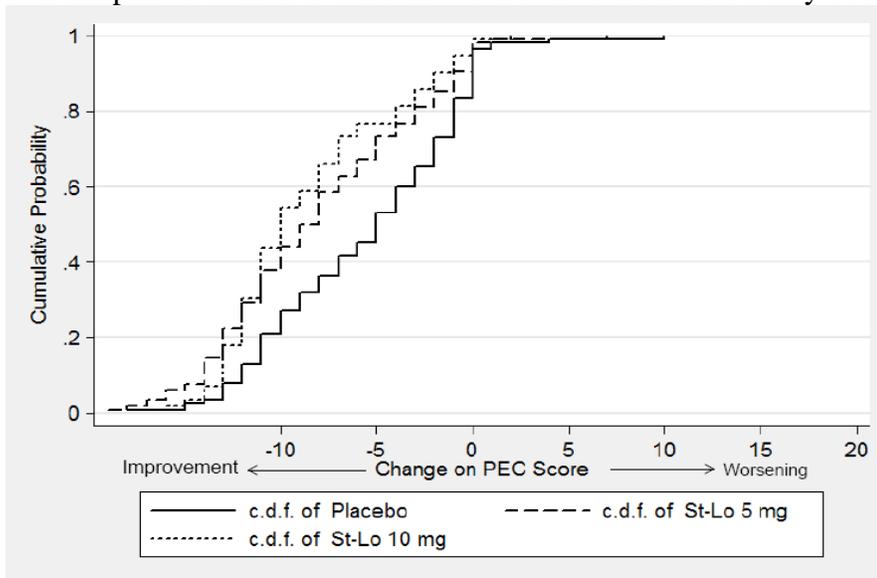
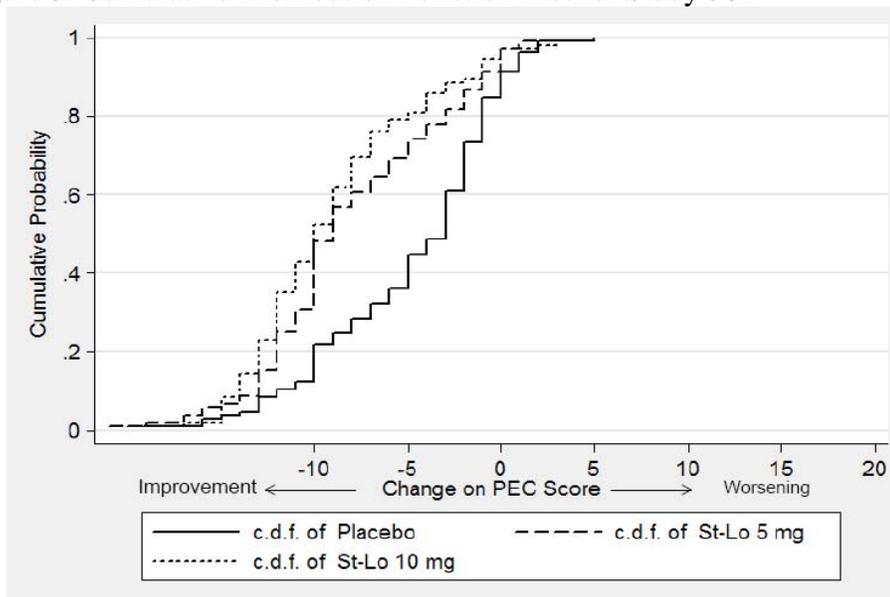


Figure 3. Cumulative Distribution Function Plot for Study 302



## 3.2 EVALUATION OF SAFETY

Please refer to the medical review for the safety evaluation.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 GENDER, RACE and AGE

The sponsor's analysis results for the demographic subgroup analyses for both phase III studies on the primary efficacy endpoint (i.e., change in PEC score from baseline to 2 hours after Dose 1) are shown in Tables 3.3.7 and 3.3.8. Based on the results, the sponsor concluded that although there were small differences in mean values between subgroups within a treatment group, no discernable trends were seen for age, sex, or race in the treatment groups in either study.

Table 3.3.7 Sponsor's Results for Demographic Subgroup Analyses for Study 004-301

(for Primary Endpoint) Demographic Characteristic	Staccato Placebo (N=115)		Staccato Loxapine 5 mg (N=116)		Staccato Loxapine 10 mg (N=112)	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Age						
≤ 43 years	49	-4.9 (5.25)	55	-7.6 (5.60)	55	-8.7 (4.17)
> 43 years	66	-6.0 (4.64)	61	-8.5 (4.76)	57	-8.5 (4.58)
Sex						
Male	80	-5.9 (4.96)	87	-7.6 (5.15)	86	-8.5 (4.22)
Female	35	-4.6 (4.75)	29	-9.4 (5.08)	26	-9.1 (4.86)
Race						
White	32	-4.9 (4.97)	48	-6.9 (4.85)	36	-7.5 (4.23)
Black	70	-5.9 (5.00)	61	-9.2 (5.02)	66	-9.0 (4.47)
Other	13	-5.4 (4.56)	7	-6.0 (6.78)	10	-9.7 (3.71)

Source: Sponsor's Table 24 in Summary of Clinical Efficacy

Table 3.3.8 Sponsor's Results for Demographic Subgroup Analyses for Study 004-302

(for Primary Endpoint) Demographic Characteristic	Staccato Placebo (N=105)		Staccato Loxapine 5 mg (N=104)		Staccato Loxapine 10 mg (N=105)	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Age						
≤ 43 years	57	-5.1 (5.15)	59	-8.4 (4.83)	61	-9.1 (4.25)
> 43 years	48	-4.6 (4.31)	45	-7.7 (5.02)	44	-8.9 (5.24)
Sex						
Male	56	-4.5 (4.79)	47	-8.3 (5.11)	53	-9.6 (4.68)
Female	49	-5.3 (4.76)	57	-7.9 (4.76)	52	-8.4 (4.62)
Race						
White	33	-4.8 (4.95)	58	-7.1 (4.88)	47	-8.3 (4.86)
Black	54	-4.4 (4.56)	38	-9.4 (5.01)	47	-9.8 (4.26)
Other	18	-6.4 (4.98)	8	-9.1 (2.64)	11	-8.6 (5.39)

Source: Sponsor's Table 25 in Summary of Clinical Efficacy

## 4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

No special subgroup analysis was performed in this review.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

For both pivotal Phase III studies, the statistical reviewer confirmed the sponsor's analysis results for the primary and secondary endpoints. For these two studies, even though the sponsor's prospectively-proposed statistical testing procedure does not completely control the overall study-wise type I error rate, due to the extremely small nominal p-values for almost all the comparisons between the drug and placebo at individual time points, the data indeed support the efficacy of Staccato Loxapine. However, statistically speaking, the treatment effect of Staccato Loxapine 5 mg at all individual time points except at 2 hours and the treatment effect of Staccato Loxapine 10 mg at time points beyond 45 minutes are not suitable to be described in the labeling since those tests were not prospectively planned in terms of controlling the study-wise type I error rate.

### 5.2 CONCLUSIONS AND RECOMMENDATIONS

The statistical reviewer confirmed the sponsor's efficacy analysis results for two phase-III studies (Studies CSR 004-301 and CSR 004-302). The data supported the efficacy of Staccato Loxapine for both 5 mg and 10 mg. However, besides at 2 hours, only the efficacy for 10 mg before an hour can be claimed in the labeling. Note that the testing for 5 mg at any time other than 2 hours and the testing for 10 mg beyond 45 minutes were not considered in the sponsor's per-specified testing procedure in terms of controlling the study-wise type I error rate.

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Yeh-Fong Chen, Ph.D.  
Mathematical Statistician

cc: NDA 22-549  
HFD-130/Dr. Laughren  
HFD-130/Dr. Mathis  
HFD-130/Dr. Levin  
HFD-130/Dr. Becker  
HFD-130/Ms. Updegraff  
HFD-700/Ms. Patrician  
HFD-710/Dr. Mahjoob  
HFD-710/Dr. Hung  
HFD-710/Dr. Yang

## **6. APPENDIX (STUDY DESCRIPTION FOR STUDY AMDC-004-201)**

Study AMDC-004-201 is titled as ‘A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Single-Dose Efficacy and Safety Study of Staccato<sup>®</sup> Loxapine for Inhalation in Schizophrenia Patients with Agitation’. The purpose of this phase II study was to assess the efficacy and the safety of Staccato Loxapine in the treatment of acute agitation in schizophrenic patients. This phase II study, not only included patients with schizophrenia, but also included some patients with schizophreniform disorder, or schizoaffective disorder. The total number of patients included in this study was 129, where 45 patients received a 5 mg dose of Staccato Loxapine, 41 received a 10 mg dose of Staccato Loxapine, and 43 received a dose of Staccato Placebo. Like the other two phase III studies, this study had the post-treatment period 24 hours and the primary endpoint was the absolute change in PEC score from baseline at 2 hours following Staccato Loxapine administration. According to the protocol, the analysis of variance (ANOVA) comparing the changes among the three treatment arms and Dunnett’s t-tests for the 2 active/placebo pair-wise comparisons (adjusted for multiple comparisons) will be used for the statistical analysis.

Table 6.1 shows patient demographic information based on the safety population. As shown in the table, most of the 129 patients who participated in this study were male (81%), Black (44%) or Caucasian (42%), with an overall mean age of 41 years, a mean height of 68.6 inches, and a mean weight of 199 pounds. The sponsor concluded that the mean ages were comparable across the three treatment groups, as were the percentages of gender, race, height, and weight among the three treatment groups.

Table 6.2 shows the sponsor’s analysis results for the primary endpoint. Based on these results, the sponsor stated that the analysis of covariance revealed that there was an overall treatment effect ( $p=0.0005$ ) and Staccato Loxapine 10 mg was superior to Staccato placebo in reducing agitation (Dunnett’s adjusted  $p = 0.0002$ ). They also concluded that although Staccato Loxapine 5 mg was not statistically significant different from Staccato Placebo in agitation at the 2-hour post dose (Dunnett’s adjusted  $p=0.088$ ), the result supports a dose-response across the 2 doses.

Table 6.1 Patient Demographic Summary for Study AMDC-004-201

		Placebo (N = 43)	<i>Staccato</i> Loxapine 5 mg (N = 45)	<i>Staccato</i> Loxapine 10 mg (N = 41)	Overall (N = 129)
<b>Age</b>					
Mean (SD)		43.5 (7.70)	40.8 (7.45)	39.3 (8.77)	41.2 (8.09)
Median		44.0	42.0	37.0	41.0
Minimum, Maximum		21.0, 57.0	26.0, 57.0	23.0, 61.0	21.0, 61.0
<b>Gender</b>					
Male	N (%)	33 (77%)	38 (84%)	34 (83%)	105 (81%)
Female	N (%)	10 (23%)	7 (16%)	7 (17%)	24 (19%)
<b>Race</b>					
Caucasian	N (%)	21 (49%)	19 (42%)	15 (37%)	55 (43%)
Black	N (%)	16 (37%)	20 (44%)	21 (51%)	57 (44%)
Hispanic	N (%)	4 (9%)	5 (11%)	4 (10%)	13 (10%)
Asian	N (%)	1 (2%)	0	1 (2%)	2 (2%)
Other	N (%)	1 (2%)	1 (2%)	0	2 (2%)
<b>Height (in)</b>					
Mean (SD)		67.9 (3.73)	68.6 (3.31)	69.4 (3.46)	68.6 (3.53)
Median		68.0	70.0	69.0	69.0
Minimum, Maximum		61.0, 74.0	60.0, 74.0	62.0, 80.0	60.0, 80.0
<b>Weight (lb)</b>					
Mean (SD)		193 (42.89)	206 (48.13)	199 (46.72)	199 (45.91)
Median		185	195	193	191
Minimum, Maximum		120, 320	115, 321	128, 316	115, 321

Source: Sponsor's Table 11-1 of CSR

Table 6.2 Sponsors Analysis Results for the Primary Efficacy Endpoint for Study AMDC-004-201

	Placebo	5 mg	10 mg
Mean (SD)	-4.98 (4.13)	-6.71 (5.14)	-8.56 (4.90)
P-value* (vs. Placebo)		0.088	0.0002

\* p-values (adjusted) using Dunnett's t-test with ANCOVA model with terms for baseline PEC, treatment and pseudo-center. Source: Sponsor's Figure 11-1 of CSR

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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YEH FONG CHEN  
09/07/2010

PEILING YANG  
09/08/2010

KOOROS MAHJOOB  
09/08/2010

Review was discussed with me. My views and comments are incorporated in this version and I concur with it.

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number:** 22549

**Applicant:** ZLEXZA

**Stamp Date:** Jan 21, 2010

**Drug Name:** Staccato®  
(Loxapine for inhalation)

**NDA/BLA Type:** Standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	×			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	×			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	×			The subgroup analysis results are contained in '273-004-sum-clin-efficacy-agitation.pdf' of m2.
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	×			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?**   Yes  

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

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.				
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.				
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.				
Appropriate references for novel statistical methodology (if present) are included.				
Safety data organized to permit analyses across clinical trials in the NDA/BLA.				
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.				

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

(b) (6)  
\_\_\_\_\_  
Date 1/21/2010  
Reviewing Statistician  
(b) (6)  
\_\_\_\_\_  
Date 1/21/2010  
Supervisor/Team Leader

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22549

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ORIG-1

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ALEXZA  
PHARMACEUTICA  
LS INC

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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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YEH FONG CHEN  
01/27/2010