The Staccato® System: Inhaler Design Characteristics for Rapid Treatment of CNS Disorders

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**KEYWORDS:** Staccato, loxapine, agitation, condensation, vaporization

**SUMMARY**

*Staccato*® Loxapine is a drug-device combination product that combines a proprietary condensation aerosol generation system from Alexza Pharmaceuticals with loxapine, a dopamine-blocking agent. The breath-actuated vaporization technology results in an aerosol that is delivered efficiently (~90% emitted dose), with a highly respirable particle size distribution (MMAD ~ 2.0 microns, GSD ~ 2.0). The emitted aerosol consists of only drug (purity >99%), as neither excipients nor propellants are required for delivery. Because of the efficient delivery to the lungs and rapid absorption into the systemic circulation, *Staccato*® Loxapine is being developed for the rapid and non-invasive acute treatment of agitation in patients with schizophrenia and bipolar disorder. An Investigational New Drug (IND) application was filed with FDA in 2005, and since then, the clinical program was completed, including two pivotal Phase 3 studies treating agitation in patients with schizophrenia or bipolar disorder. Clinical results show, relative to placebo, a statistically significant reduction in agitation as soon as 10 minutes after dosing and as long as 24 hours after dosing. A New Drug Application (NDA) for *Staccato*® Loxapine was submitted in December 2009.

**BACKGROUND**

The *Staccato* system is a hand held pulmonary drug delivery platform that supports a pipeline of products under development to address disorders of the central nervous system (CNS). Oral inhalation through the product initiates controlled and rapid heating of a thin film of excipient-free drug to form a highly pure drug vapor. The vapor condenses into aerosol particles with a size distribution appropriate for efficient lung delivery (1, 2). The CNS drug candidates utilizing the proprietary delivery system are all low molecular weight and lipophilic, and such compounds are known to rapidly and efficiently absorb into the bloodstream from the lung to provide peak plasma levels within minutes after administration (3-5).
The actual Staccato single-dose system is shown in Figure 1. The main features of the system – the breath sensor, the heat package, and the airway – are shown schematically in Figure 2 and are briefly described below.

The breath sensor detects the patient’s inhalation and initiates the chemical reaction in the heat package; no coordination or timed inhalation is required by the patient. The heat package is a sealed assembly, comprised of reactant coated on the interior surfaces of stainless steel substrates, which generates heat to vaporize the drug and produce the aerosol. The airway is the channel formed by the medical-grade polycarbonate plastic housings surrounding the heat package; it controls and directs the airflow over the vaporizing drug. The drug for vaporization can be coated on one side or both sides of the heat package to allow for a range of product dosage strengths.

Figure 1. Staccato single-dose system.

Figure 2. Schematic Cross-Section View of Staccato single-dose system (not to scale).

The lead compound being developed using the Staccato system is loxapine, a dopamine blocking agent being developed for the treatment of agitation. It was previously approved for the treatment of schizophrenia in both oral and intramuscular (IM) dosage forms. Agitation associated with schizophrenia and bipolar disorder is a condition that can benefit from rapid treatment and for which oral and IM formulations of antipsychotics can be relatively slow to take effect, invasive to deliver, or both. Combining a compound with the appropriate pharmacological activity, such as loxapine, with the non-invasive delivery and rapid pharmacokinetics provided by the Staccato system presents an opportunity to satisfy an unmet medical need. A development program for Staccato Loxapine has been conducted from IND application to NDA submission in less than 5 years, comprised of: pivotal and non-pivotal human clinical studies to demonstrate safety and efficacy; several animal studies to demonstrate the safety of loxapine for acute administration via the inhalation route; and all of the Chemistry, Manufacturing & Controls (CMC) development efforts needed to demonstrate the performance and robustness of the product design and manufacturing processes. Details on key aspects of the development efforts, including the core technology, product performance attributes and a summary of the clinical program, are presented in the following sections.
CORE TECHNOLOGY

As detailed in later sections, the Staccato technology produces a highly respirable aerosol for inhalation with a high degree of efficiency, purity and reproducibility. The core of this technology is the ability to control the temperature and minimize the time required for vaporizing the drug into the airstream. The primary components influencing these parameters are the heat package, which is the source of the thermal energy for vaporization, and the drug film coating.

Heat Package

The heat package, shown in Figure 3, is a seam-welded stainless steel container which contains chemical reactants to rapidly generate the energy necessary to vaporize the drug.

![Heat package from the Staccato single-dose system.](image)

When a patient inhales, the breath sensor initiates electrical current flow to the heat package. This heats a small amount of a pyrotechnic mixture, causing it to emit sparks that initiate the exothermic thermite reaction on the inside of the heat package. The thermite reaction rapidly propagates (in approximately 0.1 second) and generates heat nearly instantaneously. This thermal energy conducts through the stainless steel and raises the surface temperatures to approximately 400°C, which quickly heats and vaporizes the drug film (typically ~1 to 10 microns thick) coated on the exterior. While sufficient to vaporize the drug film, the total energy produced by the thermite reaction is relatively low. The rapid heating and short residence time of the drug at high temperature serves to mitigate the potential for thermal degradation of the drug or significant heating of the inhaled air and surrounding device components.

In the design of the heat package, only exothermic chemical systems that do not produce gaseous byproducts were considered, in order to avoid the potential for over-pressurization of the stainless steel container. Thermite reactions, in which a metal undergoes an oxidation-reduction reaction with the oxide of a different metal, were the leading candidates. Zirconium (Zr) was selected as the metal based on rapid propagation rates. The literature suggests that other metal candidates would yield slower thermite reaction rates (6). Molybdenum trioxide (MoO₃) was selected as the metal oxide based on similar considerations. A Zr-rich mixture of the two reactants is used to keep the reaction temperature from getting too elevated.

Development studies on the heat package design show that the selection of these reactants is ideal for reproducibility of the vaporization process. Figure 4 shows how the peak external surface temperature of the stainless steel substrate varies with the total mass of reactants applied to the internal surface. The surface temperature is measured using infrared thermography.
As is shown in Figure 4, the thermal performance of the heat package can be controlled via the mass of reactant coated on the inside of the foils. The coated mass of the reactant is controlled during the manufacturing process, and the resulting thermal performance is such that the nominal temperature of 390°C is maintained within a tolerance band of ±50°C with a process capability index (Cpk) well in excess of 1.0.

**Drug Film Coating**

In addition to the temperature of the substrate during vaporization, another important characteristic for the desired product aerosol performance is the thickness of the drug film coated onto the substrate. The drug coating is achieved using a standard ultrasonic spray nozzle. The crystalline state of the drug coating can be controlled via various spray coating parameters. However, due to the phase change that occurs during the vaporization process, the crystalline state of the drug coating has no impact on the resulting aerosol properties.

The film thickness, also represented by the coated density of the drug (mass per unit area), is a determining factor in the residence time of the drug on the heated surface in that a thicker film will take more time to heat up and vaporize. In theory, the increased residence time should lead to increased drug degradation. Therefore, a thicker drug film should typically result in lower purity of the emitted dose. Figure 5 presents emitted purity vs. coated density for loxapine, produced on an early-stage prototype of the Staccato system. Emitted purity was measured by collecting the emitted aerosol on a glass fiber filter at a flow rate of 20 L/min and with a vaporization temperature of 380°C. The emitted aerosol was extracted from the filter with a solvent and analyzed for purity via reverse-phase HPLC.

Figure 5 shows that the emitted purity for loxapine is relatively insensitive to coated density over the range from 0.3 to 1.1 mg/cm². Similar results are seen with the current version of the system, where the emitted purity is consistently greater than 99.5%. Loxapine demonstrates a high degree of thermal robustness in this range of coated density values, which represent dose strengths as high as 15 mg in the Staccato system.
In addition to film thickness, the vaporization temperature could also have an effect on emitted purity, in that higher temperatures should result in lower purity. However, characterization experiments have shown that the emitted purity for loxapine does not change as the temperature varies over a range from 325°C to 450°C. Additionally, the profile of individual impurities remains unchanged as well, with no individual impurities present above the regulatory reporting threshold of 0.1% (7) across that temperature range. Similar to the purity vs. coated density data in Figure 5, these results show that loxapine is very robust to the heating process, thereby making it an ideal candidate for delivery using the Staccato technology. As described earlier, the range of vaporization temperatures is 390°C ± 50°C which is within the range of temperatures over which the purity of loxapine is unchanged.

**PRODUCT PERFORMANCE**

In general, the Staccato technology produces a highly respirable aerosol for inhalation with a high degree of efficiency, purity and reproducibility, and this also holds true for Staccato Loxapine. The emitted dose from the product is typically 90% of the drug coated on the heat package. The mass median aerodynamic diameter (MMAD) of the emitted aerosol is approximately 2 µm with a geometric standard deviation (GSD) of approximately 2.0, resulting in roughly 90% of the aerosol mass under 5 µm in size. The emitted purity is typically greater than 99.5%.

**CMC Performance Summary**

In order to support the Phase 3 clinical program and registration stability studies for Staccato Loxapine, Alexza manufactured 5 lots each of the 5 and 10 mg strengths, or 10 lots total. Figure 6 presents the results of the emitted dose (ED) content uniformity testing for those 10 lots normalized to the proposed emitted dose label claims. N=100 measurements are shown, since n=10 measurements are needed per lot following the draft guidance for inhalers (8). Emitted dose is measured by collecting the emitted aerosol on a glass fiber filter using a DUSA apparatus per USP <601> (9) at a flow rate of 28.3 L/min. The emitted aerosol is extracted from the filter with a solvent and analyzed via UPLC.
In Figure 6, devices #1-50 are from the 5 mg dose group (proposed emitted dose label claim = 4.5 mg) and devices #51-100 are from the 10 mg dose group (proposed emitted dose label claim = 9.1 mg). Figure 6 shows that all of the individual emitted dose measurements are well within the 75-125% range relative to label claim prescribed in the draft guidance (represented by the dashed horizontal lines in Figure 6). The high degree of reproducibility both device-to-device and lot-to-lot is in large part due to the robustness of the underlying technology.

A broad range of in vitro characterization studies was conducted to support product registration. These studies included testing the system: at high and low ambient temperature and humidity; at high and low flow rates; at simulated high altitude (8000 ft.); in a vertical orientation vs. the standard horizontal orientation; and after exposure to mechanical vibration, shock and dropping. Figure 7 presents the MMAD measurements for each of these test conditions. MMAD is measured by drawing the emitted aerosol through a Next Generation Impactor (NGI) apparatus per USP <601> (9) at a flow rate of 30 L/min. The emitted aerosol is extracted from each stage with a solvent and analyzed for quantification via UPLC. The values for GSD were relatively constant, ranging from 2.0 to 2.4 for the conditions shown in Figure 7.
Figure 7 shows that the key aerosol performance metrics stay roughly constant regardless of the test condition. The only discernable trends are ED increasing and MMAD decreasing as flow rate increases. The increase in ED with higher flow rate is not substantial and is due to slightly more efficient entrainment of the vaporized drug in the inhalation air stream. The trend of MMAD decreasing with flow rate is due to the fact that at higher flow rates the concentration of drug particles in air is lower and therefore the particles are less susceptible to aggregation. However, the Stokes number for the aerosol particles, which determines the probability for upper airway deposition, stays approximately constant because the decrease in MMAD compensates nearly exactly for the increase in air velocity. This aspect of the aerosolization process is predicted to contribute to a relatively uniform lung deposition pattern across a broad range of flow rates (10, 11). The emitted purity is not shown in Figure 7 because there were no changes in aerosol purity relative to the standard test condition.

Clinical Program Summary

The clinical program for Staccato Loxapine included two pivotal Phase 3 studies – one with schizophrenia patients and one with bipolar disorder patients. The first-in-man Phase 1 study demonstrated good tolerability and IV-like pharmacokinetics in healthy volunteers, with a median plasma T\text{max} of loxapine less than 2 minutes and good dose proportionality (12). A multi-dose study in non-agitated patients who were on stable doses of antipsychotics demonstrated the safety and tolerability of three repeat doses of Staccato Loxapine in individual doses of 5 mg or 10 mg separated by 4 hours (maximum of 30 mg per day). A study with smokers and non-smokers showed no significant effect of smoking status on absorption or metabolism of inhaled loxapine. Additional studies that support the safety of Staccato Loxapine for the NDA filing included assessment of cardiac safety (Thorough QT study) and pulmonary safety in healthy subjects as well as subjects with asthma and subjects with COPD.

The two pivotal Phase 3 studies were in-clinic, multi-center, randomized, double-blind, placebo-controlled studies. The first Phase 3 study enrolled 344 patients with schizophrenia and the second Phase 3 study enrolled 314 patients with bipolar disorder. The primary endpoint for both studies was the change from baseline in the PANSS (Positive and Negative Symptom Scale) Excited Component score, also known as PEC score, measured at 2 hours after the first dose. If required, up to two additional doses of study medication, as well as rescue medication (IM lorazepam) were allowed after the 2-hour timepoint. Additional timepoints for the PEC score were also studied.

In both Phase 3 studies, Staccato Loxapine was tested at two dose levels, 5 mg and 10 mg. Both doses met the primary endpoint in both studies, showing a highly statistically significant improvement in the PEC score compared to placebo (p<0.001) two hours after dosing. Additionally, both doses of Staccato Loxapine exhibited a rapid onset of effect. At 10 minutes post-dose (the first assessment following dosing), the planned analysis for the 10 mg dose showed a highly statistically significant improvement in the PEC score compared to placebo (p<0.001) and a post-hoc analysis of the 5 mg dose showed a similarly significant effect. Staccato Loxapine was also well tolerated in these studies. Most adverse events (AEs) were mild or moderate, and there were no treatment-related serious adverse events (SAEs). The most common AEs were sedation and dizziness (known effects of loxapine) and dysgeusia (common with inhaled drugs).

In addition to Staccato Loxapine for agitation, the Staccato technology has been the platform for five additional product candidates that are in various stages of clinical development. The compounds being studied are all for CNS therapies, and they include: prochlorperazine for...
migraine; a lower dose of loxapine, also for migraine; alprazolam for acute anxiety and panic disorder; zaleplon for insomnia; and fentanyl for breakthrough pain. All of these product candidates share the key \textit{in vitro} and \textit{in vivo} characteristics of \textit{Staccato} Loxapine for agitation: highly efficient and reproducible aerosol generation; a high degree of aerosol purity; and IV-like pharmacokinetics.

\textbf{CONCLUSIONS}

The development of the \textit{Staccato} system has demonstrated the viability of thermal vaporization as a robust aerosol generation platform for drug delivery to the systemic circulation via the lungs. Through careful selection of core technology characteristics such as reactants for heat generation, drug compounds for vaporization and the coating thickness of the drug films, a high degree of \textit{in vitro} efficiency, reproducibility and purity has been achieved. These characteristics have also translated into good \textit{in vivo} outcomes for \textit{Staccato} Loxapine, as the clinical development program has also demonstrated safety, efficacy, and rapid onset of clinical effect. The \textit{Staccato} system has the potential to be the basis for several future drug products in the CNS therapeutic area, with five additional product candidates at present in various stages of clinical development.

\textbf{ACKNOWLEDGEMENT}

The authors gratefully acknowledge the contributions of Steve Larsen, Amy Lu, Qiang Chen, Khe Dinh and Tamara Shmidt.
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