

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-360

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

CLINICAL PHARMACOLOGY REVIEW

| | | | |
|---------------------------------|---|---------------------------|-------------------------|
| <i>NDA</i> | 22-360 | <i>Submission Date(s)</i> | 7/18/2008, 2/19/2009 |
| <i>Brand Name*</i> | -Original proposal: Commit® Mini Mint Lozenges -New proposal: Nicorette Mini Lozenges | | |
| <i>Generic Name</i> | Nicotine Polacrilex | | |
| <i>Reviewer</i> | Ping Ji, Ph.D. | | |
| <i>Team Leader</i> | Suresh Doddapaneni, Ph.D. | | |
| <i>OCP Division</i> | Division of Clinical Pharmacology-2 | | |
| <i>OND Division</i> | Division of Anesthesia, Analgesia, and Rheumatology | | |
| <i>Sponsor</i> | GlaxoSmithKline Consumer Healthcare | | |
| <i>Relevant IND(s)</i> | IND 56, 295 | | |
| <i>Submission Type; Code</i> | 505 (b) (1) | S | |
| <i>Formulation; Strength(s)</i> | 2 mg and 4 mg | | |
| <i>Indication</i> | Reduces withdrawal symptoms, including nicotine craving associated with quitting smoking | | |
| <i>Proposed Dosing Regimen</i> | Take one lozenge every 1 to 2 hours and at least 9 lozenges each day for the first 6 weeks. After six weeks, take one lozenge every two to four hours. Take one every 4-8 hours between week 10 and 12. Stop taking it after week 12. | | |

*Throughout this review, the product is referred to as Commit® Mini Mint Lozenges as the new proposal is under review at the time of finalizing the review.

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1 Executive Summary

1.1 Recommendations

The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background Nicotine Polacrilex Lozenges (Commit[®] Lozenges), 2 and 4 mg, (NDA 21-330), was originally developed by GlaxoSmithKline (GSK) for the indication of reducing withdrawal symptoms, including nicotine craving associated with quitting smoking. The Commit[®] Mini Mint Lozenges, subject of NDA 22-360, have been specifically designed to overcome the disadvantages associated with the large size of the currently marketed Commit[®] Nicotine Polacrilex Lozenges under the approved NDA 21-330. The Commit[®] mini Mint Lozenges, 2mg and 4mg, are considered to be a line extension of the currently marketed Commit Lozenges (original, mint, and cherry flavor) which are available in the same strengths, contain the same active ingredient, Nicotine Polacrilex, and identical indication. The sponsor's rationale for developing the mini lozenge is that at _____, Commit[®] lozenge is quite large, takes some time to dissolve, and is therefore somewhat less than discreet for some individuals who use the product throughout the day in a public setting. The mini lozenges weigh _____

b(4)

b(4)

The clinical development program for Commit[®] Mini Mint Lozenges focused on establishing bioequivalence between the currently marketed lozenges with the newly developed mini lozenges. A total of 3 bioequivalences studies were performed in support of this submission. All the three studies were designed to assess the bioequivalence between the Commit[®] Mini mint nicotine lozenge and the original Commit[®] Nicotine Polacrilex Lozenge, which was used as the reference drug.

Biopharmaceutics Three separate bioequivalence studies were conducted to establish the bioequivalence of the Commit[®] Mini mint Nicotine Lozenge to the currently marketed lozenge formulation, Commit[®] Nicotine Polacrilex Lozenges. Studies S3010445 and S3010466 (pilot studies) were 2-period cross-over studies to compare the nicotine PK profiles between the two products at 2 mg and 4 mg, respectively. Study S3010567 (pivotal BE study) was a single dose, 4-period cross-over study to compare the nicotine PK profiles between the two products at both 2 mg and 4 mg dosage strength. All studies were conducted using healthy volunteer smokers who were instructed not to

smoke (or take other nicotine products) before and during the assessment period. Bioequivalence criteria were met in all the three studies.

During bio-analytical inspection of this study (S3010567), two concerns were raised by the Division of Scientific Investigations (DSI): 1) the quality control samples (3.00, 30.0 and 150 ng/mL) and calibration range (1.00 to 200 ng/mL) for nicotine used in the study were not representative of the nicotine plasma concentrations observed in study plasma samples; 2) the LC/MS/MS assay (LLOQ=1.00 ng/mL) did not have sufficient sensitivity to measure nicotine levels for at least three half lives in the study of 2 mg lozenges. In response to the FDA 483 observations, sponsor reanalyzed all the pharmacokinetic plasma samples from study S3010567. In the reanalysis, quality control samples were selected at concentrations of 0.60, 3.00 and 7.50 ng/mL, and calibration standards in the range of 0.20 to 10.0 ng/mL were utilized. The QC samples and calibration curve range in the reanalysis were found to be representative of the plasma nicotine concentrations generated in the study. The new LC/MS/MS assay (LLOQ = 0.20 ng/ml) was able to measure nicotine levels more than three half lives at both 2 and 4 mg doses. The results from the pivotal BE study S3010567 with the updated analytical method are shown in Figure 1.3 and Table 1.3.

Figure 1.3: Mean Nicotine Plasma Concentration-Time Profiles (Study S3010567)

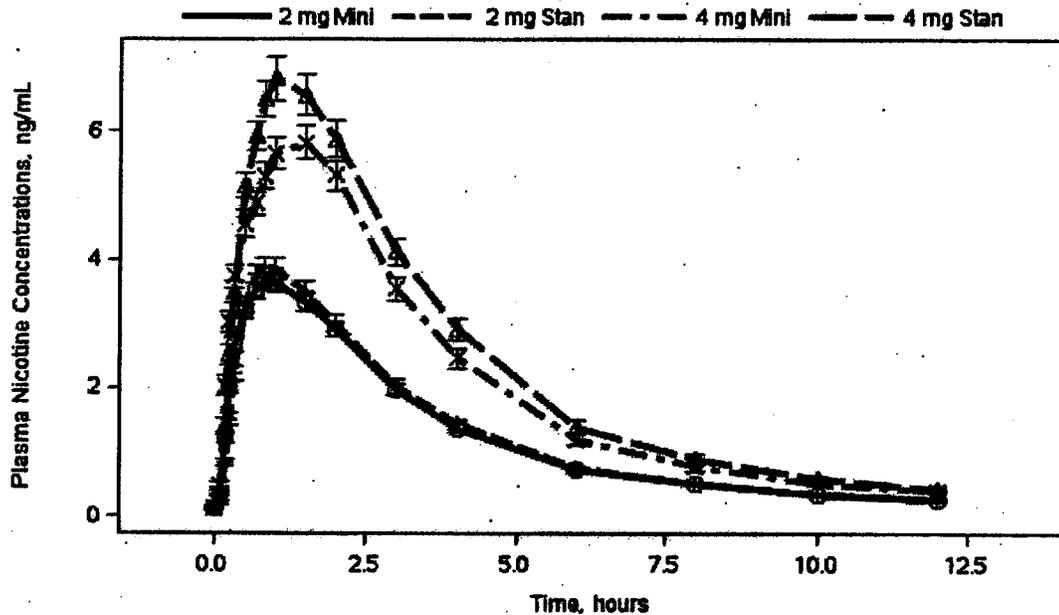


Table 1.3: Statistical Comparison between Mini Lozenge and Standard Lozenge (Study S3010567).

Table 1: 2mg PK Parameters Based on Adjusted Concentrations

| Parameter | (N) Mean ¹ ± S.D. | | *Ratio: Mini/Standard | |
|------------------------------------|------------------------------|----------------------|-----------------------|-------------------|
| | Mini | Standard | Estimate | 90% CI |
| C _{max} (ng/ml) | (38) 3.93 ± 1.14 | (35) 4.18 ± 1.34 | 95.12% | [90.37%, 100.11%] |
| AUC ₍₀₋₄₎ (ng·hr/ml) | (38) 14.02 ± 5.18 | (35) 14.98 ± 5.97 | 94.09% | [90.22%, 98.12%] |
| AUC _(0-∞) (ng·hr/ml) | (38) 15.30 ± 5.74 | (35) 16.32 ± 6.39 | 93.92% | [90.04%, 97.97%] |

Table 2: 4mg PK Parameters Based on Adjusted Concentrations

| Parameter | (N) Mean ¹ ± S.D. | | *Ratio: Mini/Standard | |
|------------------------------------|------------------------------|-----------------------|-----------------------|------------------|
| | Mini | Standard | Estimate | 90% CI |
| C _{max} (ng/ml) | (32) 6.28 ± 2.04 | (35) 7.40 ± 2.77 | 85.40% | [80.35%, 90.78%] |
| AUC ₍₀₋₄₎ (ng·hr/ml) | (32) 24.06 ± 9.14 | (35) 27.32 ± 12.19 | 90.39% | [85.91%, 95.09%] |
| AUC _(0-∞) (ng·hr/ml) | (32) 25.72 ± 9.98 | (34) 29.61 ± 13.11 | 90.57% | [86.21%, 95.15%] |

Source: Table 9.2.2.2a

¹ Unadjusted treatment means

* Ratio of geometric means

Overall, sponsor adequately addressed the Clinical Pharmacology and Biopharmaceutics aspects of the NDA.

2 Question-Based Review

2.1 General Attributes

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Nicotine Polacrilex Lozenges (Commit[®] Lozenges), 2 and 4 mg, (NDA 21-330), was originally developed by GlaxoSmithKline (GSK) for the indication of reducing withdrawal symptoms, including nicotine craving associated with quitting smoking. The Commit[®] Mini Mint Lozenges, subject of NDA 22-360, have been specifically designed to overcome the disadvantages associated with the large size of the currently marketed Commit[®] Nicotine Polacrilex Lozenges under the approved NDA 21-330. The Commit mini Mint Lozenges, 2mg and 4mg, are considered to be a line extension of the currently marketed Commit Lozenges (original, mint, and cherry flavor) which are available in the same strengths, contain the same active ingredient, Nicotine Polacrilex, and identical indication. The sponsor's rationale for developing the mini lozenge is that at _____ Commit[®] lozenge is quite large, takes some time to dissolve, and is therefore somewhat less than discreet for some individuals who use the product throughout the day in a public setting. The mini lozenges weigh _____

b(4)

b(4)

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The drug substance nicotine polacrilex, is identical to that used in the previously approved applications for Commit Lozenges and flavor variants (NDA 21-330 and supplements). It is produced _____

b(4)

_____ The lozenges are white to off-white oval tablets embossed with logos of "M" or "F" for the 2 mg and 4 mg lozenges respectively. The quantitative composition of the Mini Mint Lozenge in comparison to the standard Commit Lozenge is shown in the Table 2.1.2A and Table 2.1.2B.

Table 2.1.2A: Quantitative composition of mini mint 2 mg lozenge

| Name of Ingredients | Reference to Standard | Composition | |
|--|-------------------------|-------------------|---------------------|
| | | Mini Lozenge 2 mg | Conmit Lozenge 2 mg |
| Active substance Nicotine Polacrilex ¹ (equivalent to Nicotine) | USP | | |
| Excipients Mannitol ² | USP DMF | | |
| Sodium Alginate ² | NF DMF DMF DMF | | |
| Sodium Carbonate | NF | | |
| Calcium Polycarbophil ² | USP | | |
| Magnesium Stearate | NF | | |
| Xanthan Gum ² | NF | | |
| Acetulfame-k | NF | | |
| Potassium Bicarbonate ² | USP | | |
| | USP | | |
| Total lozenge weight | | | |

b(4)

b(4)

b(4)

b(4)

b(4)

1
2
3

Source: P4 3.2.P.2.2 Drug Product

Table 2.1.2B: Quantitative composition of mini mint 4 mg lozenge
Quantitative Composition of Nicotine Mini Mint 4mg Lozenge

| Name of Ingredients | Reference to Standard | Composition | |
|--|-----------------------|-------------------|---------------------|
| | | Mini Lozenge 4 mg | Commit Lozenge 4 mg |
| Active substance Nicotine Polacrilex ¹ (equivalent to Nicotine) | USP | b(4) | b(4) |
| Excipients Mannitol ² | USP | | |
| [redacted] | DMF | | |
| Sodium Alginate ² | NF | | |
| [redacted] | DMF | | |
| [redacted] | DMF | | |
| DMF | DMF | | |
| Sodium Carbonate | NF | | |
| Calcium Polycarbophil ² | USP | | |
| Magnesium Stearate | NF | | |
| Xanthan Gum ² | NF | | |
| Acaculfame-k | EP | | |
| [redacted] | NF | | |
| Potassium Bicarbonate ² | USP | | |
| [redacted] | USP | | |
| Total lozenge weight | - | b(4) | b(4) |

1
2
3

Source: P5 3.2.P.2.2 Drug Product

2.2.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dosing regimen of mini mint nicotine lozenge is identical to the approved Commit® lozenge as follows:

Take a Commit® Mini Mint Lozenge every 1 to 2 hours and at least 9 lozenges each day for the first 6 weeks to help prevent unexpected cravings and improve the chances of quitting. Place the lozenge in mouth and allow the lozenge to slowly dissolve (about 10 minutes). Minimize swallowing. Do not chew or swallow the lozenge. After six weeks, take one lozenge every two to four hours. At the beginning of week 10, take one every 4-8 hours. Stop using it at the end of 12 weeks. (*Source: user's guide*)

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A total of 3 biopharmaceutics studies were performed in support of this submission. All three studies were designed to assess the bioequivalence between the Commit® Mini mint nicotine lozenge and the original Commit® Nicotine Polacrilex Lozenge, which was used as the reference drug. Approval is sought for 2 mg and 4 mg dosage strengths. Studies S3010445 and S3010466 were 2-period cross-over studies to assess bioequivalence of the two products at 2 mg and 4 mg, respectively. Both studies showed bioequivalence. However, review of the data in these two studies by the sponsor showed some anomalies with respect to C_{max} and AUC values. For efficiency reasons, these two studies were conducted in two different geographical regions. Study S3010445, assessing the 2 mg strength, was conducted in India yielded similar C_{max} and AUC values to those obtained in study S3010466, assessing the 4 mg strength, conducted in the U.S. (see table 2.6.3). Two reasons were attributed to this anomaly. Lower body Mass Index and slower elimination rate constants of the Indian subjects compared to the American subjects. However, in order to further explore this issue, sponsor conducted study S3010567 assessing the bioequivalence of the 2 mg and 4 mg strengths in the U.S. population. Study S3010567 was a single dose, 4-period cross-over study to compare the nicotine PK profiles between the two products at both 2 mg and 4 mg dosage strength. All three studies were conducted using healthy volunteer smokers who were instructed not to smoke (or take other nicotine products) before and during the assessment period. Bioequivalence criteria were met in all the three studies.

2.2.2 What are the known PK characteristics of nicotine?

The following summary is a brief literature review of nicotine PK.

Absorption Nicotine is a tertiary amine, with a pK_a of 8.0 (weak base). The extent of buccal absorption varies with the pH; nicotine is well absorbed in the mouth from alkaline smoke (cigar) and buffered moist snuff or chewing gum, but little is absorbed from acidic smoke (cigarette). The oral bioavailability of nicotine is about 25 to 30%. Nicotine absorption from cigarette smoking is very rapid and is completed when the person stops smoking, whereas, input from the nicotine gum (or smokeless tobacco) has a

small lag time, peaks and declines during the 30minute period of chewing, then continues for more than 30 minutes after oral nicotine use has stopped. This prolonged absorption is probably related to the absorption of swallowed nicotine (Benowitz NL, 1990). In contrast to inhalation, the oral route of absorption is expected to result in gradual increase in nicotine concentrations in the brain with relatively little arteriovenous disequilibrium.

Metabolism and Excretion Nicotine is extensively metabolized to a number of metabolites, all of which are less active than the parent compound. Cotinine is the major metabolite, and is formed by two-step process, via CYP450 enzyme (CYP2A6) and aldehyde oxidase. As cotinine has a half-life of 15-20 hours and its blood levels are 10 times higher than nicotine, it is often used as a marker to confirm smoking abstinence. Plasma nicotine levels decline in a bi-exponential manner, with a short initial half life of approximately 7-10 minutes followed by an elimination half-life of approximately 2 hours (range 1-4 hours). Total clearance for nicotine following intravenous infusion ranges from approximately 62 to 89 L/h. Renal clearance for nicotine is estimated to be about 5-25% of total clearance. Nicotine and its metabolites are excreted almost exclusively in the urine. The renal excretion of unchanged nicotine is highly dependent on urinary pH; urinary pH < 5, an average 23% of the nicotine dose is excreted unchanged. When urinary pH is maintained above 7.0, urinary excretion of unchanged nicotine reduces to 2%. Average renal clearance is 1L/h in alkaline urine and 14.7 L/h in acidic urine.

2.3 Intrinsic Factors

Pharmacokinetics of nicotine from Mini Mint Lozenges was not studied with regard to intrinsic factors such as age, renal and hepatic impairment, pregnancy, labor and delivery, nursing mothers, and ambulatory patients, etc. Since this is just a reformulated product and was bioequivalent to the approved Commit® lozenges, these data are not required to be acquired for this product

2.4 Extrinsic Factors

Pharmacokinetics of nicotine from Mini Mint Lozenges was not studied with regard to interactions with drugs, herbal products, diet, and smoking, etc. Since this is just a reformulated product and was bioequivalent to the approved Commit® lozenges, these data are not required to be acquired for this product

2.5 General Biopharmaceutics

2.5.1 Was bioequivalence demonstrated between the proposed to-be-marketed formulation and the reference formulation?

BE was demonstrated for nicotine between Mini Mint Lozenge and commercial Commit Lozenge.

Three BE studies (2 mg strength in study S3010445, 4 mg strength in S3010466, and 2 mg and 4 mg strengths in study S3010567) were conducted to demonstrate the bioequivalence of nicotine between Mini Mint Lozenges and Commit Lozenge. The BE

criteria were met in all the three studies. Among the three studies, study S3010567 was considered to be the pivotal study. For the pivotal BE study S3010567, the least squares geometric mean ratios, test-to-reference, for C_{max} , $AUC_{(0-t)}$, and $AUC_{(0-inf)}$ ranged from 85.40% to 95.12% and the associated 90% confidence intervals were within the 80%-125% equivalence window, demonstrating that the two products were bioequivalent. The mean nicotine conc.-time profiles and the statistical analysis are shown in Figure 2.5.1 and Table 2.5.1, respectively.

Figure 2.5.1: Mean Nicotine Plasma Concentration-Time Profiles (Study S3010567)

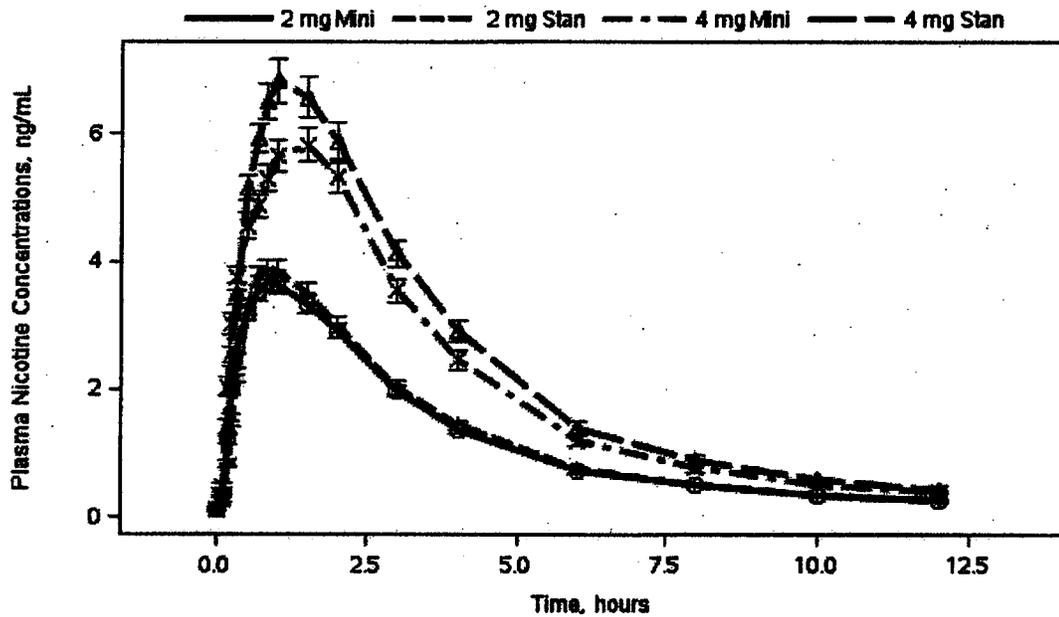


Table 2.5.1. Statistical Comparison between Mini Lozenge and Standard Lozenge (Study S3010567).

Table 1: 2mg PK Parameters Based on Adjusted Concentrations

| Parameter | (N) Mean ¹ ± S.D. | | *Ratio: Mini/Standard | |
|------------------------------------|------------------------------|----------------------|-----------------------|-------------------|
| | Mini | Standard | Estimate | 90% CI |
| C _{max} (ng/ml) | (38) 3.93 ± 1.14 | (35) 4.18 ± 1.34 | 95.12% | [90.37%, 100.11%] |
| AUC ₍₀₋₄₎ (ng·hr/ml) | (38) 14.02 ± 5.18 | (35) 14.98 ± 5.97 | 94.09% | [90.22%, 98.12%] |
| AUC _(0-∞) (ng·hr/ml) | (38) 15.30 ± 5.74 | (35) 16.32 ± 6.39 | 93.92% | [90.04%, 97.97%] |

Source: Table 9.2.2.1a

¹ Unadjusted treatment means

* Ratio of geometric means

Table 2: 4mg PK Parameters Based on Adjusted Concentrations

| Parameter | (N) Mean ¹ ± S.D. | | *Ratio: Mini/Standard | |
|------------------------------------|------------------------------|-----------------------|-----------------------|------------------|
| | Mini | Standard | Estimate | 90% CI |
| C _{max} (ng/ml) | (32) 6.28 ± 2.04 | (35) 7.40 ± 2.77 | 85.40% | [80.35%, 90.78%] |
| AUC ₍₀₋₄₎ (ng·hr/ml) | (32) 24.06 ± 9.14 | (35) 27.32 ± 12.19 | 90.39% | [85.91%, 95.09%] |
| AUC _(0-∞) (ng·hr/ml) | (32) 25.72 ± 9.98 | (34) 29.61 ± 13.11 | 90.57% | [86.21%, 95.15%] |

Source: Table 9.2.2.2a

¹ Unadjusted treatment means

* Ratio of geometric means

Source: CSR s3010567 p10

2.5.2 Were there any issues during the bio-analytical inspection and if yes, was it resolved?

Yes, two potential issues were raised during the bio-analytical inspection by the Division of Scientific Investigations (DSI). Sponsor adequately addressed these two issues by reanalyzing the plasma samples from study S3010567 using new QC samples and calibration curve range.

During DSI inspection, two issues were raised resulting in the issuance of Form 483 to the firm. Following is an extract of the issues (in bold) and DSI's assessment of these issues in italics (see DSI review dated 02/25/2009 by Dr. Xikui Chen for additional details):

"1) The quality control samples (3.00, 30.0 and 150 ng/mL) and calibration range (1.00 to 200 ng/mL) for nicotine used in the study were not representative of the nicotine plasma concentrations observed in study plasma samples. For example, the mean peak nicotine concentrations (C_{max}) following dosing of 2 and 4 mg lozenge were 4.3 to 4.5 ng/mL and 6.7 to 7.7 ng/mL, respectively. These mean C_{max} values were much lower than the mid QC value (30 ng/mL).

"In response to the FDA 483 observations, MDSPS reanalyzed all the study plasma samples collected in the 2 and 4 mg nicotine lozenges studies. In the reanalysis, quality control samples at concentrations of 0.60, 3.00 and 7.50 ng/mL, and calibration range of 0.20 ng/mL to 10.0 ng/mL were utilized. The QC samples and calibration curve range used in the reassay (December 19, 2008 to January 6, 2009), were found to be representative of the plasma nicotine concentrations generated in the studies.

2) The LC/MS/MS assay (LLOQ = 1.00 ng/mL) does not have sufficient sensitivity to measure nicotine levels for at least three half lives in the study of 2 mg lozenges. The total AUC (AUC_{0-inf} values included a large extrapolated component. For example: the ratio of AUC_{0-4} / AUC_{0-inf} was 0.73 for test group, and 0.75 for reference group.

Upon the request of the sponsor, MDSPS reanalyzed all the study samples from the 2 and 4 mg nicotine lozenges study using 0.20 ng/ml as the lower limited of quantitation (LLOQ). The LLOQ at 0.2 ng/mL was validated and the supporting data are provided in Amendment 2 of the Validation Report. This LC/MS/MS assay (LLOQ = 0.20 ng/ml) was able to measure nicotine levels for more than three half lives in both the 2 and 4 mg nicotine lozenges studies. Please note that the study plasma samples were stored at -20°C for 10 months prior to the reanalysis performed in December 2008. A review of stability data in Validation Amendment 2 showed that plasma samples were stable for 521 days when stored at -20°C.

Following our evaluation of the inspectional findings and the response, DSI is of the opinion that MDSPS has adequately addressed the Form FDA-483 Observations, and we recommend that the clinical and analytical data of Study S3010567 be accepted for review."

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutical studies?

Method 1 (SIT-BAM-48) The quantitative determination of nicotine in human plasma was done by a validated HPLC/MS/MS method. Specifically, human plasma containing nicotine and the internal standard nicotine-d3, were extracted with an organic solvent (acetonitrile) and the supernatant was transferred onto an Applied Biosystems API 4000 LC-MS-MS in positive ion MRM mode equipped with a HPLC column. The peak area of the m/z 163.1→132.1 nicotine product ion was measured against the peak area of the m/z

166.2→132.1 for the nicotine-d3 internal standard product ion. Quantitation was performed using separate weighted ($1/x^2$ for each analyte) linear least squares regression analyses generated from fortified plasma calibration standards prepared immediately prior to each run. This analytical method was used in studies S3010445 and S3010456.

Method 2 (MDS study AA33664) The quantitative determination of nicotine in human plasma was done by a validated HPLC/MS/MS method. An aliquot of human plasma (EDTA) containing each analyte and internal standard was extracted using a solid phase extraction procedure. The extracted samples were analyzed by an HPLC equipped with an AB | MDS Sciex API 5000 mass spectrometer. Positive ions were monitored in the multiple reaction monitoring (MRM) mode. Quantitation was determined using a weighted linear regression analysis ($1/x^2$) of peak area ratios of each analyte and internal standard. This analytical method was used in study S3010567.

2.6.2 How was the assay performed for nicotine?

The assay performance from all the studies is shown in Table 2.6.2.

Table 2.6.2 The Analytical Assay Performance.

| Study | SIT-BAS48 (S3010445 and S3010456) | AA33664 (S3010567) | |
|-----------------------------|---|---------------------------------------|--|
| | | Old Assay | New Assay |
| Measured Conc. range | | 1.01-16.1 ng/mL | 0.2-15.8 ng/mL |
| Calibration standard | | | |
| Range | 1.00-50ng/mL | 1.00-50.0 ng/mL | 0.2-10.0 ng/mL |
| Precision | 3.1-4.4% | 1.8-3.8% | 2.9-4.1% |
| bias | -0.8-0.8% | -1.5-0.8% | -2.0%-2.4% |
| Linearity (R^2) | >0.989 | >0.995 | >0.993 |
| QC sample | | | |
| Range | 2.50, 5.00, 15.0 ng/mL | 3.00, 30.00, 150, and 300 ng/mL | 0.600, 3.00, and 7.50 ng/mL |
| precision | 2.8-4.8% | 3.5-4.6% | ≤6.5% |
| bias | -1.5-2.4% | -8.0-1.3% | -7.5—1.0% |
| Stability | | | |
| Long-term stability | 56 days in plasma at -20 °C | 139 days in plasma at -20 °C | 521 days in plasma at -20 °C |
| Short-term stability | 26 h at RT | 25 h at RT | 27 hr in polypropylene tubes at RT |
| Freeze-thaw stability | 3 cycles | 6 cycles | 6 cycles |
| Post-preparative stability | 17 days in methanol for | 116 days in methanol at 5 | 135 hr in a polypropylene 96 well plate at 5 °C |

| | | | |
|----------------------------|------------------------------|---------------|---|
| | stock solution at - 20 °C | °C | |
| Processed sample integrity | 68 h at 5 °C, 26 h at RT | 135 h at 5 °C | 138 h in a polypropylene 96 well plate at 5 °C |

2.6.3 What was the variability in the PK parameter estimates in this application?

*The within study variability (CV%) ranged from 25% to 46% for C_{max}, from 37% to 70% for AUC_{0-t}, and from 33% to 69% for AUC_{inf} for 2 and 4 mg Mini Lozenge combined. The estimated C_{max} varied from 3.93 to 6.88 ng/mL, AUC_{0-t} from 10.68 to 26.91 ng*h/mL, and AUC_{inf} from 14.89 to 31.43 ng*h/m for 2 mg Mini Lozenge. The estimated C_{max} varied from 6.28 to 7.23 ng/mL, AUC_{0-t} from 20.67 to 24.69 ng*h/mL, and AUC_{inf} from 25.60 to 28.68 ng*h/m, for 4 mg Mini Lozenge.*

As shown in the table below, the within study variability (CV%) ranged from 25% to 46% for C_{max}, from 37% to 70% for AUC_{0-t}, and from 33% to 69% for AUC_{inf} for nicotine cross all the doses and formulations investigated. The estimated C_{max} varied from 3.93 to 6.88 ng/mL, AUC_{0-t} from 10.68 to 27.31 ng*h/mL, and AUC_{inf} from 14.89 to 31.77 ng*h/mL at 2 mg cross all formulations. The estimated C_{max} varied from 6.28 to 7.61 ng/mL, AUC_{0-t} from 20.67 to 27.32 ng*h/mL, and AUC_{inf} from 25.60 to 30.26 ng*h/mL at 4 mg cross all formulations. The big variability of nicotine exposure at 2 mg across different studies might be attributed to race difference (Nakajima, CPT, 2006). Study S2010445 was conducted in India, where all the subjects were Asians. The studies S3010456 and S3010567 were conducted in US, where majority of the study subjects were white.

Table 2.6.3: PK parameter estimates from in vivo studies.

| Study | Batch No. | Dose (mg) | C _{max} mean (CV%) (ng/mL) | AUC _{0-t} mean (CV%) (ng*h/mL) | AUC _{inf} mean (CV%) (ng*h/mL) |
|-------------------------|-------------|-----------|--|---|---|
| S3010445 | | | | | |
| | GSK5497B021 | STD: 2 mg | 6.58 (29) | 27.31 (44) | 31.77 (33) |
| S3010456 | | | | | |
| | GSK5498B021 | STD: 4 mg | 7.61 (37) | 25.63 (57) | 30.26 (56) |
| S3010567 (old assay) | | | | | |
| | 8A21 | STD: 2 mg | 4.32 (30) | 11.36 (48) | 15.59 (39) |
| | | | | | |
| | 8A07 | STD: 4 mg | 7.24 (38) | 22.63 (50) | 27.55 (47) |
| S3010567 (new assay) | | | | | |
| | 8A21 | STD: 2 mg | 4.18 (32) | 14.98 (40) | 16.32 (39) |
| | | | | | |
| | 8A07 | STD: 4 mg | 7.40 (37) | 27.32 (45) | 29.61 (44) |

3 Detailed Labeling Recommendations

(From a Clinical Pharmacology perspective, there are no new labeling changes proposed by the sponsor.

4 Appendices

4.1 Proposed Package Insert

b(4)

b(4)

6 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

b(4)

4.2. Individual Study Review

S3010445

Study Title: A Single Dose Bioavailability Study of 2 mg Nicotine Polacrilex Mini Lozenge

Objectives: Compare the pharmacokinetic profile of 2 mg nicotine polacrilex mini lozenge and 2 mg nicotine polacrilex standard lozenge.

Study Design: This Phase II pharmacokinetic (PK) clinical study was a single-center, open-label, randomized, two-way crossover design. The study treatments were a single dose of 2 mg nicotine polacrilex mini lozenge (batch number GSK5517B011) and 2 mg nicotine polacrilex standard lozenge (batch number GSK5497B021). Subjects were confined to the study site for approximately 36 hours during each study session, 24 hours before study treatment dosing and 12 hours post dosing during which the PK samples were obtained. Subjects abstained from smoking during the confinement period. The study periods were separated by a washout of at least 48 hours during which subjects were allowed to smoke. Blood samples for PK analyses were taken at post dosing- 5, 10, 15, 20, 30, 40, and 50 minutes and 1, 1.5, 2, 3, 4, 6, 8, 9, 10 and 12 hours post-dose in each treatment period.

Study Population: A total of 28 healthy male (n=24) and female (n=4) subjects between 21 and 43 years of age who smoked their first cigarette more than 30 minutes of awakening, were generally healthy, had a body mass index of 19-27 kg/m², were enrolled in this study. All subjects were Asian. All subjects completed the study.

Bioanalytical Analysis: Nicotine plasma concentrations were measured by an HPLC equipped with a MDS Sciex API 4000 mass spectrometer. Positive ions were monitored in the multi reaction-monitoring (MRM) mode. Quantification was by peak area ratio. (AA40098)

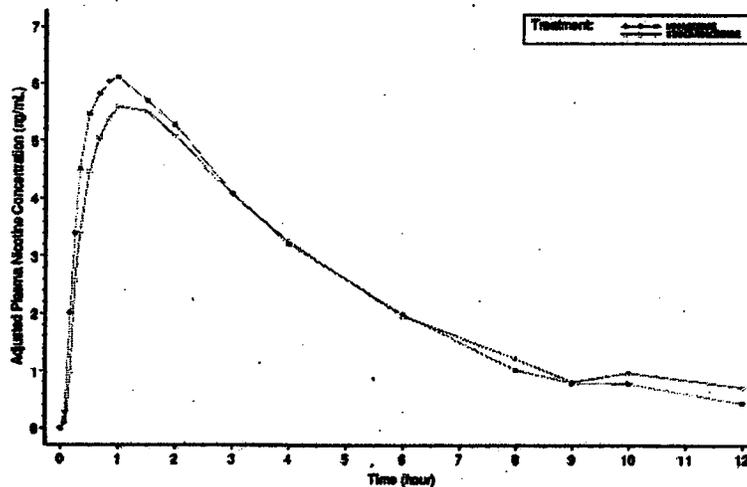
Table: Summary of assay performance of nicotine.

| Analyte | SC Range | SC precision | SC accuracy | QC Samples | QC precision | QC accuracy |
|----------|-----------------|--------------|-------------|----------------------------------|--------------|-------------|
| nicotine | 1.00-50.0 ng/mL | 2.8-3.9% | 98.5-101% | 2.50, 15.0, 5.00, and 37.5 ng/mL | 2.8-4.2% | 99.2-102.4% |

Data Analysis: Average bioequivalence between the 2 mg mini lozenge (test product) and the 2 mg standard lozenge (reference) was assessed using the two one-sided tests procedure for $AUC_{(0-t)}$ and C_{max} . Linear mixed effects models were used to estimate treatment effects. The treatment difference and its confidence interval (CI) were exponentiated to obtain the ratio of the geometric means between the test and reference products and its CI. If this CI lay within the range of 0.80 to 1.25 for $AUC_{(0-t)}$ and C_{max} , then it was concluded that the products were bioequivalent.

Pharmacokinetic Results: Mean ratios for $AUC_{(0-t)}$ and C_{max} for 2 mg mini lozenge versus 2 mg standard lozenge were similar. The 95% CI for $AUC_{(0-t)}$ and C_{max} all lay entirely within the interval of [80%,125%], indicating that the 2 mg mini lozenge is bioequivalent to the 2 mg standard lozenge. The results of the PK analysis performed on the unadjusted data were similar to the results for baseline-adjusted data.

Figure: Mean Adjusted Nicotine Plasma Concentrations



Source: Figure 9.2.1.1 in P50 of CSR

Table: Summary of Baseline-Adjusted Nicotine Pharmacokinetic Variables

| Parameter | Means* | | Ratio: Mini/Standard | |
|-----------------------------|--------|----------|----------------------|------------------|
| | Mini | Standard | Estimate | 90% CI |
| C _{max} (ng/ml) | 6.88 | 6.58 | 104.86% | [98.70%,113.27%] |
| AUC(0-t) (ng*hr/ml) | 26.91 | 27.31 | 98.55% | [88.57%,109.86%] |

*Geometric adjusted means calculated by exponentiating adjusted mean log

Source: Table 3 in P29 of CSR

In addition, T_{max}, k_{el} and T_{1/2} were all comparable.

Conclusion: The 2 mg nicotine polacrilex mini lozenge was bioequivalent to the 2 mg nicotine polacrilex standard lozenge.

S3010466

Study Title: A Single Dose Bioavailability Study of 4 mg Nicotine Polacrilex Mini Lozenge

Objectives: Compare the pharmacokinetic profile of 4 mg nicotine polacrilex mini lozenge and 4 mg nicotine polacrilex standard lozenge.

Study Design: This Phase II pharmacokinetic (PK) clinical study was a single-center, open-label, randomized, two-way crossover design. The study treatments were a single dose of 4 mg nicotine polacrilex mini lozenge (batch number GSK5526B011) and 4 mg nicotine polacrilex standard lozenge (batch number GSK5498B021). Subjects were confined to the study site for approximately 36 hours during each study session, 24 hours before study treatment dosing and 12 hours post dosing during which the PK samples were obtained. Subjects abstained from smoking during the confinement period. The study periods were separated by a washout of at least 48 hours during which subjects were allowed to smoke. Blood samples for PK analyses were taken at post dosing- 5, 10, 15, 20, 30, 40, and 50 minutes and 1, 1.5, 2, 3, 4, 6, 8, 9, 10 and 12 hours post-dose in each treatment period.

Study Population: Male or female volunteers aged 18 to 55 years who smoked their first cigarette within 30 minutes of awakening, were generally healthy, had a body mass index of 19-27 kg/m², and provided written consent were invited to enter this study. Twenty-eight subjects were randomly assigned to treatment as planned. A total of 28 healthy male (n=19) and female (n=9) subjects between 20 and 51 years of age were enrolled in this study. Ethnic origin was 97% white (n=27) and 3% black (n=1). Of these 28 subjects, 27 completed at least one study treatment and 24 completed both study treatments with determinable PK parameters. Four subjects withdrew consent and did not complete the study.

Bioanalytical Analysis: Nicotine plasma concentrations were measured by an HPLC equipped with a MDS Sciex API 4000 mass spectrometer. Positive ions were monitored in the multi reaction-monitoring (MRM) mode. Quantification was by peak area ratio.

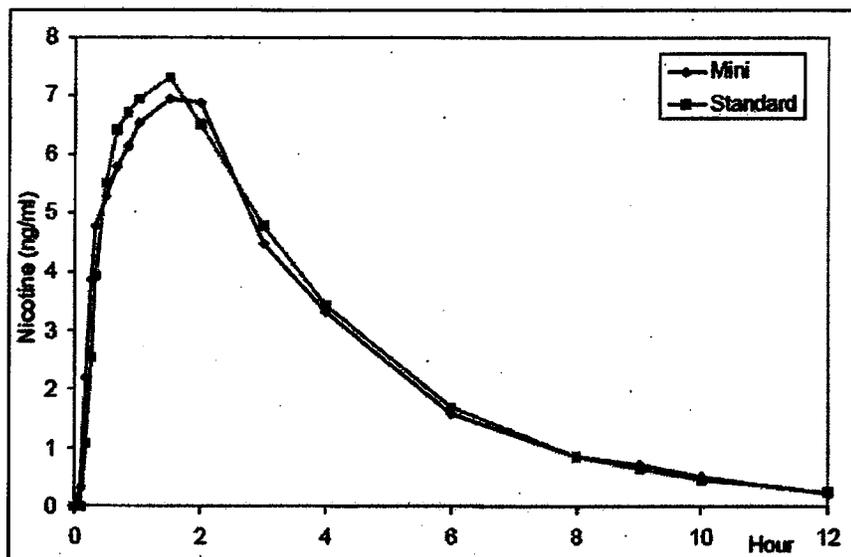
Table: Summary of assay performance of nicotine.

| Analyte | SC Range | SC precision | SC accuracy | QC Samples | QC precision | QC accuracy |
|----------|-----------------|--------------|-------------|----------------------------------|--------------|-------------|
| nicotine | 1.00-50.0 ng/mL | 3.1-4.2% | 99.2-100.8% | 2.50, 15.0, 5.00, and 37.5 ng/mL | 3.3-4.8% | 98.7-101.6% |

Data Analysis: 4 mg standard lozenge (reference) was assessed using the two one-sided tests procedure for $AUC_{(0-t)}$ and C_{max} . Linear mixed effects models were used to estimate treatment effects. The treatment difference and its confidence interval (CI) were exponentiated to obtain the ratio of the geometric means between the test and reference products and its CI. If this CI lay within the range of 0.80 to 1.25 for $AUC_{(0-t)}$ and C_{max} , then it was concluded that the products were bioequivalent.

Pharmacokinetic Results: Mean ratios for $AUC_{(0-t)}$ and C_{max} for 4 mg mini lozenge versus 4 mg standard lozenge were similar. The 95% CI for these all lay entirely within the interval of [0.80 -1.25], indicating that the 4 mg mini lozenge is bioequivalent to the 4 mg standard lozenge. The PK analysis performed on the unadjusted data was very similar to the results for baseline-adjusted data.

Figure: Mean Adjusted Nicotine Plasma Concentrations



Source: Figure 9.2.1.1 in P34 of CSR

Table: Summary of Baseline-Adjusted Nicotine Pharmacokinetic Variables

| Parameter | Means* | | Ratio: Mini/Standard | |
|------------------------------------|--------|----------|----------------------|----------------|
| | Mini | Standard | Estimate | 90% CI |
| C _{max} (ng/mL) | 7.23 | 7.61 | 95.0% | [87.4%,103.3%] |
| AUC _(0-t) (ng*hr/mL) | 24.39 | 25.63 | 95.2% | [89.8%,100.9%] |

| Parameter | (N) Mean/Median | | Ratio: Mini/Standard | |
|--------------------------------------|-----------------|------------|----------------------|----------------|
| | Mini | Standard | Estimate | 90% CI |
| C _{max} (ng/mL)* | (26) 7.23 | (25) 7.61 | 95.0% | [87.4%,103.3%] |
| AUC _(0-t) * (ng*hr/mL) | (26) 24.39 | (25) 25.63 | 95.2% | [89.8%,100.9%] |
| AUC _(0-∞) * (ng*hr/mL) | (25) 28.68 | (25) 30.26 | 94.8% | [89.2%,100.7%] |
| T _{max} (hr) ** | (26) 1.50 | (25) 1.25 | | |
| K _{el} (1/hr) ** | (25) 0.36 | (25) 0.33 | | |
| T _{1/2} (hr) ** | (25) 1.90 | (25) 2.12 | | |

* Geometric adjusted means calculated by exponentiating adjusted mean log

** Median

Source: Table 4 in P34 of CSR

Conclusions: The 4 mg nicotine polacrilex mini lozenge was bioequivalent to the 4 mg nicotine polacrilex standard lozenge.

S3010567

Study Title: A Single Dose Bioequivalence Study of 2 and 4 mg Mini Nicotine Lozenges

Objectives: to confirm bioequivalence of the following treatments in terms of nicotine AUC_(0-t) and C_{max}:

- 2 mg nicotine polacrilex mini lozenge (2 mg mini lozenge) bioequivalent to 2mg nicotine polacrilex standard lozenge (2 mg standard lozenge)
- 4 mg nicotine polacrilex mini lozenge (4 mg mini lozenge) bioequivalent to 4mg nicotine polacrilex standard lozenge (4 mg standard lozenge).

Study Design: This study was a single center, randomized, open label, single dose, and four-way crossover in design. The study treatments were a single dose of 2 mg mini lozenge (batch number GSK5583B011), 2 mg standard lozenge (lot number 8A21), 4mg mini lozenge (batch number GSK5584B011) and 4 mg standard lozenge (lot number 8A07). Eligible study subjects were confined in the study facility for approximately 36 hours during each study session (for 24 hours pre dosing and for 12 hours post dosing)

during which pharmacokinetic blood samples were obtained. Subjects abstained from smoking during the confinement periods and were subjected to random measurements of expired carbon monoxide (CO) to confirm abstinence. Study sessions were separated by at least a 48-hour washout period during which subjects were allowed to smoke ad libitum.

Study Population: Male or female volunteers aged 18 to 55 years who smoked their first cigarette within 30 minutes of awakening, were generally healthy, had a body mass index of 19-27 kg/m², and provided written consent were invited to enter this study. A total of 40 healthy male (n=27) and female (n=13) subjects between 20 and 56 years of age were enrolled in this study. Ethnic origin was 85% white (n=34), 7.5% black (n=3), Asian (n=1), 2.5% Hispanic (n=1), and 2.5% American Indian (n=1). Eight subjects did not complete the four study treatment, two due to the withdrawal of consent, 3 due to no show up after check-in of Period 2, one due to failed drug screen at the check-in in Period 3, and one due to adverse event, and one due to tooth extraction after the Period 2.

Bioanalytical Analysis: Nicotine plasma concentrations were measured by an HPLC equipped with a MDS Sciex API 4000 mass spectrometer. Positive ions were monitored in the multi reaction-monitoring (MRM) mode. Quantification was by peak area ratio.

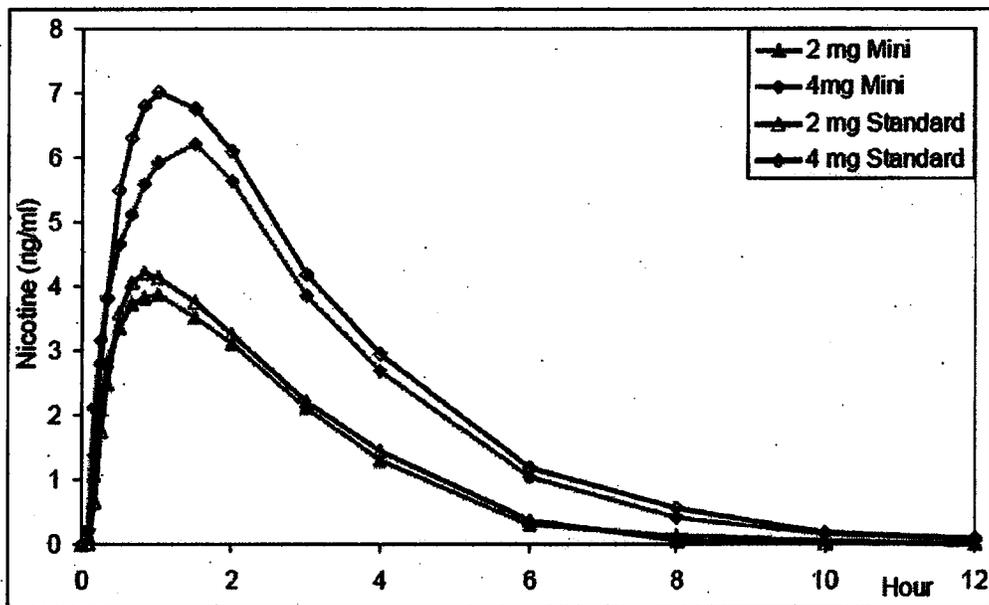
Table: Summary of assay performance of nicotine.

| Assay | SC Range | SC precision | SC accuracy | QC Samples | QC precision | QC accuracy |
|-------------|-----------------|--------------|-------------|----------------------------------|--------------|-------------|
| Old SIT-BAM | 1.00-50.0 ng/mL | 1.8-3.8% | 98.5-100.8% | 2.50, 15.0, 5.00, and 37.5 ng/mL | <= 4.6% | 92.0-101.3% |
| new AA33664 | 0.20-10.0 ng/mL | 2.9-4.1% | 98-102.4% | 0.600, 3.00, and 7.50 ng/mL | <= 6.5% | 92.5-101% |

Data Analysis: Average bioequivalence between the 2 mg mini lozenge (test product) and the 2 mg standard lozenge (reference) as well between the 4 mg mini lozenge (test product) and the 4 mg standard lozenge (reference) was assessed using the two one-sided tests procedure for AUC_(0-t) and C_{max}. Linear mixed effects models were used to estimate treatment effects. The treatment difference and its 90% confidence interval (CI) were exponentiated to obtain the ratio of the geometric means between the test and reference products and its CI.

Pharmacokinetic Results: Mean ratios for 2 mg mini lozenge versus 2 mg standard lozenge were around 0.95 for both AUC_(0-t) and C_{max}. The 90% CI for these all lay entirely within the interval of [0.8, 1.25], indicating that the 2 mg mini lozenge is bioequivalent to the 2 mg standard lozenge. Mean ratios for 4 mg mini lozenge versus 4 mg standard lozenge were around 0.90 for both AUC_(0-t) and C_{max}. Furthermore, the 90% CI for these all lay entirely within the interval of [0.80, 1.25], indicating that the 4 mg mini lozenge is bioequivalent to the 4 mg standard lozenge.

Figure: Mean Adjusted Nicotine Plasma Concentrations (Old Assay)



Source: Figure 9.2.1 in P32 of CSR

Table: 2 mg PK Parameters Based on Adjusted Concentrations (Old Assay)

| Parameter | Mean (N) | | *Ratio: Mini/Standard | |
|-------------------------------|------------|------------|-----------------------|-------------------|
| | Mini | Standard | Estimate | 90% CI |
| C_{max} (ng/ml) | 4.27 (38) | 4.49 (35) | 95.12% | [90.00%, 100.53%] |
| $AUC_{(0-4)}$ (ng-hr/ml) | 11.94 (38) | 12.35 (35) | 94.12% | [87.78%, 100.92%] |
| $AUC_{(0-\infty)}$ (ng-hr/ml) | 16.39 (36) | 16.48 (34) | 95.44% | [88.22%, 103.25%] |

| Parameter | Median (N) | | Difference: Mini - Standard | |
|-------------------|------------|-----------|-----------------------------|---------|
| | Mini | Standard | Median | P-Value |
| T_{max} (hours) | 0.87 (37) | 0.84 (34) | 0.000 | 0.7377 |
| $T_{1/2}$ (hours) | 1.85 (35) | 1.97 (33) | -0.046 | 0.5786 |
| K_{el} (1/hour) | 0.37 (35) | 0.35 (33) | 0.009 | 0.5189 |

Table: 4 mg PK Parameters Based on Adjusted Concentrations (Old Assay)

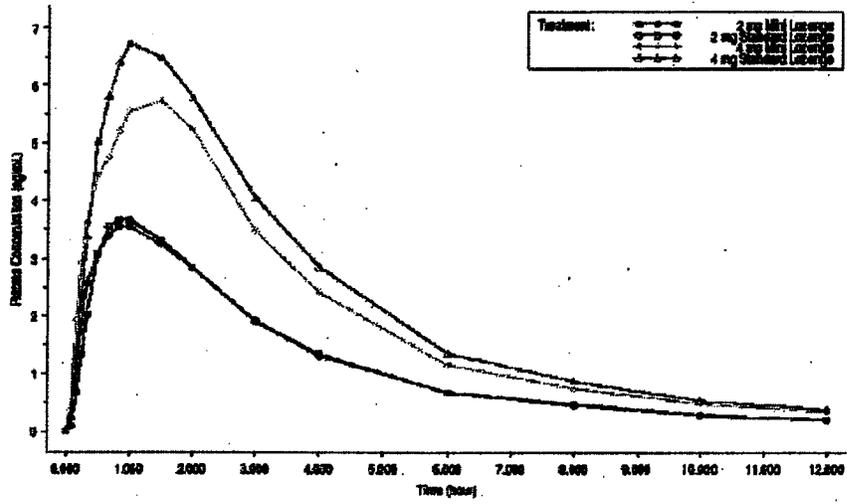
| Parameter | Mean (N) | | *Ratio: Mini/Standard | |
|----------------------------------|------------|------------|-----------------------|---------------------|
| | Mini | Standard | Estimate | 90% CI |
| C_{max} (ng/ml) | 6.74 (32) | 7.71 (35) | 88.39% | [82.85%, 94.32%] |
| $AUC_{(0-t)}$ (ng-hr/ml) | 22.71 (32) | 25.41 (35) | 91.32% | [85.29%, 97.78%] |
| $AUC_{(0-\infty)}$ (ng-hr/ml) | 27.12 (31) | 30.33 (32) | 92.92% | [87.33%, 98.87%] |

| Parameter | Median (N) | | Difference: Mini - Standard | |
|-------------------|------------|-----------|-----------------------------|---------|
| | Mini | Standard | Median | P-Value |
| T_{max} (hours) | 1.00 (32) | 1.00 (34) | 0.016 | 0.2809 |
| $T_{1/2}$ (hours) | 1.93 (31) | 1.92 (31) | 0.081 | 0.5943 |
| K_{el} (1/hour) | 0.36 (31) | 0.36 (31) | -0.010 | 0.5804 |

Source: P31 and P34 of CSR

Results from the new analytical method are listed below:

Figure 1: Mean Adjusted Nicotine Plasma Concentrations



Source: Table 9.2.1a, Figure 9.2.1.1a

Source: Figure 1 in P11 of CSR

Table 1: 2mg PK Parameters Based on Adjusted Concentrations

| Parameter | (N) Mean ¹ ± S.D. | | *Ratio: Mini/Standard | |
|------------------------------------|------------------------------|----------------------|-----------------------|-------------------|
| | Mini | Standard | Estimate | 90% CI |
| C _{max} (ng/ml) | (38) 3.93 ± 1.14 | (35) 4.18 ± 1.34 | 95.12% | [90.37%, 100.11%] |
| AUC _(0-t) (ng·hr/ml) | (38) 14.02 ± 5.18 | (35) 14.98 ± 5.97 | 94.09% | [90.22%, 98.12%] |
| AUC _(0-∞) (ng·hr/ml) | (38) 15.30 ± 5.74 | (35) 16.32 ± 6.39 | 93.92% | [90.04%, 97.97%] |

Source: Table 9.2.2.1a

¹ Unadjusted treatment means

* Ratio of geometric means

Table 2: 4mg PK Parameters Based on Adjusted Concentrations

| Parameter | (N) Mean ¹ ± S.D. | | *Ratio: Mini/Standard | |
|------------------------------------|------------------------------|-----------------------|-----------------------|------------------|
| | Mini | Standard | Estimate | 90% CI |
| C _{max} (ng/ml) | (32) 6.28 ± 2.04 | (35) 7.40 ± 2.77 | 85.40% | [80.35%, 90.78%] |
| AUC _(0-t) (ng·hr/ml) | (32) 24.06 ± 9.14 | (35) 27.32 ± 12.19 | 90.39% | [85.91%, 95.09%] |
| AUC _(0-∞) (ng·hr/ml) | (32) 25.72 ± 9.98 | (34) 29.61 ± 13.11 | 90.57% | [86.21%, 95.15%] |

Source: Table 9.2.2.2a

¹ Unadjusted treatment means

* Ratio of geometric means

Source: P10 of CSR

Conclusions: The results from both the analytical methods demonstrated bioequivalence between the 2 mg mini lozenge and 2 mg standard lozenge and between the 4 mg mini lozenge and 4 mg standard lozenge.

4.3 Cover Sheet and OCP Filing/Review Form

| | |
|---|-------------|
| Office of Clinical Pharmacology | |
| New Drug Application Filing and Review Form | |
| <u>General Information About the Submission</u> | |
| Information | Information |

| | | | |
|----------------------------------|--|-------------------------|---|
| NDA Number | 22-360 | Brand Name | Commit® Mini Mint Lozenges |
| OCP Division (I, II, III) | II | Generic Name | Nicotine Polacrilex |
| Medical Division | Anesthesia, analgesia, and rheumatology products | Drug Class | |
| OCP Reviewer | Ping Ji, PhD | Indication(s) | Reduction of withdrawal Symptoms, Including Nicotine Craving associated with Quitting Smoking |
| OCP Team Leader | Suresh Doddapaneni, Ph.D. | Dosage Form | lozenge |
| | | Dosing Regimen | Take one lozenge every 1 to 2 hours and at least 9 lozenges each day for the first 6 weeks. After six weeks, take one lozenge every two to four hours. Take one every 4-8 hours between week 10 and 12. Stop taking it after week 12. |
| Date of Submission | July 18, 2008 | Route of Administration | Oral |
| Estimated Due Date of OCP Review | March 27, 2009 | Sponsor | GlaxoSmithKline Consumer Healthcare |
| PDUFA Due Date | May 18, 09 | Priority Classification | S |
| Division Due Date | | | |

Clin. Pharm. and Biopharm. Information

| | "X" included if filing at | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|--|---------------------------|-----------------------------|----------------------------|--|
| STUDY TYPE | | | | |
| 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 | | | same as referenced product Commit 2 and 4 mg |
| Reference Bioanalytical and Analytical Methods | x | | | MDS pharma is the CRO |
| Biopharmaceutics | | | | |
| Absolute bioavailability: | | | | |
| Relative bioavailability - solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| Bioequivalence studies - traditional design; single dose: | x | 3 | 3 | S3010445, S3010446, and S3010567 |
| replicate design; single / multi dose: | | | | |

| | | | | |
|---|-------------------|-----------------|----------|--|
| Food-drug interaction studies: | | | | |
| Dissolution: | | | | |
| Effects of attempt to defeat CRT on the PK | | | | |
| (IVIVC): | | | | |
| Bio-wavier request based on BCS | | | | |
| BCS class | | | | |
| Other biopharmaceutical studies | | | | |
| Other Clin Pharm Studies | | | | |
| Genotype/phenotype studies: | | | | |
| Chronopharmacokinetics | | | | |
| Pediatric development plan | | | | |
| Literature References | | | | |
| Total Number of Studies | | 5 | 5 | |
| Filability and QBR comments | | | | |
| | "X" if yes | Comments | | |
| Application filable ? | x | | | |
| Comments sent to firm ? | | | | |
| QBR questions (key issues to be considered) | | | | |
| Other comments or information not included above | | | | |
| Primary reviewer Signature and Date | | | | |
| Secondary reviewer Signature and Date | | | | |

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

/s/

Ping Ji
4/1/2009 09:49:50 AM
UNKNOWN

Suresh Doddapaneni
4/2/2009 07:12:32 AM
BIOPHARMACEUTICS