CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-330

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	21-330
Brand Name:	[redacted]
Generic Name:	Nicotine Polacrilex
Dosage form and Strength:	2 and 4 mg
Route of administration:	Oral (Buccal)
Indication:	[redacted]
Sponsor:	GlaxoSmithKline (GSK)
Type of submission:	Amendment to a pending application
Clinical Division:	Anesthetic, Clinical Care, and Addiction (HFD-180)
OCPB Division:	HFD-870/DPE II
Priority:	Standard
Submission date:	03/11/02 (Dissolution Data/Information)
OCPB Consult date:	09/06/02
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Suresh Doddapaneni, Ph.D.

I. Executive Summary

Nicotine as a nicotine replacement therapy (NRT) is available in many different formulations, such as polacrilex chewing gum, transdermal patch, inhaler and nasal spray. On 12/15/00, the sponsor submitted NDA 21-330 for a new dosage form, Nicotine Procrilex 2 and 4 mg Lozenges.

This NDA was deemed approvable (letter dated 10/19/01) with several deficiencies identified. The Agency's Comment # 4 indicated as follows (page 3):

"The following comments pertain to the specification for dissolution.

a. Provide acceptance criteria as follows:

1 hour: minimum and maximum

3 hours: minimum and maximum

6 hours: minimum

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b. Provide acceptance criteria in the USP Chapter <711> or Chapter <724> format.

c. Provide data and analysis to support the proposed acceptance criteria."

On 03/11/02, the sponsor responded with additional dissolution data and proposed new specifications. The sponsor's new data for nicotine 2 and 4 mg lozenges, and proposed specifications are reviewed and found acceptable.

A. Recommendation

The 03/11/02 submission addressing deficiency # 4 of the 10/19/01 aprovable letter has been reviewed and found to be acceptable. The proposed specifications as shown below for nicotine 2 and 4 mg lozenges at 1, 3, and 6 hrs are acceptable;

At 1 hr: ———
At 3 hr: ———
At 6 hr: Q: = ——

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09/10/02
Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Suresh Doddapaneni, Ph.D. 09/13/02

FT initialed by Suresh Doddapaneni, Ph.D. 09/13/02

cc: NDA 21-330, HFD-170 (C. Winchell, M. Theodorakis, D. Koble, V. Kao), HFD-870 (H. Malinowski, S. Doddapaneni, T. M. Chen).

II. Table of Contents

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

In the original submission, the dissolution methodology and specifications were as follows:

Apparatus Type: USP Type I, basket
Media: Phosphate buffer (pH 7.4)
Volume: 900 mL
Speed of Rotation: 100 rpm
Sampling Time(s): 1 hour and 8 hours
Dissolution Specification: Q —— at 1 hour and Q —— at 8 hours.

In the 10/19/01 approvable letter, the Agency's Comment # 4 indicated as follows (page 3):

"4. The following comments pertain to the specification for dissolution.

a. Provide acceptance criteria as follows:

1 hour: minimum and maximum

3 hours: minimum and maximum

6 hours: minimum

b. Provide acceptance criteria in the USP Chapter <711> or Chapter <724> format.

c. Provide data and analysis to support the proposed acceptance criteria."

On 03/11/02, the sponsor submitted additional dissolution data (5 stability batches per strength) with the following specifications proposed.

At 1 hr: ——
At 3 hr: ——
At 6 hr: Q = ——

Please see Appendix 1 for individual and mean dissolution data for details. Submitted and reviewed also was the survey of the dissolution data (at 1 and 8 hrs) from [redacted] commercial batches manufactured for non-US markets ([redacted]

The above new dissolution data were reviewed and it is concluded that the proposed specifications are acceptable.

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IV. Question Based Review

A. General Biopharmaceutics

1. Are the proposed dissolution specifications at 1, 3, and 6 hrs adequately validated and acceptable?

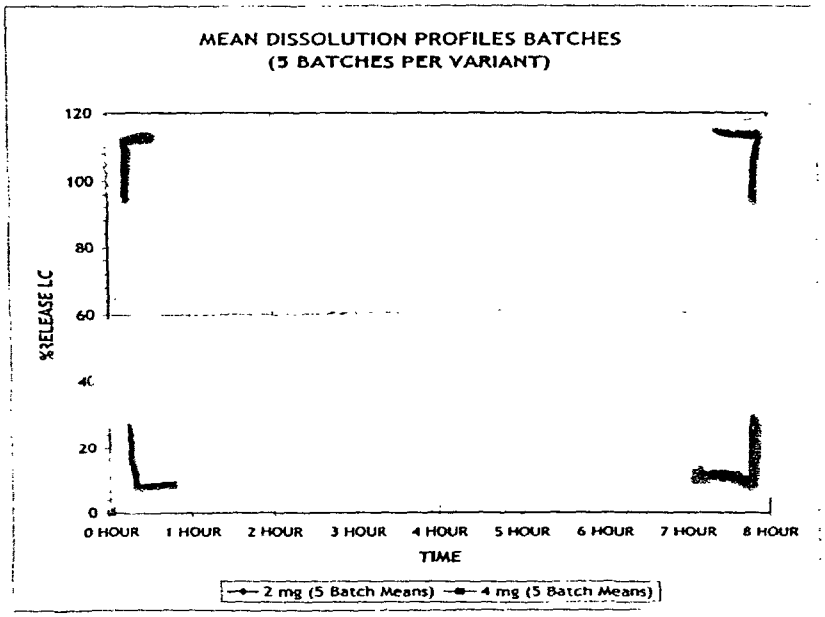
Yes. Review of individual data (n= [redacted] batch and 5 initial stability batches/per strength), showed that all had [redacted] dissolved at 6 hrs. The survey of [redacted] commercial batches (UK), however, showed that in 2 batches of 4 mg lozenge, it had one individual lozenge each dissolved [redacted] at 8 hrs [redacted] and [redacted] For the consideration of shelf life of the lozenges, the specification, i.e., Q= [redacted] at 6 hr proposed by the sponsor is, therefore, acceptable. The mean dissolution data and profiles of nicotine 2 and 4 mg lozenges are shown below:

Table 2. Mean Dissolution Data

Initial Stability Dissolution Profiles - All Batches (2 mg/4 mg)

	MEAN	MINIMUM	MAXIMUM	MEDIAN	STD DEV	%RSD
1 Hour	34			34	1.49	4.38
2 Hour	50			50	1.71	3.45
3 Hour	63			64	2.21	3.50
4 Hour	75			75	2.59	3.44
5 Hour	84			84	2.25	2.76
6 Hour	91			91	2.73	3.00
7 Hour	96			96	2.21	2.30
8 Hour	99			99	2.10	2.11

Figure 1. Mean Dissolution Profiles for Nicotine 2 and 4 mg Lozenges



V. Appendix

Appendix 1

Individual and Mean Dissolution Data

Initial Dissolution Profiles - 2 mg Stability Batches (5)

	BATCH NUMBER: 9009FP-									
Time	8001	9004	9005	0001	0002	AVERAGE MEAN	STD DEV	%RSD	MINIMUM	MAXIMUM
1 Hour						35	0.8	2.4		
2 Hour						50	1.5	3.0		
3 Hour						64	2.2	3.4		
4 Hour						77	2.4	3.1		
5 Hour						86	2.6	3.0		
6 Hour						92	2.9	3.2		
7 Hour						97	2.4	2.5		
8 Hour						100	2.3	2.3		
SSR NO:	P1901/01	P1901/02	P1901/03	P1954/01	P1954/02					

Initial Dissolution Profiles - 4 mg Stability Batches (5)

	BATCH NUMBER 9010FP-									
Time	8001	9004	9005	0001	0002	AVERAGE MEAN	STD DEV	%RSD	MINIMUM	MAXIMUM
1 Hour						33	0.8	2.6		
2 Hour						49	1.6	3.4		
3 Hour						62	2.1	3.3		
4 Hour						74	2.4	3.2		
5 Hour						83	2.4	3.0		
6 Hour						90	2.3	2.5		
7 Hour						95	1.9	2.0		
8 Hour						99	2.0	2.1		
SSR No:	P1900/01	P1900/02	P1900/03	P1956/01	P1956/02					

PROJECT ONE CENT (NICOTINE POLACRILEX LOZENGES)
INITIAL DISSOLUTION PROFILES FOR PACKAGE STABILITY BATCHES
2 MG VARIANT - MFC# 10449-002-0002

BATCH NO	SSR REF NO	LOZENGE SAMPLE	1 HOUR	2 HOUR	3 HOUR	4 HOUR	5 HOUR	6 HOUR	7 HOUR	8 HOUR
9009FP-8001	P1901/01									
		1								
		2								
		3								
		4								
		5								
		6								
		MEAN	36	51	66	78	86	93	97	100
		STD. DEV	0.8	1.8	0.8	0.8	1.2	1.4	1.5	1.7
		%RSD	2.3	3.5	1.2	1.1	1.4	1.5	1.5	1.7
9009FP-9004	P1901/02									
		1								
		2								
		3								
		4								
		5								
		6								
		MEAN	34	50	63	74	83	90	95	99
		STD. DEV	1.3	1.6	2.7	2.7	2.3	2.1	2.1	2.0
		%RSD	3.9	3.2	4.3	3.7	2.8	2.4	2.3	2.0
9009FP-9005	P1901/03									
		1								
		2								
		3								
		4								
		5								
		6								
		MEAN	35	48	61	74	83	88	94	96
		STD. DEV	1.3	1.4	3.1	1.2	1.9	1.4	1.2	1.5
		%RSD	3.5	2.8	5.0	1.6	2.3	1.5	1.3	1.6
9009FP-0001	P1954/01									
		1								
		2								
		3								
		4								
		5								
		6								
		MEAN	33	51	65	78	87	94	98	101
		STD. DEV	1.1	1.0	1.3	1.4	1.2	1.0	1.5	1.2
		%RSD	3.3	2.0	1.9	1.8	1.3	1.1	1.5	1.2
9009FP-0002	P1954/02									
		1								
		2								
		3								
		4								
		5								
		6								
		MEAN	36	52	66	79	89	95	100	102
		STD. DEV	0.9	1.4	1.4	1.9	1.6	1.0	1.5	1.4
		%RSD	2.5	2.7	2.1	2.4	1.8	1.1	1.5	1.3
ALL FIVE (5) BATCHES (30 Data Points)										
		MEAN	35	50	64	76	86	92	97	100
		STD. DEV	1.2	1.8	2.8	2.6	2.8	2.9	2.9	2.9
		%RSD	3.5	3.7	4.3	3.4	3.3	3.0	2.8	2.7

SOURCE DATE: SB Participany LIMS Sample Data Reports; Courtesy: H. Ochola, 27-Sept-2000

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PROJECT ONE CENT (NICOTINE POLACRILEX LOZENGES)
INITIAL DISSOLUTION PROFILES FOR PACKAGE STABILITY BATCHES
4 MG VARIANT - MFG# 10449-003-0002

BATCH NO	SSR REF NO	LOZENGE SAMPLE	1 HOUR	2 HOUR	3 HOUR	4 HOUR	5 HOUR	6 HOUR	7 HOUR	8 HOUR
9010FP-8001	P1900/01									
		1								
		2								
		3								
		4								
		5								
		6								
		MEAN	33	48	62	74	82	89	94	97
		STD. DEV	2.3	0.8	0.6	1.4	1.2	1.4	0.9	0.6
		%RSD	7.1	1.7	1.0	1.9	1.5	1.6	1.0	0.7
9010FP-9004	P1900/02									
		1								
		2								
		3								
		4								
		5								
		6								
		MEAN	32	47	60	71	80	87	93	97
		STD. DEV	1.8	2.7	3.0	3.4	3.0	1.8	1.9	1.5
		%RSD	5.7	5.6	5.0	4.8	3.8	2.1	2.1	1.6
9010FP-9005	P1900/03									
		1								
		2								
		3								
		4								
		5								
		6								
		MEAN	32	48	61	73	82	89	95	99
		STD. DEV	1.5	2.5	3.3	2.6	2.2	1.4	1.3	1.4
		%RSD	4.6	5.2	5.3	3.6	2.6	1.5	1.4	1.4
9010FP-0001	P1956/01									
		1								
		2								
		3								
		4								
		5								
		6								
		MEAN	34	51	65	76	85	91	96	99
		STD. DEV	0.0	0.0	0.5	0.0	0.0	0.9	1.0	1.0
		%RSD	2.7	1.2	0.8	1.0	0.9	1.0	1.0	1.0
9009FP-0002	P1956/02									
		1								
		2								
		3								
		4								
		5								
		6								
		MEAN	33	50	64	77	86	93	98	102
		STD. DEV	0.8	1.5	1.1	0.8	1.0	0.9	1.0	1.2
		%RSD	2.4	3.1	1.7	1.1	1.1	1.0	1.1	1.1
ALL FIVE (5) BATCHES										
		MEAN	33	49	62	74	83	90	95	99
		STD. DEV	1.6	2.2	2.6	2.9	2.8	2.4	2.2	2.3
		%RSD	5.0	4.4	4.1	3.9	3.4	2.7	2.4	2.3

SOURCE DATE: SD Parsippany LWG Sample Data Reports; Courtesy: H. Ochola, 27-Sept-2000

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/s/

Tien-Mien Chen
9/13/02 02:22:04 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
9/17/02 03:36:07 PM
BIOPHARMACEUTICS

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Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	N 21-330	Brand Name	Nicotine polacrilex lozenge
OCPB Division (I, II, III)	DPE-II	Generic Name	Nicotine
Medical Division	HFD-170	Drug Class	Lozenge
OCPB Reviewer	Shinja Kim	Indication(s)	Nicotine replacement therapy
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	2 and 4 mg
		Dosing Regimen	See the Review
Date of Submission	12/15/00	Route of Administration	Oral
Estimated Due Date of OCPB Review	08/15/01	Sponsor	SmithKline Beecham
PDUFA Due Date	10/15/01	Priority Classification	S
Division Due Date	10/15/01		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	[redacted]	[redacted]	[redacted]	[redacted]
Table of Contents present and sufficient to locate reports, tables, data, etc.	x	[redacted]	[redacted]	
Tabular Listing of All Human Studies	x	[redacted]	[redacted]	
HPK Summary	x	[redacted]	[redacted]	
Labeling	x	[redacted]	[redacted]	OTC product
Reference Bioanalytical and Analytical Methods	x	[redacted]	[redacted]	
I. Clinical Pharmacology	[redacted]	[redacted]	[redacted]	[redacted]
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	[redacted]	[redacted]	[redacted]	[redacted]
Healthy Volunteers-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:				
multiple dose:				
Patients-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:	x			Cigarette smokers
multiple dose:	x	1		
Dose proportionality -	[redacted]	[redacted]	[redacted]	[redacted]
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -	[redacted]	[redacted]	[redacted]	[redacted]
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -	[redacted]	[redacted]	[redacted]	[redacted]
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 2:				
Phase 3:				
PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:				

Data sparse:				
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:				
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:	x			Single dose
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	x			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]			

Filability and QBR comments

	"X" if yes	Comments
Application filable?	x	
Comments sent to firm?		See the review package
QBR questions (key issues to be considered)	1. What are the pharmacokinetics differences between NPA lozenge and Nicorette® gum? 2. Is the pharmacokinetics of the drug linear? 3. Dose the sponsor proposed dosing regimen appropriate per PK perspective? 4. What would be the effects of incorrect use (misuse) of this product? 5. Does the dissolution test conditions and specifications appear to be appropriate to the physiological state, and related to in vivo PK studies?	
Other comments or information not included above		
Primary reviewer Signature and Date	Shinja R. Kim, Ph.D.	
Secondary reviewer Signature and Date	Suresh Doddapaneni, Ph.D.	

cc: NDA (21,330), HFD-170 (Division File; MilsteinJ), HFD-850 (Lesko), HFD-870 (KimSh, DoddapaneniS, MalinowskiH), CDR (Zom Zadeng)

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-330 **Submission Date:** December 15, 2000
Drug Name, Dose and Formulation: Nicotine Polacrilex Lozenges, 2 and 4 mg
Sponsor: SmithKline Beecham Consumer Healthcare, LP., Parsippany NJ 07054-3884
Type of Submission: Original NDA **Reviewer:** Shinja R. Kim, Ph.D.

SYNOPSIS:

Nicotine as a nicotine replacement therapy (NRT) is available in many different formulations, such as, polacrilex chewing gum (Nicorette®), transdermal patch, inhaler and nasal spray. NRT products are different in their patterns, rates and quantities of dosing and in resultant pharmacological effects.

Five pharmacokinetic studies have been conducted in humans to characterize the PK profile of Nicotine Polacrilex (NPA) Lozenges. Initially two pilot single dose studies were conducted comparing NPA lozenge with Nicorette® gum at 2 and 4-mg dose levels (Studies N98001 and N96016). Based on the findings from these early development studies, the sponsor has conducted additional PK studies: (1) Bioequivalence study comparing 3 mg NPA lozenge and 4 mg Nicorette® gum (S1410092). (2) Multiple dose study applying different dosing regimens to NPA lozenge and Nicorette® gum (S1410091). (3) A study to compare the PK profiles when the lozenge was administered as directed and not as directed (S1410090). Also, a simulation was carried out to predict the C_{max} and the extent of absorption if the lozenge were to be administered every 60 minutes (as opposed to q90 min in S1410091). Additionally, the sponsor provided the dissolution method and the proposed Specification. Overall, these 5-PK studies provided the adequate PK characterization of the NPA lozenges, however the Proposed Dissolution Specification was less than satisfactory.

Comment to the sponsor: The Agency recommends that 3-point dissolution specification as follows;

At 1 hr: [redacted]
At 3 hr: [redacted]
At 6 hr: [redacted]

RECOMMENDATION:

The NDA 21-330 is acceptable from the Clinical Pharmacology and Biopharmaceutics perspective provided the sponsor takes the above comment under consideration. Above comment should be conveyed to the sponsor.

Shinja R. Kim, Ph.D.
Division of Pharmaceutical Evaluation II

Suresh Doddapaneni, Ph.D., Team Leader

cc: NDA (21,330), HFD-170 (Division File; MilsteinJ), HFD-850 (Lesko), HFD-870 (KimSh, DoddapaneniS, MalinowskiH), CDR (Zom Zadeng)

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BACKGROUND: The following describes the nicotine ADME Properties.

Absorption: Nicotine is a tertiary amine, with a pKa 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 30-minute 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/hr. 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.

SUMMARY

1. What are the characteristics of the to-be-marketed Nicotine Polacrilex lozenge formulation?

The drug substance, Nicotine Polacrilex (NPA), is produced by ion-exchange reaction of Nicotine USP and [redacted] in aqueous media followed by [redacted]
A compressed tablet (lozenge) formulation was chosen for development, and would provide a different oral formulation of NRT. The lozenge was formulated as a mild mint-flavored oral lozenge that releases nicotine upon exposure to an aqueous media. This lozenge formulation has the same drug substance, used in the OTC formulations for Nicorette® 2 and 4 mg gum manufactured by Pharmacia & Upjohn. The quantitative compositions of the 2 and 4 mg NPA lozenges are shown in table below.

Ingredient Name	Composition (mg/lozenge)	
	2 mg lozenge	4 mg lozenge
Nicotine Polacrilex, USP[1]	[redacted]	[redacted]
Mannitol, USP[2]	[redacted]	[redacted]
Sodium Alginate, NF[2]	[redacted]	[redacted]
Xanthan Gum, NF[2]	[redacted]	[redacted]
Potassium Bicarbonate, USP[2]	[redacted]	[redacted]
Calcium Polycarbophil, USP[2]	[redacted]	[redacted]
Sodium Carbonate, NF[2]	[redacted]	[redacted]
Aspartame, NF	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Magnesium Stearate NF	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Total lozenge weight	1200.000	1200.000

[1] Amount of Nicotine Polacrilex, USP will vary depending upon the potency (nominally [redacted] w/w nicotine).

[2] Amount of these ingredients (added as [redacted] is adjusted dependent on the calculated quantity of Nicotine Polacrilex, USP used.

[3] Used as a [redacted] and evaporates during the [redacted]

2. What are the PK parameter values of the NPA lozenge?

Parameters	Mean ± SD
C_{max} (ng/ml/mg-base)	2.3 ± 0.3
AUC (ng.h/ml/mg-base)	8.6 ± 1.5
T_{max} (hr)	1.0 ± 0.06
$t_{1/2}$ (hr)	2.3 ± 0.3
Accumulation factor	2.8[a], 3.9[b]

[a]Every 90 min dose [b]Every 60 min dose

3. Is the pharmacokinetics of the drug linear?

It appears that C_{max} and AUC proportionally increase as dose increased from 2 to 4 mg.

4. What are the pharmacokinetics differences between NPA lozenge and Nicorette® gum?

Although the released nicotine undergoes similar buccal absorption and/or ingestion (swallowing), nicotine is not completely released from the gum base (the sponsor indicated that

the amount of nicotine released from the gum was approximately 30% lower than that from the lozenger). This difference in nicotine availability appears to be responsible for difference in PK between these two formulations: the mean C_{max} and $AUC_{0-\infty}$ achieved from the lozenge was approximately 7-10% and 20-30%, respectively, higher than those obtained from the gum (single dose). Mean T_{max} and $t_{1/2}$ were similar between the lozenger and the gum (*i.e.*, 1.0 ± 0.06 *vs.* 0.85 $\pm$ 0.04 hour for T_{max} and 2.3 ± 0.3 *vs.* 2.1 ± 0.4 hour for $t_{1/2}$).

5. Dose the sponsor proposed dosing regimen appropriate per PK perspective?

Since C_{max} and $AUC_{0-\infty}$ achieved from the lozenge were higher than those from the gum after single dose, a multiple dose study (S1410091) was conducted applying dosing intervals q90min for lozenge and q60min for gum. The study results showed that approximately 20% lower steady state C_{max} from the lozenge compared to that from the gum. Therefore, a simulation of the plasma concentration-time curves for 4 mg lozenge administered every 60 min was performed; The model generated steady state C_{max} from lozenge was 34.9 ng/ml (by this reviewer's simulation), which was about 8% higher than observed C_{max} from Nicorette® gum. The sponsor proposed an initial (*i.e.*, 1-6 week) lozenge dosing regimen of 'one lozenge every [redacted] to 2 hours' with the maximum of [redacted] lozenges a day', as opposed to 'one piece every 1-2 hrs' without exceeding [redacted] a day for the Nicorette® gum. Dosing regimens for rest of weeks (i.e., 7-12 weeks) are the same for both formulations. Alternatively, the lozenge could be given q 1-2 hrs for initial period if C_{max} of 34.9 ng/ml is considered to be safe in order to lessen the confusion of dosing regimen between NPA lozenge and Nicorette® gum.

6. What would be the effects of incorrect use (misuse) of this product?

When the lozenge was administered as directed (*i.e.*, Treatment A = move the lozenge from side to side in their mouths every 4 seconds until complete dissolution of the lozenge, S1410090), the nicotine C_{max} and AUC were higher compared to two other modes of administration representing misuse; *i.e.*, Treatment B = chewed and immediately swallowed; Treatment C = chewed, held in the mouth for 5 minutes and then swallowed. Chew and swallowing immediately (Treatment B) resulted in about 30% lower C_{max} and AUC.

7. Are the bioanalytical methodology validated appropriately?

Determination of nicotine in plasma samples from the PK studies were carried out by LC/MS/MS. This analytical method was specific, sensitive and adequately validated. The assay results were found to be overall acceptable; cotinine (major metabolite) level in plasma was not measured, however, this is not an essential information that needs to be obtained.

8. Does the dissolution test conditions and specifications appear to be appropriate to the physiological state, and related to in vivo PK studies?

The sponsor developed the *in vitro* dissolution method in which the drug is released within 8 hours, although NPA lozenge dissolves approximately in 20-30 minutes *in vivo*. However, the proposed method can be used appropriately for characterizing the quality of the drug product as a quality control measurement and thus ensures batch-to-batch consistency. On the other hand, the sponsor's proposed Specification is not adequate.

APPENDIX

STUDY N98001

Study Type: Single dose PK/Relative Bioavailability

Protocol Title: Single-Dose Pharmacokinetics of Nicotine Following Oral Administration of a 2 mg Nicotine Lozenge and a 2 mg Nicorette® Gum in Healthy Volunteers.

Volume: Electronic submission

Clinical Investigators: [redacted]

Study Design: Open-Label, single dose, randomized, two-way cross-over, at least 3 days washout period, over night fast of 12 hours. The subjects were required to chew the Nicorette® gum approximately once every 4 seconds over 30 minutes or to move the nicotine lozenge in theirs mouths approximately once every 4 seconds over 20 minutes to achieve complete dissolution of the lozenge.

Subject Breakdown

Demographics	
Gender	12 Males, 13 females
Age (mean±SD, range)	33.7±11.5 years (18.8-52.3 years)
Body mass index (mean±SD)	25.4±4.2

Formulation:

Treatment Group	Dose	Dosage Form	Strength	Lot
Treatment A	2 mg	Lozenge	2 mg	98Z074
Treatment B	2 mg	Nicorette® gum	2 mg	ZD705A

Analytical Methodology

Plasma Sampling Times: blood samples were collected at 0 hour (predose), at 2.5, 5, 10, 20, 30, 45 minutes, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours postdose. In addition, the used Nicorette® gums were collected and analyzed for residual nicotine contents.

Assay Method: LC/MS/MS

Assay Sensitivity: LOQ of [redacted] for nicotine. [redacted] for nicotine.

Accuracy and Precision: [redacted]

Labeling Claims: None (OTC)

Objective: To evaluate (1) PK of nicotine after administration of a 2 mg nicotine lozenge dosage form and 2 mg Nicorette® gum (primary); (2) subjective characterization of the two dosage forms (secondary).

Results: The mean ± SD nicotine plasma concentration-time curves and PK parameters of the two dosage forms are shown in Figure 1 and Table 1, respectively. T_{max} of nicotine occurred significantly later for the nicotine lozenge (median 1.0 h) than Nicorette® gum (median 0.75 h, $p = 0.02$). Approximately 10 and 30% larger C_{max} and $AUC_{0-\infty}$, respectively for the lozenge compared to the gum (the sponsor claims that this is due to the higher dose of nicotine available from the lozenge). The time to complete lozenge dissolution ranged from [redacted] with

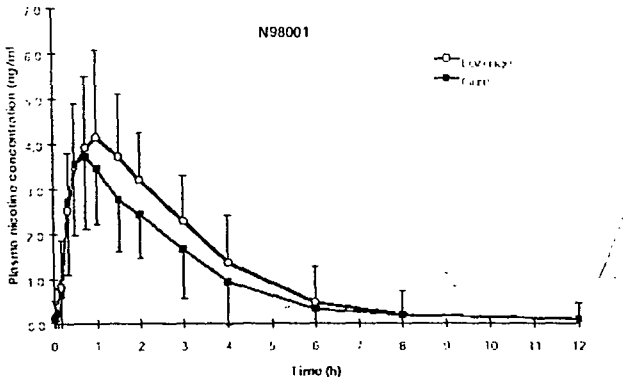
a mean ± SD of 20.8 ± 1.3 minutes. It was reported that there was no definitive preference expressed by the subjects for either of the study dosage forms.

Table 1. Summary of pharmacokinetic parameters.

Parameter	2 mg NPA Lozenge (Treatment A)	2 mg Nicorette® gum (Treatment B)	90% CI A/B
C_{max}, ng/mL	**4.4 ± 1.7**	**4.0 ± 1.5**	**0.97-1.22**
T_{max}[a], hours	**1.0 ± 0.4**	**0.8 ± 0.2**	-
AUC_{0-12}, ng hour/mL	**13.5 ± 7.4**	**10.7 ± 6.6**	-
$AUC_{0-\infty}$, ng hour/mL	**14.1 ± 9.2**	**11.3 ± 7.6**	**1.15-1.45**
$T_{1/2}$, hours	**2.3 ± 1.0**	**2.5 ± 1.2**	

[a]significant p = 0.02

Figure 1. Mean±SD nicotine plasma concentrations after administration of the 2 mg nicotine lozenge and 2 mg Nicorette® gum in 23 healthy volunteer smokers.



STUDY N96016

Study Type: Single dose PK/Relative Bioavailability

Protocol Title: Single-dose Pharmacokinetics of Nicotine Following Oral Administration of a Novel 4 mg Nicotine Lozenge Dosage Form and Nicorette® Gum in Healthy Volunteers.

Volume: Electronic submission

Clinical Investigators:

Study Design: Open-Label, single dose, randomized, four-period cross-over, at least 3 days washout period, overnight fast of at least 8 hrs. Each volunteer received each dosage form twice during the study to provide an internal replicate control: During each treatment period, one 4 mg nicotine lozenge (move periodically in the buccal cavity approximately once every 4 seconds) or one piece of 4 mg Nicorette™ gum (chew at a rate of approximately once every 4 seconds) was administered over an approximately 30-minute period.

Subject Breakdown

Demographics	
Gender	6 Males, 6 females
Age (mean±SD, range)	31 ± 6 years (21-42 years)
Body mass index	24.6 ± 4.3 (range 17.4-31.5)

Formulation:

Treatment Group	Dose	Dosage Form	Strength	Lot
Treatment A	4 mg	Lozenge	4 mg	96Z194
Treatment B	4 mg	Nicorette™ gum	4 mg	6H07CD

Analytical Methodology

Plasma Sampling Times: blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8 and 12 hr post dose. In addition, the used Nicorette® gums were collected and analyzed for residual nicotine contents.

Assay Method: LC/MS/MS

Assay Sensitivity: LOQ of [redacted] nicotine and cotinine, respectively. Assay was [redacted] nicotine and cotinine, respectively.

Accuracy and Precision: [redacted]

Labeling Claims: None (OTC)

Objective: To evaluate (1) pharmacokinetics of nicotine after administration of a 4 mg nicotine lozenge dosage form and 4 mg Nicorette™ gum (primary); (2) the subjective characterization of the two dosage forms (secondary).

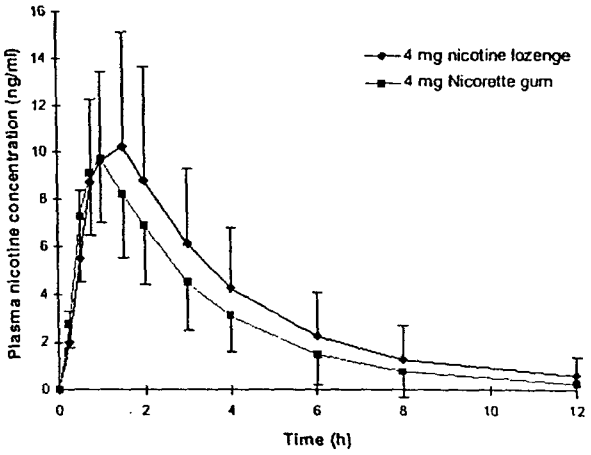
Results: The mean ± SD nicotine plasma concentration-time curves of the two dosage forms are shown in Figure 1 and Table 1. Approximately 10% higher C_{max} and an approximately 30% greater $AUC_{0-\infty}$ for the lozenge (The sponsor claims that this is due to the higher dose of nicotine available from the lozenge). The time to complete lozenge dissolution ranged from 27 to 41 minutes, with a mean ± SD of 33 ± 4 minutes. It was reported that subjective responses following the completion of each study period were similar for the gum and lozenge.

Table 1. Pharmacokinetic parameters of nicotine after replicate administration of the 4 mg nicotine lozenge and the 4 mg Nicorette® gum to 12 healthy volunteer smokers.

Parameter	4 mg NPA Lozenge (Treatment A)	4 mg Nicorette™ gum (Treatment B)	90% CI A/B
C_{max}, ng/mL	**10.8 ± 4.7**	**10.0 ± 2.9**	**0.86-1.35**
T_{max}[a], hours	**1.1 ± 0.3**	**0.9 ± 0.2**	-
AUC_{0-12}, ng hour/mL	**41.6 ± 23.6**	**33.1 ± 15.0**	-
$AUC_{0-\infty}$, ng hour/mL	**44.0 ± 26.5**	**34.6 ± 17.6**	**0.97-1.50**
$T_{1/2}$, hours	**2.3 ± 0.6**	**2.1 ± 0.7**	

[a]significant p = 0.03

Figure 1. Mean adjusted plasma nicotine concentrations: Lozenge vs. Nicorette gum



STUDY S1410090

Study Type: Single dose PK/Relative Bioavailability (misuse)

Protocol Title: A Single Dose Pharmacokinetic Study of 4 mg Nicotine Lozenge to Determine Potential Misuse.

Volume: Electronic submission.

Clinical Investigators: [redacted]

Study Design: Open-Label, single dose, randomized, three-way cross-over, at least 24 hours washout period, overnight fast of at least 8 hrs. Each volunteer was randomized to receive the following treatment: Treatment A = use as directed; Treatment B = chewed into pieces and immediately swallowed; Treatment C = chewed into pieces and the residue and saliva held in the mouth for 5 minutes before swallowing.

Subject Breakdown

Demographics	
Gender	11 Males, 11 females
Age	30.3 ± 9.2 years (range, 20-50 years)
Weight	68.5 ± 12.5 (range, 49.6-105.2 kg)
Race	22 Caucasians

Formulation: For treatments A, B, and C: Nicotine 4 mg lozenge manufactured by SmithKline Beecham Consumer Healthcare, Lot No: 9010FP-9006, Expiration date: 30 Jun 2000.

Analytical Methodology

Plasma Sampling Times: blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8 and 12 hr post dose for analysis of nicotine plasma concentrations.

Assay Method: LC/MS/MS

Assay Sensitivity: LOQ of [redacted] nicotine and cotinine, respectively. [redacted] nicotine and cotinine, respectively.

Accuracy and Precision: [redacted]

Labeling Claims: None (OTC)

Objective: To demonstrate the pharmacokinetic profile from a single dose of a 4 mg nicotine lozenge when the normal use of the lozenge was compared to the use of the lozenge contrary to label instructions, as follows: When the lozenge was chewed and immediately swallowed or when the lozenge was chewed, retained in the mouth, and then swallowed.

Results: The arithmetic means of plasma nicotine pharmacokinetic parameters, and statistical comparison for ln-transformed parameters, are summarized in the following Tables 1 and 2. As shown in tables and Figure 1, AUCs and C_{max} from NPA lozenge were higher when used as directed compared to when it was misused.

Table 1. Summary of the pharmacokinetic parameters of plasma nicotine for Treatment B and A.

Pharmacokinetic	Treatment B		Treatment A		90% CI	% Mean
Parameters	Mean	SD	Mean	SD		Ratio
Cmax (ng/mL)	5.667	2.185	7.800	2.438		
Tmax (hr)	1.29	0.439	0.974	0.323		
AUC$_{0-t}$ (ng*hr/mL)	18.78	8.042	25.16	9.826		
AUC$_{0-\infty}$ (ng*hr/mL)	24.60	6.970	30.78	9.887		
T1/2 (hr)	2.27	0.827	2.55	1.33		
Kel (1/hr)	0.333	0.0913	0.322	0.121		
LN(Cmax)	1.657	0.4193	1.999	0.3688	61.2-82.3	71.0
LN(AUC$_{0-t}$)	2.816	0.5449	3.133	0.4845	61.7-85.8	72.8
LN(AUC$_{0-\infty}$)	3.162	0.2997	3.378	0.3224	67.9-80.1	73.8

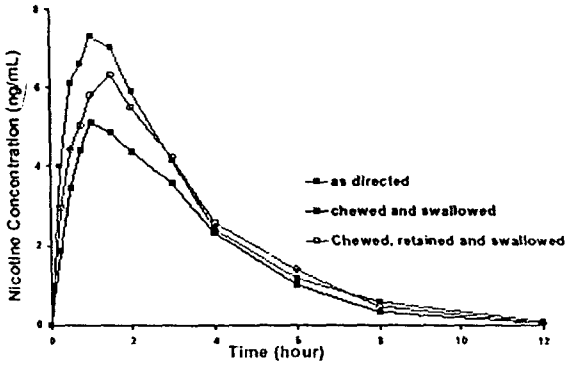
Treatment B = Lozenge was chewed and immediately swallowed.
Treatment A = Lozenge was used as directed (reference)

Table 2. Summary of the pharmacokinetic parameters of plasma nicotine for Treatment C and A.

Pharmacokinetic	Treatment C		Treatment A		90% CI	% Mean
Parameters	Mean	SD	Mean	SD		Ratio
Cmax (ng/mL)	6.779	2.115	7.800	2.438		
Tmax (hr)	1.44	0.467	0.974	0.323		
AUC$_{0-t}$ (ng*hr/mL)	23.19	10.54	25.16	9.826		
AUC$_{0-\infty}$ (ng*hr/mL)	28.73	10.35	30.78	9.887		
T1/2 (hr)	2.15	0.578	2.55	1.33		
Kel (1/hr)	0.344	0.0887	0.322	0.121		
LN(Cmax)	1.870	0.3030	1.999	0.3688	76.0-102.2	88.1
LN(AUC$_{0-t}$)	3.058	0.4201	3.133	0.4845	78.9-109.7	93.0
LN(AUC$_{0-\infty}$)	3.307	0.3164	3.378	0.3224	85.5-100.3	92.6

Treatment C = Lozenge was chewed, held in the mouth for 5 minutes, and then swallowed.
Treatment A = Lozenge was used as directed (reference)

Figure 1. Mean baseline adjusted plasma nicotine concentration-time profiles after 4 mg NPA Lozenge



STUDY S1410091

Study Type: Multiple dose PK/Relative Bioavailability

Protocol Title: An open label, four-way crossover study to determine the steady state PK of four nicotine dosage forms.

Volume: Electronic submission.

Clinical Investigators:

Study Design: Open-Label, randomized, four-way cross-over design. Subjects dosed every 90 minutes for 9 doses (2-mg and 4-mg lozenges) or every 60 minutes for 13 doses (2-mg and 4-mg gum), with minimum 8 hrs of overnight fast, and minimum of 4-day washout period.

Subject Breakdown

Demographics	
Gender	12 Males, 14 females
Age (mean±SD, range)	29 ± 11 years (26-54 years)
Weight (mean±SD, range)	154 ± 23 (120-201 lbs)

Formulation:

Treatment Group	**Dose**	**Dosage Form**	**Strength**	**Lot**
Treatment A	2 mg	Lozenge	2 mg	9009FP8001
Treatment B	4 mg	Lozenge	4 mg	9010FP8001
Treatment C	2 mg	Nicorette® gum	2 mg	ZM751A
Treatment D	4 mg	Nicorette® gum	4 mg	AA752A

Analytical Methodology

Plasma Sampling Times: During Treatments A and B, subsequent blood samples were collected immediately before the 7th, 8th, and 9th dose, and following the 9th dose, every 10 min for 90 min. During Treatments C and D, subsequent blood samples were collected immediately before the 11th, 12th, and 13th dose, and following the 13th dose, every 10 min for 60 minutes.

Assay Method: LC/MS/MS

Assay Sensitivity: LOQ [redacted] nicotine and cotinine, respectively. [redacted]
[redacted] for nicotine and cotinine, respectively.
Accuracy and Precision: [redacted] nicotine and cotinine, respectively. [redacted] nicotine and cotinine, respectively.

Labeling Claims: Sponsor proposed the following dosage schedule for NPA lozenge.

Week 1 through 6	Week 7 through 9	Week 10 through 12
1 lozenge every [redacted] -2 hrs	1 lozenge every 2-4 hrs	1 lozenge every 4-8 hrs

Discontinue use of the lozenge at the end of 12 weeks (3 months)
Do not use more than [redacted] lozenges per day

Objective: To characterize the PK parameters and bioavailability of 2-mg and 4-mg nicotine lozenges in comparison to 2-mg and 4-mg Nicorette® gum at steady state.

Results: The arithmetic means of plasma nicotine pharmacokinetic parameters, and statistical comparison for ln-transformed parameters, are summarized in the following Tables 1 and 2. As shown in tables and Figure 1, dosing every 90 minutes for lozenge and every 60 minutes for gum resulted in higher steady state AUC_{0-T} and C_{max} with gum compared to those with lozenge in this study. Therefore, it appears that in order to achieve comparable effect (concentrations) with gum the lozenge dosage form may needs to be frequently administered than every 90 minutes. Additionally, it appears that dose proportionality has been achieved between 2 and 4 mg for two dosage forms.

Table 1. Steady State Pharmacokinetics Parameters for Plasma Nicotine after 2 mg NPA lozenge administered every 90 minutes and 2 mg nicorette® gum administered every 60 minutes.

	2 mg Lozenge[1]		2 mg Nicorette Gum[2]			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
Cmax (ng/mL)	12.688	6.184	16.084	7.284	64.8 - 95.4	80.1
Cmin (ng/mL)	9.352	5.125	12.364	7.059	58.5 - 91.7	75.1
Tmax (hr)	0.547	0.295	0.593	0.153	72.9 - 113.5	93.2
AUC_{0-T} (ng*hr/mL)	31.76	17.23	41.34	20.28	60.8 - 91.9	76.3
LN(Cmax)	2.461	0.3806	2.693	0.4189	73.8 - 88.2	80.7
LN(AUC_{0-T})	3.364	0.4069	3.628	0.4339	71.1 - 83.7	77.2

T = 180 minutes.
AUC_{0-T} for lozenge was AUC_{0-T} multiplied by 2 and AUC_{0-T} for gum was AUC_{0-T} multiplied by 3.

[1] Dosing every 90 minutes
[2] Dosing every 60 minutes

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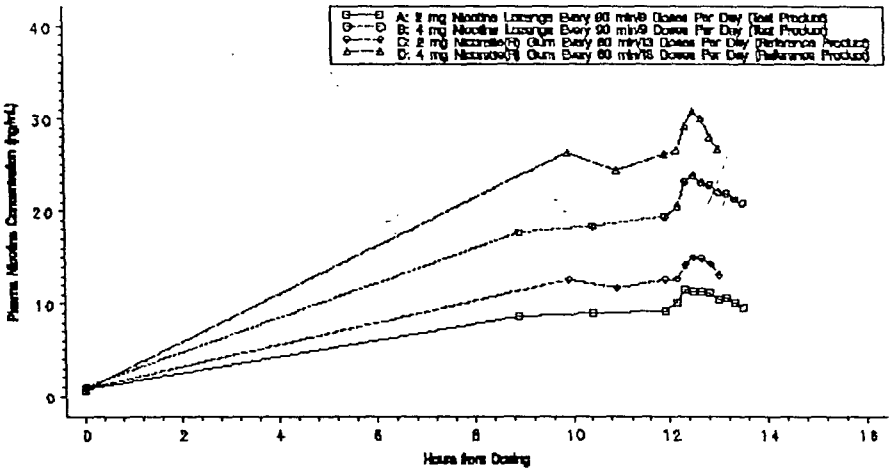
Table 2. Steady State Pharmacokinetics Parameters for Plasma Nicotine after 4 mg NPA lozenge administered every 90 minutes and 4 mg nicorette® gum administered every 60 minutes

	4 mg Lozenge[1]		4 mg Nicorette Gum[2]			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
Cmax (ng/mL)	26.019	13.071	32.243	13.746	73.1 – 88.5	80.8
Cmin (ng/mL)	19.717	11.806	26.943	12.837	65.8 – 81.0	73.4
Tmax (hr)	0.649	0.367	0.535	0.180	99.1 – 143.9	121.5
AUC_{0-T} (ng*hr/mL)	67.27	37.05	87.75	39.24	69.6 – 84.3	77.0
LN(Cmax)	3.168	0.4112	3.401	0.3758	72.2 – 86.2	78.9
$LN(AUC_{0-T})$	4.106	0.4288	4.396	0.3925	69.0 – 81.2	74.9

T = 180 minutes.
AUC_{0-T} for lozenge was AUC_{0-T} multiplied by 2 and AUC_{0-T} for gum was AUC_{0-T} multiplied by 3.

1 Dosing every 90 minutes
2 Dosing every 60 minutes

Figure 1.



STUDY S1410092

Study Type: Bioequivalence
Protocol Title: A Single Dose Pharmacokinetic Study of Two Nicotine Dosage Forms.
Volume: Electronic submission.
Clinical Investigators:
Study Design: Open-Label, randomized, two-way cross-over design. Overnight fast of at least 8 hrs, and washout period of minimum of 4 days. Subjects were required to move the nicotine lozenge in their mouth every 4 seconds to achieve complete dissolution of the lozenge (Treatment A) or to chew the Nicorette® gum once every 4 seconds over 30 minutes (Treatment B).

Subject Breakdown

Demographics	
Gender	38 Males, 27 females
Age (mean±SD, range)	30 ± 10 years (19-54 years)
Weight (mean±SD, range)	163 ± 29.3 (111-236 lbs)

Formulation:

Treatment Group	Dose	Dosage Form	Strength	Lot
Treatment A	3 mg	Lozenge	3 mg	9014FP9008
Treatment B	4 mg	Nicorette® gum	4 mg	AA752A

Analytical Methodology

Plasma Sampling Times: t = 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post dose.

Assay Method: LC/MS/MS

Assay Sensitivity: LOQ for nicotine and cotinine, respectively.

or nicotine and cotinine, respectively.

Accuracy and Precision:

Labeling Claims: None (OTC)

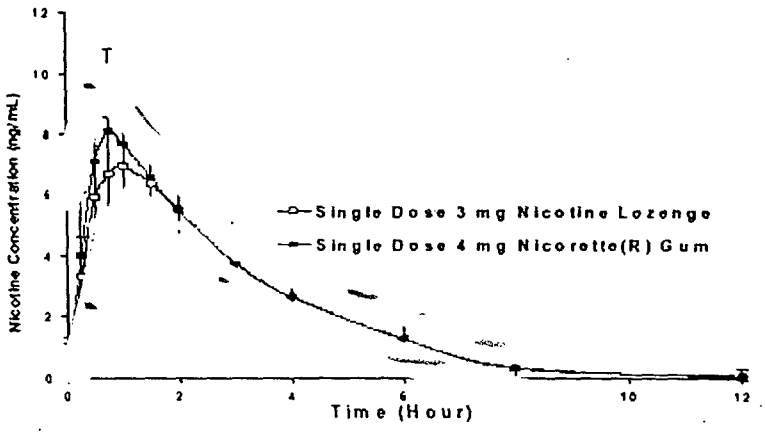
Objective: To demonstrate bioequivalence of single dose 3 mg nicotine lozenge to single dose 4 mg Nicorette® gum.

Results: Bioequivalence was demonstrated between 3 mg NPA lozenge and 4 mg Nicorette gum as shown in Table 1.

Table 1. Baseline Adjusted Pharmacokinetic Parameters for Plasma Nicotine after Single Dose 3 mg Lozenge and 4 mg Nicorette® Gum

	3 mg Lozenge		4 mg Nicorette Gum			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	Mean Ratio
Cmax (ng/mL)	7.1475	1.8611	8.0428	2.7716		
Tmax (hr)	0.940	0.340	0.837	0.274		
AUC$_{0t}$ (ng*hr/mL)	20.79	6.175	21.36	8.144		
AUC$_{0\infty}$ (ng*hr/mL)	25.74	6.719	25.43	8.998		
T$_{1/2}$ (hr)	1.88	0.743	1.66	0.629		
Kel (hr)	0.443	0.221	0.494	0.239		
LN(Cmax)	1.933	0.2633	2.029	0.3388	84.2 – 97.7	90.7
LN AUC$_{0t}$	2.987	0.3214	2.994	0.3721	91.9 – 107.4	99.3
LN AUC$_{0\infty}$	3.212	0.2769	3.177	0.3440	96.4 – 111.5	103.7

Figure 1. Mean±SD Plasma Nicotine Concentrations after NPA Lozenge 3 mg and 4 mg Nicorette® Gum



PK Modeling Report

Study Type/Title: Modeling/Simulation of multidose plasma levels for 4 mg nicotine polacrilex lozenge administered every 60 minutes.

Objectives: (1) Development of a PK model for nicotine polacrilex lozenge formulations based on single dose plasma data for the 3 mg nicotine polacrilex lozenge; (2) Simulation of steady state plasma curves for the 4 mg nicotine polacrilex lozenge administered at 60 minutes.

Data: PK model for nicotine polacrilex lozenge was constructed based on the data following an administration of 3 mg nicotine polacrilex lozenge (Study S1410092). Curve fitting of plasma data was performed using WinNonlin software, assuming 1-compartment, first order elimination model with no lag time. The following parameter estimates were obtained: Volume/F = 0.287283 L, K_a = 1.719248 hr^{-1}, K_e = 0.440215 hr^{-1}.

Simulation: The sponsor used Prediction error (%PE) to evaluate 'goodness' of simulation predictability: %PE = 100 * (observed value-simulated value)/observed value. As per the FDA guideline, %PE of ≤ 10% is considered acceptable. Based on this %PE criteria, the model predicted steady state C_{max} for the lozenge (q90 min administration) is ~14%, not close enough to be acceptable; the sponsor reported that %PE for C_{max} was 5.5% (Table 1), which was obtained by C_{max} of 23.73 ng/ml, which is not accurate value. The observed plasma level from the study S1410091 was 26.02 ng/ml (not 23.73 ng/ml).

This reviewer obtained another set of PK parameter values based on the data from study S1410091 (i.e., 4 mg nicotine polacrilex lozenge q90min), since %PE of 14% is not acceptable. As shown in Table 2-b, the simulated C_{max} and AUC_{0-90} were within 10% PE. The predicted steady state C_{max} and AUC_{0-60} were 34.9 ng/ml and 33.9 ng.hr/ml, if 4-mg nicotine polacrilex lozenge was dosed q60min (Table 2-c). This simulated C_{max} of 34.9 ng/ml is about 8% higher than observed C_{max} of 32.2 ng/ml following Nicorette® gum dosed at q60min.

Table 1: The simulated and observed C_{max} and the AUC_{0-90} values after the 9th dose (*i.e.*, steady state) of 4 mg NPA lozenge, reported by the sponsor.

Parameters	Average *Observed* Values[1]	*Simulated* Values	%PE
C_{max} (ng/ml) at steady state	23.73	22.42	5.5
AUC (ng.hr/ml) at steady state	33.64	34.68	3.1

[1] calculated based on mean plasma levels for 26 subjects (Study S1410091)

Table 2. Simulated and observed steady state C_{max} and AUC_{0-90} values of 4-mg nicotine polacrilex lozenge administered every 90 or 60 minutes.

Parameters	Mean Observed Values[1]	Simulated Values		
C_{max} (ng/ml)	26.02	22.42[a]	24.2[b]	34.9[c]
%PE	-	13.8%	7.0%	-
AUC (ng.hr/ml)	33.64	31.63[a]	33.93[b]	33.93[c]
%PE	-	6.0%	0.9%	-

[1]Based on S1410091, 4-mg lozenge q90min (n=26 subjects)
[a]Simulation by the sponsor (q90min)
[b]Simulation using Volume/F = 0.262 L, K_a = 1.72 hr^{-1}, K_e = 0.45 hr^{-1}, q90min
[c]Simulation using Volume/F = 0.262 L, K_a = 1.72 hr^{-1}, K_e = 0.45 hr^{-1}, q60min

Dissolution Method and specification

Proposed Dissolution Method and Specification for 2 mg and 4 mg Nicotine Polacrilex Lozenges are as follows:

Apparatus Type: USP Type I, basket
Media: Phosphate buffer (pH 7.4)
Volume: 900 mL
Speed of Rotation: 100 rpm
Sampling Time(s): 1 hour and 8 hours
Dissolution Specification: Q = [redacted] at 1 hour and Q = [redacted], at 8 hours.

Eight-hour dissolution profiles were generated on 5 batches each of Nicotine Polacrilex 2 mg and 4 mg Lozenges. These batches were manufactured at commercial production site, SmithKline Beecham Consumer Healthcare (SBCH) Aiken, South Carolina using t[redacted], using Nicotine Polacrilex f[redacted]. Also these batches were used in the primary package stability studies and clinical studies. Table 1 summarizes the mean rate of dissolution generated at each hourly interval for the five batches. A graphical depiction of the mean dissolution profiles for each product variant is presented in Figure 1.

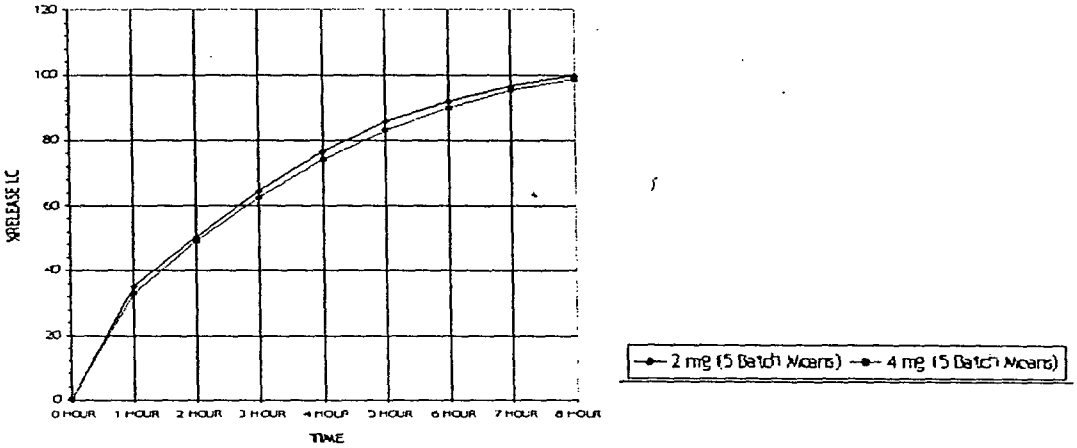
Note: The lozenge dissolves *in vivo* within ~20 to 30 minutes when used as instructed. The sponsor indicated that the proposed *in vitro* dissolution specification dose not reflect the physical erosion that occurs against the oral mucosa during the periodic manipulation of the lozenge within the mouth. However, the proposed *in vitro* test is "an appropriate quality control measure for characterizing the quality of the drug product and ensures batch-to-batch consistency".

Table 1. Dissolution Profiles for 2 mg (top panel) and 4 mg (bottom panel) NPA: Individual batch results are mean value from 6 lozenges. All batches were tested according to USP Apparatus I (basket) in 900 mL of phosphate buffer (pH 7.4) at 37 ± 0.5°C and 100 rpm.

	BATCH NUMBER: 9009FP-									
Time	8001	9004	9005	0001	0002	Average Mean	STD DEV	%RSD	Minimum	Maximum
1 Hour	36	34	35	35	36	35	0.8	2.4		
2 Hour	51	50	48	51	52	50	1.5	3.0		
3 Hour	66	63	61	65	66	64	2.2	3.4		
4 Hour	78	74	74	78	79	77	2.4	3.1		
5 Hour	86	83	83	87	89	86	2.6	3.0		
6 Hour	93	90	88	94	95	92	2.9	3.2		
7 Hour	97	95	94	98	100	97	2.4	2.5		
8 Hour	100	99	96	101	102	100	2.3	2.3		

	BATCH NUMBER: 9010FP-									
Time	8001	9004	9005	0001	0002	Average Mean	STD DEV	%RSD	Minimum	Maximum
1 Hour	33	32	32	34	33	33	0.8	2.6		
2 Hour	48	47	48	51	50	49	1.6	3.4		
3 Hour	62	60	61	65	64	62	2.1	3.3		
4 Hour	74	71	73	76	77	74	2.4	3.2		
5 Hour	82	80	82	85	86	83	2.4	3.0		
6 Hour	89	87	89	91	93	90	2.3	2.5		
7 Hour	94	93	95	96	98	95	1.9	2.0		
8 Hour	97	97	99	99	102	99	2.0	2.1		

Figure 1. Mean rate of dissolution for 2 and 4 mg NPA



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Since Nicotine Polacrilex was supplied by two sources, (comparative) dissolution studies were performed using 0.1 N HCl, Water and USP buffer medias at pH 4.5, 6.5 and 7.4; however, the results of dissolution profiles in pH 7.4 phosphate buffered media are shown here only.

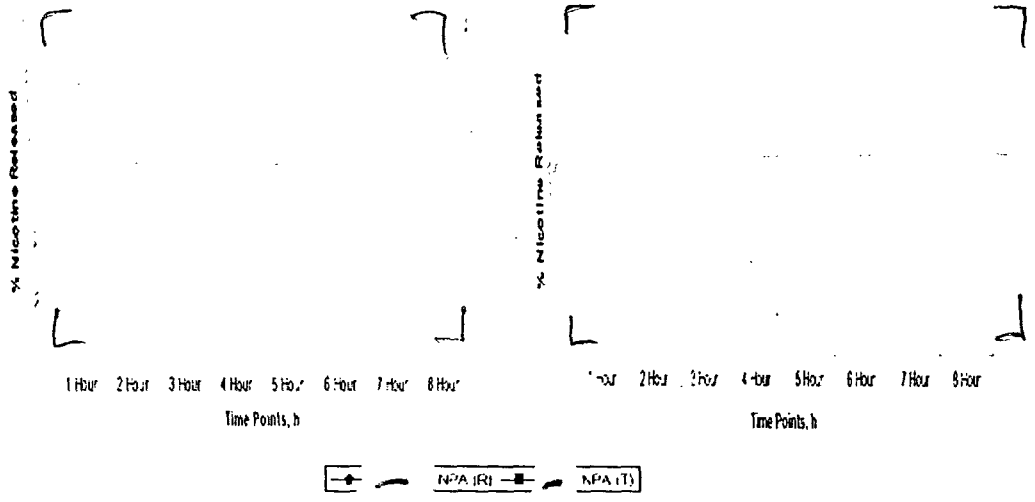
Note: (1) [redacted] However, the sponsor indicated that the physical characteristics of both NPA sources are comparable and interchangeable for pharmaceutical use. (2) The drug product batches used in each comparative dissolution study are as follows; Batches 9009FP-9009 and 9010FP-9005, for 2 and 4 mg, respectively, were made by [redacted] and 9009FP-9002 and 9010FP-9002 for 2 and 4 mg, respectively, were by [redacted]

Table 2. Dissolution Profiles of 2 mg and 4 mg Nicotine Polacrilex Lozenges in pH 7.4

	2 mg Lozenge		2 mg Lozenge		4 mg Lozenge		4 mg Lozenge	
	[redacted]	NPA)	[redacted]	NPA)	[redacted]	NPA)	[redacted]	NPA)
Time	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1 hour	33.0	1.3	32.0	0.7	31.9	1.0	31.7	0.9
2 hour	49.4	2.2	48.5	1.7	47.7	1.7	47.8	1.2
3 hour	63.8	1.6	62.9	1.5	61.2	1.8	61.5	1.7
4 hour	75.5	1.6	74.7	1.4	72.4	1.9	73.2	1.7
5 hour	83.9	1.8	83.9	1.4	81.7	2.2	82.9	2.0
6 hour	90.2	2.0	90.4	1.7	89.2	3.2	89.8	2.1
7 hour	94.1	1.7	94.5	1.4	94.0	3.2	94.3	1.8
8 hour	96.0	1.6	97.3	1.5	96.5	2.6	96.8	1.8

SD = Standard deviation. For means, n = 12.

Figure 2. Dissolution Profile Comparison for 2 (left panel) and 4 mg (right panel) Nicotine Polacrilex Lozenges in pH 7.4.



Dissolution profiles between lozenges prepared with the two sources of NPA, the sponsor made the following conclusions based on study results:

1. As a consequence of the formulation technology employed in Nicotine Polacrilex Lozenges, Water was found unsuitable as a dissolution media for testing.
2. The dissolution profiles were similar for 2 and 4 mg lozenges manufactured with the two NPA substances in the 4 dissolution media tested – namely, 0.1 N HCl, pH 4.5 Acetate Buffer, pH 6.5 Phosphate Buffer and pH 7.4 Phosphate Buffer.
3. The % Nicotine released from the lozenges tested after 1 hour reached approximately —— in 0.1N Hydrochloric Acid and —— in Phosphate buffer at pH = 6.5. After 8 hours the Nicotine was released at approximately —— in both media.
4. Relative to the other medias, significantly lower % Nicotine release was observed in Acetate buffer at pH = 4.5 (*i.e.*, approximately —— after 1 hour and approximately —— after 8 hours).
5. The Difference Factors (f_1) and Similarity Factors (f_2) determined for the 2 and 4 mg Nicotine Polacrilex lozenges in the four SUPAC medias indicate that source of NPA does not effect the *in vitro* dissolution profile of the drug products.

	Difference Factor (Acceptance Criteria: 0 – 15)				**Similarity Factor** (Acceptance Criteria: 50 – 100)			
	0.1 N HCl	Acetate Buffer pH 4.5	Phosphate Buffer pH 6.5	Phosphate Buffer pH 7.4	0.1 N HCl	Acetate Buffer pH 4.5	Phosphate Buffer pH 6.5	Phosphate Buffer pH 7.4
2 mg Lozenge Comparison								
4 mg Lozenge Comparison								

Comment: The Agency recommends that 3-point dissolution specification as follows;

At 1 hr: ——
At 3 hr: ——
At 6 hr: ——

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