CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-330

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical Studies

NDA 21-330
Name of drug: Nicotine Polacrilex Lozenge
Applicant: SmithKline Beecham
Indication: [redacted]
Documents reviewed: Volumes 1-148
Project manager: Judit Milstein
Clinical reviewer: Harold Blatt, D.D.S.
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Reviewer: Stella Grosser

Introduction

Nicotine replacement therapy (NRT) is a key element of the pharmacological treatment of addiction to tobacco and smoking. It is meant to reduce the severity of the patient's nicotine craving and withdrawal symptoms during the process of smoking cessation. The sponsor has studied a new oral form of nicotine replacement using nicotine polacrilex lozenges for smoking cessation, which they propose to sell as an over-the-counter product.

Design of efficacy study

By agreement with the FDA, a single well-controlled study was carried out. Study S1410043 was a multi-center, randomized, double-blind, placebo-controlled, parallel group study to measure the efficacy and safety of two dose levels of nicotine lozenges in smoking cessation. A 2 mg and a 4 mg dose were evaluated in parallel in populations of smokers with low and high nicotine dependence. Determination of high or low dependency, and therefore allocation to 2 mg or 4 mg, was made by time to first cigarette. The maximum duration of subject participation in the study will be 12 months. The report reviewed presents data up to and including the 6-month data base lock and reporting timepoint. Participating subjects were required to report to the clinical study site at enrollment (quit date minus 1 week), quit date (week 0), 1, 2, 4, 6 and 12 weeks, and six months post-quit for assessments. A daily telephone interactive voice response system was used to collect data on withdrawal and craving for the first 7 weeks, and on lozenge use through six months.

A total of 1818 smokers were randomized, from 2168 screened. In this, intent-to-treat, population, 917 were low-dependency smokers and randomly split between 2 mg nicotine (n=459) and 2 mg placebo (n=458), and the remainder were highly dependent and given 4 mg lozenges (n=450 and 451 assigned to nicotine and placebo, respectively).

Data were collected from 4 sites in the UK and 11 in the US.

Analysis

All analyses discussed here are based on the intent-to-treat population.

The **primary efficacy** variable was self-reported smoking cessation at 6 weeks post-quit verified by exhaled CO measurement of less than or equal to 10 ppm from week 2 post-quit on. For each dose group, comparison of treatment arms was performed using a chi-squared test for difference in proportion of successes as well as a logistic regression analysis that included terms for center and treatment in the model.

The results are in table 1 below (sponsor table 5.4.1.1). Both the 2 mg and 4 mg nicotine lozenges were significantly more effective than their matched placebos. The associated odds ratios were 2.1 (95% CI 1.6 to 2.8) and 3.7 (2.7 to 5.0) for the 2 mg and 4 mg lozenges respectively.

Table 1 Smoking Cessation Rate at 6 Weeks

	2 mg Lozenge			4 mg Lozenge		
	Success	**Failure***	**Total**	**Success**	**Failure***	**Total**
Nicotine Lozenge	211 (46%)	248 (54%)	459	219 (49%)	231 (51%)	450
Placebo enge	136 (29%)	322 (70%)	458	94 (21%)	357 (79%)	451
Total	347	570	917	313	588	901
P-value **		<0.0001			<0.0001	
Odds ratio* Nicotine: Placebo**		2.1			3.7	
95% C.I.		(1.6, 2.8)			(2.7, 5.0)	

* Includes subjects who did not provide adequate information to be considered a success

**Difference in proportion of subjects achieving a success

***Adjusted for site and treatment

Secondary endpoints included smoking cessation at three and six months, weight loss at weeks 6 and 12 and month 6, and self-reported withdrawal and craving symptoms at weeks one and two, post-quit.

The efficacy reported at 6 weeks was sustained through three and six months for both the 2 mg and 4 mg lozenge groups. At three months post-quit the 2 mg nicotine lozenge compared to placebo produced an odds ratio of 2.0, while the odds ratio for the 4 mg nicotine lozenge was 3.4. At six months post-quit the odds ratio for the 2 mg nicotine lozenge was 2.0, and for the 4 mg nicotine lozenge was 2.8.

Table 2 Smoking Cessation Rate at 12 Weeks

	2 mg Lozenge			4 mg Lozenge		
	Success	**Failure***	**Total**	**Success**	**Failure***	**Total**
Nicotine Lozenge	158 (34%)	301 (66%)	459	159 (35%)	291 (65%)	450
Placebo Lozenge	99 (22%)	359 (78%)	458	63 (14%)	388 (86%)	451
Total	257	660	917	222	679	901
P-value **		<0.0001			<0.0001	
Odds ratio* Nicotine: Placebo**		2.0			3.4	
95% C.I.		(1.5, 2.7)			(2.5, 4.8)	

*Includes subjects who did not provide adequate information to be considered a success

**Difference in proportion of subjects achieving a success

***Adjusted for site and treatment

From sponsor table 5.4.1.

Table 3 Smoking Cessation at 6 Months

	2 mg Lozenge			4 mg Lozenge		
	Success	**Failure***	**Total**	**Success**	**Failure***	**Total**
Nicotine Lozenge	111 (24%)	348 (76%)	459	106 (24%)	344 (76%)	450
Placebo Lozenge	66 (14%)	392 (86%)	458	46 (10%)	405 (90%)	451
Total	177	740	917	152	749	901
P-value **		0.0002			<0.0001	
Odds ratio* Nicotine: Placebo**		2.0			2.8	
95% C.I.		(1.4, 2.8)			(1.9, 4.0)	

*Includes subjects who did not provide adequate information to be considered a success

**Difference in proportion of subjects achieving a success

***Adjusted for site and treatment

From sponsor table 5.4.1.3

Total withdrawal symptoms score and craving score

Withdrawal and craving were assessed by a series of nine questions, each on a 5-point scale ranging from none, through slight, mild, moderate to severe.

A withdrawal score was calculated by averaging the scores on seven of these items over seven days to make a weekly average total. The items aggregated were scores for depression, insomnia, increased appetite, restlessness, difficulty concentrating, anxiety and anger/irritability/frustration as defined in DSM IV. A craving score similarly was calculated using questions about craving and urge to smoke.

An analysis of covariance was carried out (under the assumptions of normality of data) to investigate whether there was significant difference in total withdrawal symptoms and craving scores between the active and placebo dose at weeks 1 and 2. The baseline score was fitted as a covariate in the model along with the effect of center and the center by treatment interaction term. The interaction term was removed from the model if not statistically significant ($p>0.05$). Since there was evidence that, for some analyses, the residuals from the statistical model were not normally distributed with a constant

variance, non-parametric analyses were performed in these cases using the Wilcoxon rank sum test.

The tables below summarize the analyses.

Table 4 Total Withdrawal Symptoms

	2 mg versus placebo *		4 mg versus placebo**	
	Week 1	Week 2	Week 1	Week 2
n	732	548	593	463
Treatment difference nicotine – placebo***	-0.18	-0.07	-0.22	-0.22
95% C.I.	(-0.28,-0.01)	(-0.27,0.11)	(-0.32,-0.12)	(-0.34,-0.11)
p-value	0.02	0.18	<0.0001	0.0001

*Non-parametric analysis (i.e., treatment effects expressed as a difference in medians)

** Parametric analysis (i.e., treatment effects expressed as a difference in adjusted means)

*** A negative score signifies a higher level of withdrawal symptoms in the placebo group compared to active

From sponsor table 5.4.1.4

Table 5 Total Craving Symptoms

	2 mg versus placebo*		4 mg versus placebo*	
	Week 1	Week 2	Week 1	Week 2
n	533	414	596	464
Treatment difference nicotine – placebo**	-0.15	-0.21	-0.46	-0.56
95% C.I.	(-0.29,-0.02)	(-0.39,-0.02)	(-0.58,-0.34)	(-0.74,-0.39)
p-value	0.02	0.03	<0.0001	<0.0001

* Parametric analysis (i.e. treatment effects expressed as a difference in adjusted means)

**A negative score signifies a higher level of craving symptoms in the placebo group compared to active

From sponsor table 5.4.1.5

Note that the plan to use a non-parametric test, the Wilcoxon rank sum, if normality was violated, while reasonable, was not explicit in the protocol. The sponsor found cause to use the difference in medians, along with a bootstrap estimate of the variability, for withdrawal symptoms in the 2mg groups. The difference was found significant in favor of the active lozenge for week 1 but not week 2; the parametric analysis, also done by the sponsor, found a significant difference in week 2 but not week 1.

Change in body weight

A two sample t-test was carried out to investigate whether the change from baseline was significantly different between the active and placebo for each dose at weeks 6 and 12 and month 6 for all subjects providing this information. Summary statistics, mean differences between treatment groups and associated 95% confidence intervals are presented for each of the above time points analyzed along with the respective p-values. The data from the analysis are summarized in table 6 below and show that for the full ITT population there are no significant differences between the 2 mg nicotine lozenge and its matched placebo group in terms of change in body weight at any of the timepoints analyzed. For the 4 mg lozenge compared to its matched placebo group there are small but statistically significant differences between the active treatment and placebo at six weeks post-quit ($p<0.0001$) and twelve weeks post-quit ($p=0.0412$) but not six months post-quit. At all timepoints shown the placebo group showed an increased weight gain compared to the 4 mg nicotine lozenge group.

Table 6 Weight Gain over Time

Dependency group	Time	n	Mean change in bodyweight (kg)		Treatment difference Nicotine - Placebo (95% CI)	p-value
			Active	Placebo		
Low Dependency (2 mg versus Placebo)	Week 6	394	1.43	1.54	-0.11 (-0.52,0.30)	0.59
	Week 12	324	2.25	2.31	-0.06 (-0.65,0.53)	0.85
	Month 6	229	3.17	3.15	0.02 (-0.95,0.99)	0.97
High Dependency (4 mg versus Placebo)	Week 6	344	1.27	2.30	-1.03 (-1.48,-0.57)	<0.0001
	Week 12	271	2.67	3.40	-0.73 (-1.43,-0.03)	0.0412
	Month 6	199	4.30	4.74	-0.44 (-1.68,0.80)	0.4858

A negative score signifies a higher bodyweight in the placebo group compared to active.
From sponsor table 5.4.1.7

A variety of sub-groups were examined in exploratory efficacy analyses:

Subjects using greater than the median dose were compared to those using fewer for each of the high and low dependency groups performed, in order to establish whether increased usage was associated with improved efficacy;

Since allocation to high or low dependency, and therefore to 2 mg or 4 mg, was made by time to first cigarette, analyses were performed to examine sub-groups of subjects who would have been allocated to high or low dependency by cigarettes per day;

Subjects using greater than 15 tablets were compared to those using fewer for each of the high and low dependency groups.

This last analysis was of particular interest. Although the maximum specified in the label used in the course of the trial was 20 tablets per day, the sponsor wishes to label the final product for a maximum of 15 per day (the sponsor's stated logic is that this is the maximum allowed in certain countries. It may also be that the sponsor hopes that this will allay safety concerns related to the maximum plasma concentration of nicotine as well.) However, as Dr. Celia Winchell notes, while the treatment was efficacious in the groups using no more than 15 lozenges, it is impossible to know how the population as a whole would have reacted had the instructions been to take no more than 15 (rather than no more than 20). Would everyone have taken fewer? Or would only the people who consumed more than 15 have taken fewer?

In general, efficacy of the lozenge was seen regardless of the subgroup examined. A detailed description of these subgroup analyses, including discussion of related safety issues, can be found in the clinical review.

Demographic subgroups

Summary statistics only are also provided for the primary efficacy variable (CO-verified 28 day smoking abstinence at six weeks) by treatment group for the following demographic subgroups: ethnic group (i.e., Caucasian, Black, Asian, Other as per CRF); age (55 years or more, less than 55 years); and gender. Success rates for the nicotine lozenge ranged from 40% to 64%. Placebo rates were the same as active in one subgroup (2mg lozenge, 55 and over) but otherwise ranged from 13 to as much as 35 percentage points less.

Conclusions

Both the 2 mg and 4 mg nicotine lozenge appear to be effective at the primary evaluation time of 6 weeks, as well at later times in this 6-month report. The chance of ceasing to smoke is statistically significantly higher for a subject using a nicotine lozenge than taking a placebo. Secondary measures of the effects of the nicotine lozenge are also favorable.

Labeling Comments

Since the sponsor would like this product approved directly for OTC marketing, the label should reflect the conditions it was tested under, especially any directions for use given to study subjects.

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