

The following is a very brief summary of bupropion sustained-release pharmacokinetic data, which are reviewed separately.

Following multiple-dose oral administration of bupropion immediate-release tablets to healthy male volunteers, the drug and its basic metabolites were found to exhibit linear kinetics over the range of 300 to 450 mg/day. In animal models, the three metabolites of the immediate-release formulation (306U73, 494U73, and 17U87) are, respectively 0.568, 0.208, and 0.208 times as potent as the parent drug. The metabolites are thought to contribute significantly to the therapeutic effect of bupropion because of their relatively higher plasma concentrations. Oral absolute bioavailability of bupropion in humans has not been determined because an intravenous formulation for human use is not available. In rats and dogs, the absolute bioavailability of bupropion ranges from 5% to 20%. Bupropion is extensively metabolized in the liver. Following oral administration of the immediate-release formulation, time to peak plasma concentration is up to two hours. The elimination half-life of bupropion immediate-release following single-dose administration is about 14 hours, with a range of 8 to 24 hours. Bupropion is about 80% bound to human albumin at plasma concentrations up to 200 µg/mL. Following oral administration of 200 mg <sup>14</sup>C-bupropion HCl aqueous solution in man, 87% and 10% of the radioactive dose was recovered in urine and feces, respectively. The fraction of the oral dose of bupropion excreted unchanged in urine was only 0.5%.

Following single-dose oral administration of bupropion sustained-release tablets to healthy male volunteers, peak plasma levels were achieved within three hours for the parent compound and within six hours for its metabolites. Peak plasma levels of bupropion were about 50% of that for the immediate-release tablet when given in equal single doses. At steady state, peak plasma levels of bupropion for the 150 mg bupropion sustained-release tablet given b.i.d. were about 15% lower than that for the 100 mg immediate-release tablet given t.i.d. Peak levels of the metabolites were similar following both the sustained and immediate-release tablets. Trough and average plasma levels of bupropion and its metabolites for the 150 mg b.i.d. sustained-release tablet were similar to those for the 100 mg t.i.d. immediate-release tablet. The 90% confidence intervals for the geometric mean AUC over the whole 24-hour dosing interval for bupropion and its three primary metabolites and the pharmacologic activity-weighted composite fell within the range of equivalence criteria of 80% to 125% of the immediate-release drug.

## 7.0 Efficacy Findings

### 7.1 Overview of Studies Pertinent to Efficacy

The bupropion sustained-release NDA comprises reports of two phase 2-3 clinical trials that were intended, for the most part, to explore antidepressant efficacy of several different dosing levels of the drug. Studies 203 and 205 were both U.S. placebo-controlled fixed dose studies. One open trial of bupropion sustained-release was also conducted (Study 208), which will be reviewed below in brief.

### 7.2 Summary of Studies Pertinent to Efficacy

#### 7.2.1 Study 203

##### 7.2.1.1 Investigators and Location

Six U.S.A. sites participated in this trial. The principal investigators were L. A. Cunningham at the Vine Street Clinic, Springfield, IL, L. F. Fabre at Research Testing, Inc., Houston, TX, J. P. Feighner at the Feighner Research Institute, San Diego, CA, E. A. Gardner of Washington, D.C., F. W. Reimherr at the University of Utah, Salt Lake City, UT, and E. C. Settle, Jr. and S. C. Lerfeld of Charleston, WV.

### 7.2.1.2 Study Plan

#### 7.2.1.2.1 Objectives/Rationale

The objective of this trial was to compare the safety and efficacy of two doses of bupropion sustained-release and placebo in the treatment of patients with major depression.

#### 7.2.1.2.2 Population

The following summarizes inclusion criteria for the study:

- Age greater than 17 years old
- Good physical health
- Meeting DSM-III-R criteria for Major Depressive Disorder, with a current Major Depressive Episode of between four weeks and two years duration
- Score of at least 20 on the first 17 items of the 28-item Hamilton Depression Scale (HAMD) at both time of screening and after one week of placebo washout, with a drop of not more than 20 per cent over the week of placebo washout.

Patients were excluded for the following:

- Predisposition to seizures, either by personal or family history, or by concurrent brain tumor or seizure-threshold-lowering medications
- Presence of a significant DSM-III-R Axis II diagnosis that would suggest non-responsiveness to pharmacotherapy for depression
- History of diagnosis of anorexia nervosa or bulimia
- Presence of medical disorder that would interfere with drug levels or with the accurate assessment of depression.
- Females who were pregnant, breast-feeding, or unwilling to employ appropriate contraceptive methods during the study
- History within one year of alcohol or substance abuse
- Receipt of fluoxetine or an investigational drug within four weeks of the treatment phase, receipt of an MAOI drug or protriptyline within two weeks of the treatment phase, or receipt of any other psychoactive drug within one week of the treatment phase.
- History of treatment with bupropion
- Incapable of spontaneous conversation or activity
- Active suicidality.

#### 7.2.1.2.3 Planned Study Conduct/Dosing Plan

Following one week of single-blind b.i.d. placebo washout, this trial was an eight week, parallel, double blind study; patients were randomly assigned to receive placebo, or one of two dose levels of bupropion sustained-release. Patients were randomized in blocks of six, with equal chances of receiving any of the three treatments. Medication consisted of identically-appearing tablets containing either placebo or 150 mg bupropion sustained-release. Each patient received a blister card containing a ten day supply of medication each week. They were instructed to take one tablet in the morning and one each evening and to return the blister card with all unused tablets. On this schedule, patients either received placebo b.i.d., 150 mg bupropion sustained-release qam and placebo qpm, or 150 mg bupropion sustained-release b.i.d. To adjust to the dosage, patients in the latter group received placebo in the evening for the first three days of the study. Patients who experienced intolerable adverse effects from their assigned dose were to be discontinued from the trial. Except for chloral hydrate that was permitted as a supplement in the first two weeks of the study, concomitant psychoactive medications were not permissible. Compliance was assessed by weekly review of the blister card.

#### 7.2.1.2.4 Efficacy Assessments

The 17-item HAMD, a 28-item HAMD including eight atypical vegetative symptom items and three items addressing helplessness, hopelessness, and worthlessness, the Clinical Global Impression for Severity of Illness (CGI-S), and the Clinical Global Impression for Improvement of Illness (CGI-I) constituted the efficacy measures and were performed at each weekly visit. A screening visit occurred at the onset of placebo washout. A baseline (Day 0) visit occurred one week later at which time participating patients were randomly assigned to receive treatment. The remaining visits occurred at one week intervals over the following eight weeks.

#### 7.2.1.2.5 Safety Assessments

Safety assessments included physical examinations, clinical laboratory tests, electrocardiograms at the discretion of the individual investigators, and an adverse experience probe by investigators.

#### 7.2.1.2.6 Analysis/Plan

The sponsor designated the following *a priori* efficacy parameters: 17-item HAMD score, the 28-item HAMD, HAMD depressed mood (item #1), CGI-S rating, and CGI-I rating. The analyses were performed using observed scores and last observation carried forward scores. Parametric analysis and non-parametric "responder" analysis was specified for the data.

#### 7.2.1.3 Study Conduct/Outcome

##### 7.2.1.3.1 Patient Disposition

A total of 362 patients constituted the baseline sample and the intent-to-treat sample (those patients receiving at least one dose of their assigned medication and having at least one efficacy assessment after baseline) constituted 342 patients. The intent-to-treat sample consisted of 116 patients assigned to placebo, 113 patients assigned to 150 mg/d bupropion sustained-release and 113 patients assigned to 300 mg/d bupropion sustained-release. Forty-eight per cent of placebo patients, 57 per cent of 150 mg/d drug-treated, and 55 per cent of 300 mg/d drug-treated patients completed the study. Overall, 182 patients (53% of the intent-to-treat sample) completed the study. Appendix 7.2.1.3 shows the patient completion rates by week for each treatment group.

The highest proportion of dropouts occurred in the placebo group and the lowest in the 300 mg/d drug group. An ill-characterized category of "consent withdrawn" was the most common cause for early termination among drug-treated groups, while inadequate response was the most common cause for early termination among placebo patients. Because some of the patients may have experienced adverse events before withdrawing consent to participate, the actual role of adverse experiences leading to premature study discontinuation may be larger than stated by the sponsor. Table 7.2.1.3.1 lists reasons for premature discontinuation by treatment group.

Table 7.2.1.3.1 Reasons for Premature Study Discontinuation from Protocol 203						
	Bupropion Sustained-Release Dosage Group					
	150 mg/d (N=121)		300 mg/d (N=120)		Placebo (N=121)	
	#	% of N	#	% of N	#	% of N
Consent Withdrawn	22	18.2%	22	18.3%	21	17.4%
Inadequate Response/ Condition Deteriorated	15	12.4%	12	10.0%	27	22.3%
Adverse Experience	10	8.3%	13	10.8%	4	3.3%
Lost to Follow-up	5	4.1%	2	1.7%	7	5.8%
Protocol Violation	3	2.5%	4	3.3%	1	0.8%
Total	55	45.5%	53	44.2%	60	49.6%

#### 7.2.1.3.2 Demographic Characteristics

Appendix 7.2.1.3 presents the demographic characteristics of the patients enrolled. The majority were female, consistent with typical gender patterns for major depression. There were no appreciable differences between treatment groups on the basis of age or race, although fewer of the placebo-treated patients (59%) were female than of the drug-treated groups (75%). Sixty-three per cent, 57 per cent, and 63 per cent, respectively, of patients in the 150 mg, 300 mg, and placebo groups were experiencing a recurrent episode of depression. The three groups were roughly comparable as to characterization of the present episode as agitated vs. retarded vs. uncomplicated, or typical vs. atypical depression.

#### 7.2.1.3.3 Baseline Illness Severity

Appendix 7.2.1.3 presents the baseline and follow-up measures of illness severity. Pairwise contrasts of baseline symptom scores on the efficacy measures across treatment groups based on means and standard deviations supplied by the sponsor were performed using t-tests (cf: Stanton A. Glantz, *Primer of Biostatistics*, 1992, p. 81). There were no statistically significant differences between groups.

#### 7.2.1.3.4 Dosing Information

The sponsor calculated mean daily dosages of medication intake as of the fourth day of the study (by which time patients had been titrated up to the full dosage level) through day of discontinuation. The mean daily dose of bupropion sustained-release ingested by the 150 mg/d group was 147 mg. The mean daily dose of bupropion sustained-release ingested by the 300 mg/d group was 290 mg.

#### 7.2.1.3.5 Concomitant Medications

Concomitant medication was administered to 75% of 150 mg/d patients, 71% of 300 mg/d patients, and 64% of placebo patients. The most commonly administered medications were non-narcotic analgesics, miscellaneous cold preparations or antihistamines, female hormones or birth control pills, and antibiotic or antiviral agents.

## 7.2.1.3.6

## Efficacy Results

As noted previously, the sponsor focused on the following as key efficacy variables: the 17-item HAMD, the 28-item HAMD, item #1 of the HAMD, the Clinical Global Impression for Severity of Illness (CGI-S), and the Clinical Global Impression for Improvement of Illness (CGI-I). Appendix 7.2.1.3 presents the data for these key efficacy variables with both the observed case (OC) and the last observation carried forward (LOCF) analyses. Two-tailed t-tests were used to compare changes in each of these variables in the drug- vs. placebo-treated groups at each week of the study. In addition, chi square "responder analyses" were conducted to test for differences in the proportions of responders in the treatment groups. For the HAMD analyses, a patient whose total score was reduced by 50 per cent or more between baseline and discontinuation was considered a responder. For the CGI-I analysis, a patient who was rated as "very much improved" or "much improved" at discontinuation was considered a responder. The following sections are a brief summary of the findings.

Table 7.2.1.3.6 displays a summary of the statistical comparisons between placebo and both drug treatment groups for the outcome variables. The reader should note that these are not independent scales.

Table 7.2.1.3.6 Summary of Efficacy Variables in Study 203 (?? = $p \leq 0.10$ , ? = $p \leq 0.05$ , + = $p \leq 0.01$ , p values were not corrected for multiple time-points or multiple dose-sizes comparisons testing)											
Week	Daily Dose (mg)	17-HAMD		28-HAMD		HAMD-#1		CGI-S		CGI-I	
		LOCF	OC	LOCF	OC	LOCF	OC	LOCF	OC	LOCF	OC
1	150										
	300										
2	150							??	??		
	300										
3	150	?	??	?	??			?	?	?	?
	300							??		??	
4	150	?	?	??	?			+	+	+	+
	300			??						??	
5	150	??						?	?	?	?
	300									??	
6	150	??				??		??		?	
	300			??		??		?		?	
7	150	?		??		?		+	??	?	
	300	??		??		??		??		?	
8	150	?		??		??		?		+	??
	300	?		??		?		?		+	??

#### 7.2.1.3.6.1 17-Item HAMD

The LOCF analyses showed p values of less than 0.05 favoring drug over placebo at three, four, seven, and eight weeks for 150 mg/d and at eight weeks for 300 mg/d. The OC analysis showed p values of less than 0.05 favoring drug over placebo at four weeks for 150 mg/d and at no time for 300 mg/d. Had the sponsor corrected their analysis for multiple-comparisons, no significant differences would have been demonstrated at any time point. Fifty-five of 120 (46%) 150 mg/d patients, 52 of 113 (46%) 300 mg/d patients, and 41 of 117 (35%) placebo patients were considered treatment responders at time of discontinuation. A Pearson chi-square analysis comparing the proportion of responders across the treatment groups showed no difference between the three treatment groups ( $X^2=3.78$ ,  $df=2$ ,  $p=0.151$ ).

#### 7.2.1.3.6.2 28-Item HAMD

The LOCF analyses showed p values of less than 0.05 favoring drug over placebo at three weeks for 150 mg/d and at no time for 300 mg/d. The OC analysis showed p values of less than 0.05 favoring drug over placebo at four weeks for 150 mg/d and at no time for 300 mg/d. Had the sponsor corrected their analysis for multiple-comparisons, no significant differences would have been demonstrated at any time point. Fifty-four of 120 (45%) 150 mg/d patients, 54 of 113 (48%) 300 mg/d patients, and 39 of 117 (33%) placebo patients were considered treatment responders at time of discontinuation. A Pearson chi-square analysis comparing the proportion of responders across the treatment groups showed a trend toward one of the three groups being of different efficacy than the others ( $X^2=5.60$ ,  $df=2$ ,  $p=0.061$ ).

#### 7.2.1.3.6.3 HAMD-Item #1

The LOCF analyses showed p values of less than 0.05 favoring drug over placebo at seven weeks for 150 mg/d and at eight weeks for 300 mg/d. The OC analysis showed p values of less than 0.05 favoring drug over placebo at no time for either dosage. Had the sponsor corrected their analysis for multiple-comparisons, no significant differences would have been demonstrated at any time point.

#### 7.2.1.3.6.4 CGI-S

The LOCF analyses showed p values of 0.05 or less favoring drug over placebo at three, four, five, seven, and eight weeks for 150 mg/d and at six and eight weeks for 300 mg/d. The OC analysis showed p values of 0.05 or less favoring drug over placebo at three through five weeks for 150 mg/d and at no time for 300 mg/d. Had the sponsor corrected their analysis for multiple-comparisons, significant differences would have been demonstrated in the LOCF analysis at four and seven weeks for 150 mg/d and in the OC analysis at four weeks for 150 mg/d, but not at any other time point on any other CGI-S analysis.

#### 7.2.1.3.6.5 CGI-I

The LOCF analyses showed p values of 0.05 or less favoring drug over placebo at three through eight weeks for 150 mg/d and at six through eight weeks for 300 mg/d. The OC analysis showed p values of less than 0.05 favoring drug over placebo at three through five weeks for 150 mg/d and at eight weeks for 300 mg/d. Had the sponsor corrected their analysis for multiple-time point comparisons, significant differences would have remained at four and eight weeks for 150 mg/d and at eight weeks for 300 mg/d on the LOCF analysis, and at four weeks for 150 mg/d on the OC analysis. Fifty-eight of 120 (48%) 150 mg/d patients, 59 of 113 (52%) 300 mg/d patients, and 42 of 116 (36%) placebo patients were considered treatment responders at time of discontinuation. A Pearson chi-square analysis comparing the proportion of responders across the treatment groups showed at least one of the three groups being of different efficacy than the others ( $X^2=6.48$ ,  $df=2$ ,  $p=0.039$ ). Looking at the individual dosage groups vs. placebo, the response rate showed a trend (Yates  $X^2=3.07$ ,  $df=1$ ,  $p=0.080$ ) toward

statistical significance between the 150 mg/d group and placebo and a significant difference (Yates  $X^2=5.32$ ,  $df=1$ ,  $p=0.021$ ) between the 300 mg/d group and placebo.

#### 7.2.1.4 Conclusions

(203)

The parametric analyses show inconsistent results across outcome measures, no clear evidence of an expected dose-response relationship, nor a consistency between LOCF and OC analyses. Had there been statistical correction for multiple-time-point or multiple-dose testing, then the data in favor of efficacy of either dose of bupropion sustained-release tested would be even weaker. Except for the CGI-I scale, the non-parametric analyses are not consistent across outcome measures, do not provide clear evidence of a dose-response relationship, and do not provide statistically significant evidence of the effect of bupropion sustained-release. The non-parametric analysis of the CGI-I scale alone does support the efficacy of 300 mg/d of bupropion sustained-release. On balance, although no specific standard of efficacy was established in the design of this study, the data from protocol 203 fail to show convincing evidence of the efficacy of either of the two doses of bupropion sustained-release that were tested.

#### 7.2.2 Study 205

##### 7.2.2.1 Investigators and Location

Eleven U.S.A. sites participated in this trial. The principal investigators were J. T. Apter at Princeton Biomedical Research, Princeton, NJ, R. J. Bielski at the Institute for the Study of Mood Disorders, Okemos, MI, J. L. Claghorn of Houston, TX, D. Dunner of Seattle, WA, J.M. Ferguson at Pharmacology Research Corporation, Murray, UT, J. W. Jefferson at Dean Foundation, Madison, WI, B. L. Kennedy at the University of Louisville, Louisville, KY, C. Merideth of San Diego, CA, R. K. Shrivastava at Eastside Comprehensive Medical Services of New York, NY, S. M. Stahl of San Diego, CA, and R. Weisler of Raleigh, NC.

##### 7.2.2.2 Study Plan

###### 7.2.2.2.1 Objectives/Rationale

The objective of this trial was to compare the safety and efficacy of four doses of bupropion sustained-release and placebo in the treatment of patients with major depression.

###### 7.2.2.2.2 Population

The following summarizes inclusion criteria for the study:

- Age greater than 17 years old
- Good physical health
- Meeting DSM-III-R criteria for Major Depressive Disorder, with a current Major Depressive Episode of between four weeks and two years duration
- Score of at least 20 on the first 17 items of the 28-item HAM-D at both time of screening and after one week of placebo washout, with a drop of not more than 20 per cent over the week of placebo washout.

Patients were excluded for the following:

- Predisposition to seizures, either by personal or family history, or by concurrent brain tumor or seizure-threshold-lowering medications
- Presence of a significant DSM-III-R Axis II diagnosis that would suggest non-responsiveness to pharmacotherapy for depression
- History of diagnosis of anorexia nervosa or bulimia
- Presence of medical disorder that would interfere with drug levels or with the accurate assessment of depression

### Study Results

Before commenting on the findings for these 3 studies, we thought it would be useful to provide our summary of the data, which we have done in Enclosures 2-5. Enclosures 2-4 (Tables 1-3) summarize the 2-sided significance levels, by week, for pairwise comparisons of bupropion SR with placebo in the 3 studies (203, 205, and 212, respectively). These are the results of analyses done on intent-to-treat samples and include the results of both LOCF and OC analyses. Enclosure 5 (Tables 4-6) summarizes treatment effect size data for these 3 studies, defined here as the difference between bupropion SR and placebo in mean change from baseline for HAMD-17 or -21 Total Score at week 8, for LOCF analyses.

### Comments on Efficacy Data for Individual Studies

Our comments will focus on "positive findings," i.e., p-values of  $\leq 0.05$ , 2-sided, for either LOCF or OC analyses, favoring bupropion SR over placebo in pairwise comparisons for any of the 8 weeks of each study.

#### **Study 203**

##### **(1) Unadjusted Results**

The results in Table 1 were unadjusted for multiple comparisons, and even without such adjustment, these data did not suggest a consistent superiority for bupropion SR, at either dose, over placebo.

The results were strongest for the 150 mg/day dose group, in particular for CGI Severity and Improvement. However, even for those variables, there was a loss of significance in the OC analyses beyond 5 weeks. There was less consistent support for this dose on the HAMD-17 total score, i.e., positive findings at weeks 3, 4, 7, and 8, but only for the LOCF analysis. There was very little support on either the HAMD-28 total score or the HAMD Item 1.

The results were weaker for the 300 mg/day dose group, with the most positive findings for CGI improvement on the LOCF analysis. For 3 of the remaining 4 variables, there were positive findings only for week 8 in the LOCF analyses, except for an additional positive result for week 6 LOCF on CGI severity. There were no positive findings for HAMD-28 total score.

##### **(2) Adjusted Results**

Given the two dose groups in this study, it was necessary to make an adjustment for multiple comparisons. One approach was to use Dunnett's test, which yielded a critical p-value of 0.025 for declaring any particular finding positive. Using this criterion p-value, the positive findings on the CGI severity and improvement scores for the 150 mg dose group generally prevailed, however, there were virtually no positive findings on the 3 HAMD variables for the 150 mg/day dose group or for any of the 5 variables for the 300 mg/day dose group.

Impression: We consider this to be a negative study that cannot provide support for the antidepressant efficacy of either the 150 or 300 mg/day bupropion SR doses.

### Study 205

#### (1) Unadjusted Results

The results in Table 2 were unadjusted for multiple comparisons, and even without such adjustment, these data did not suggest a consistent superiority for bupropion SR, at any of the 4 doses, over placebo.

The results were strongest for the 100 mg/day dose group, in particular for HAMD-28 total score and CGI Severity, but only for the LOCF analyses. There were virtually no positive findings for the OC analyses for the 100 mg/day dose group, and no consistently positive findings for either LOCF or OC analyses for any of the other higher dose groups.

#### (2) Adjusted Results

Given the four dose groups in this study, it was necessary to make an adjustment for multiple comparisons. One approach was to use Dunnett's test, which yielded a critical p-value of 0.012 for declaring any particular finding positive. Using this criterion p-value, there were only 3 significant pairwise comparisons, one for each of the higher three dose groups and all at week 7 in the OC analyses.

Impression: We consider this to be a negative study that cannot provide support for the antidepressant efficacy of any of the four dose groups.

### Study 212

#### (1) Unadjusted Results

The results in Table 3 were unadjusted for multiple comparisons, and even without such adjustment, these data did not suggest a consistent superiority for bupropion SR, at either dose, over placebo.

The results were strongest for the 150 mg/day dose group, in particular for HAMD-21, MADRS, and CGI Improvement. However, even for those variables, there was little support in the OC analyses. There was very little support on either the CGI Severity or the HAMD Item 1.

The results were very weak for the 300 mg/day dose group, with scattered positive findings at early time points and essentially no supportive findings later.

**Phase 2-3 Studies: Placebo Controlled Trials**

Protocol	Blind	Design	Centers	Length	Dosing	Setting	Diagnosis	Levels	Bupropion (po)	N*
203	Double	Parallel Group	6	8 weeks	Fixed	Outpatient	Major Depression	3	PBO am PBO pm	117
									150 mg am PBO pm	120
									150 mg am 150 mg pm	116
205	Double	Parallel Group	11	8 weeks	Fixed	Outpatient	Major Depression	5	PBO am PBO pm	118
									50 mg am 50 mg pm	115
									100 mg am 100 mg pm	115
									150 mg am 150 mg pm	113
									200 mg am 200 mg pm	114

\*Number of patients randomly assigned to treatment, after the exclusion of 9 patients from protocol 203 and 27 patients from protocol 205 for whom no treatment phase assessments were conducted.

FEB 17 1995

## Statistical Review and Evaluation

NDA#: 20-358/3-S

Sponsor: Burroughs-Wellcome

Name of Drug: Wellbutrin SR

Documents Reviewed: Vols 2.29, 2.46, Vol 11 dated 12/23/94

Medical Officer: Dan Oren, M.D., HFD-120

The sponsor has submitted 3 multidose, placebo controlled studies (203,205,212) of a sustained release formulation of Wellbutrin. Statistically significant results are scattered over various time points for several variables within each study. See Dr. Oren's review for study descriptions and a summary of results. No consistent or coherent evidence of efficacy emerges from this wealth of data. This reviewer performed a simple meta-analysis using these three studies in order to investigate whether strength of numbers would reveal a signal in the data.

This meta-analysis used the (change from baseline) HAMD 28 at 8 weeks for both observed cases and LOCF analyses. The treatment comparison was 300 mg vs PBO since 100 mg was near the high end and 300 mg was the dose common to all three trials. The 95% confidence intervals below are for the treatment difference between changes from baseline. All results are in the direction favorable for the drug.

	LOCF	OBSERVED CASES
Spons' p-value	.051	.16
<u>203</u> Conf Int	(-5.6, 0.14)	(-5.85, 1.31)
Post Hoc power	.46	.24
Spons' p-value	.39	.03
<u>205</u> Conf Int	(-4.5, 1.5)	(-7.2, 0.04)
Post Hoc power	.16	.49
Spons' p-value	.25	.14
<u>212</u> Conf Int	(-4.1, 1.0)	(-5.2, 0.7)
Post Hoc power	.21	.32

Enclosure 2

NDA 20-358

WELLBUTRIN SR (bupropion hydrochloride) Tablets

Table 1 Summary of Significance Levels <sup>1</sup> (2-sided) for Pairwise Comparisons (Bupropion SR vs Placebo) in Study 203																
Key Outcome Variables	150 mg vs Pbo								300 mg vs Pbo							
	Week <sup>2</sup>								Week							
	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8
HAMD-17 LOCF OC	-	-	*	*	t	t	*	*	-	-	-	-	-	-	t	*
HAMD-28 LOCF OC	-	-	*	t	t	-	t	t	-	-	t	t	-	t	t	t
HAMD Item 1 LOCF OC	-	-	-	t	-	t	*	t	-	-	t	-	-	t	t	*
CGI Severity LOCF OC	-	t	*	*	*	*	*	*	-	-	t	t	t	*	t	*
CGI Improvement LOCF OC	-	-	*	*	*	*	*	*	-	-	t	t	t	*	*	*

- 1   \* =  $p \leq 0.05$   
      t =  $p \leq 0.10$   
      - =  $p > 0.10$   
      \* =  $p \leq 0.025$  (criterion p-value for Dunnett's Test)

- 2   End of weeks 1-8

Table 1 Study 203 Demographic Profile of Primary Study Sample (N=353)*								
	Age (Years)		Gender		Race		Mass (kg)	
Treatment Group	Mean	Range	Male N (%)	Female N (%)	White N (%)	Non-White N (%)	Mean	Range
Dupropion Sustained-Release 150 mg/d	38	19-72	34 (28%)	86 (72%)	100 (83%)	20 (17%)	77.2	44.0-121.5
Dupropion Sustained-Release 300 mg/d	39	18-64	24 (21%)	92 (79%)	100 (86%)	16 (14%)	75.4	44.0-133.3
Placebo	40	19-69	48 (41%)	69 (59%)	100 (85%)	17 (15%)	78.8	47.6-147.8

\*The sponsor excluded nine of the 362 patients randomly assigned to a treatment condition at baseline from this table because no treatment phase assessments were available.

Table 2 Study 203 Patient Completion Rates										
Treatment Groups	Number Randomized	Intent-to-Treat Sample	Completers at Week [N (%)]							
			1	2	3	4	5	6	7	8
NUF SR 150	121	113	113 (100%)	109 (96%)	98 (87%)	89 (79%)	83 (73%)	70 (62%)	67 (59%)	64 (57%)
NUF SR 300	120	113	113 (100%)	100 (88%)	98 (87%)	87 (77%)	77 (68%)	74 (65%)	69 (61%)	62 (55%)
Placebo	121	116	116 (100%)	112 (97%)	102 (88%)	91 (78%)	75 (65%)	69 (59%)	64 (55%)	56 (48%)

Table 3  
Study 203  
Mean (X) and Mean Change (Δ) from Baseline in 17-item HAM-D

LAST OBSERVATION CARRIED FORWARD ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A
III/P SR 150 (I.)	120	23.1	113	-2.9	120	-5.6	120	-7.9	120	-8.9	120	-9.0	120	-9.4	120	-10.0	120	-10.2
III/P SR 300 (II)	113	23.4	113	-2.7	113	-4.8	113	-7.0	113	-8.0	113	-8.6	113	-8.9	113	-9.6	113	-10.2
Placebo (P)	117	23.2	116	-3.2	117	-5.2	117	-6.2	117	-7.0	117	-7.5	117	-7.6	117	-7.8	117	-8.1
2-sided p-values for pairwise comparisons																		
I. vs P	> 0.5		0.58		0.48		0.036		0.025		0.081		0.056		0.027		0.033	
II vs P	> 0.5		0.42		0.58		0.36		0.22		0.23		0.18		0.072		0.040	
OBSERVED CASES ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A
III/P SR 150 (I.)	120	23.1	113	-2.9	109	-5.9	98	-8.5	89	-10.3	83	-10.9	70	-12.4	67	-13.5	64	-14.1
III/P SR 300 (II)	113	23.4	113	-2.7	100	-4.9	98	-7.7	87	-9.3	77	-10.4	74	-11.8	69	-13.1	62	-14.8
Placebo (P)	117	23.2	116	-3.2	112	-5.2	102	-7.0	91	-8.2	75	-9.4	69	-11.4	64	-12.3	56	-12.8
2-sided p-values for pairwise comparisons																		
I. vs P	> 0.5		0.58		0.30		0.074		0.020		0.167		0.304		0.184		0.149	
II vs P	> 0.5		0.42		0.70		0.41		0.24		0.47		0.80		0.46		0.10	

**Table 4**  
**Study 203**  
**Mean (X) and Mean Change (Δ) from Baseline in 28-item HAM-D**

LAST OBSERVATION CARRIED FORWARD ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
DUP SR 150 (I)	120	31.5	113	-4.7	120	-8.2	120	-11.3	120	-12.4	120	-13.0	120	-13.2	120	-13.9	120	-14.1
DUP SR 300 (II)	113	32.2	113	-4.9	113	-8.2	113	-10.9	113	-12.1	113	-12.8	113	-13.5	113	-13.9	113	-14.5
Placebo (P)	117	32.2	116	-4.7	117	-7.6	117	-9.1	117	-10.1	117	-10.9	117	-11.2	117	-11.5	117	-11.8
2-sided p-values for pairwise comparisons																		
I vs P	> 0.2		0.98		0.48		0.042		0.051		0.10		0.11		0.066		0.088	
II vs P	> 0.5		0.77		0.56		0.10		0.093		0.13		0.077		0.072		0.051	
OBSERVED CASES ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
DUP SR 150 (L)	120	31.5	113	-4.7	109	-8.6	98	-12.1	89	-14.2	83	-15.6	70	-17.0	67	-18.6	64	-19.3
DUP SR 300 (II)	113	32.2	113	-4.9	100	-8.4	98	-11.7	87	-13.7	77	-15.2	74	-17.4	69	-18.4	62	-20.3
Placebo (P)	117	32.2	116	-4.7	112	-7.7	102	-10.0	91	-11.6	75	-13.4	69	-16.2	64	-17.6	56	-18.1
2-sided p-values for pairwise comparisons																		
I vs P	> 0.2		0.98		0.35		0.072		0.050		0.153		0.41		0.29		0.34	
II vs P	> 0.5		0.77		0.47		0.14		0.11		0.31		0.47		0.48		0.16	

**Table 5**  
**Study 203**  
**Mean (X) and Mean Change (Δ) from Baseline in HAM-D Depressed Mood Item #1**

LAST OBSERVATION CARRIED FORWARD ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
DUP SR 150 (I.)	120	2.8	113	-0.3	120	-0.7	120	-0.9	120	-1.0	120	-1.1	120	-1.2	120	-1.2	120	-1.2
DUP SR 300 (II)	113	2.9	113	-0.4	113	-0.6	113	-0.9	113	-1.0	113	-1.1	113	-1.2	113	-1.2	113	-1.3
Placebo (P)	117	2.9	116	-0.3	117	-0.6	117	-0.7	117	-0.8	117	-0.9	117	-0.9	117	-0.9	117	-1.0
2-sided p-values for pairwise comparisons																		
I. vs P	> 0.5		0.9		0.5		0.2		0.1		0.2		0.06		0.03		0.08	
II vs P	> 0.5		0.2		1.0		0.1		0.2		0.2		0.06		0.08		0.04	
OBSERVED CASES ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
DUP SR 150 (I.)	120	2.8	113	-0.3	109	-0.7	98	-0.9	89	-1.2	83	-1.3	70	-1.5	67	-1.7	64	-1.7
DUP SR 300 (II)	113	2.9	113	-0.4	100	-0.6	98	-1.0	87	-1.1	77	-1.4	74	-1.6	69	-1.6	62	-1.9
Placebo (P)	117	2.9	116	-0.3	112	-0.6	102	-0.8	91	-1.0	75	-1.2	69	-1.4	64	-1.5	56	-1.6
2-sided p-values for pairwise comparisons																		
I. vs P	> 0.5		0.9		0.6		0.3		0.2		0.3		0.6		0.4		0.6	
II vs P	> 0.5		0.2		1.0		0.1		0.2		0.2		0.5		0.6		0.3	

**Table 6**  
**Study 203**  
**Mean (X) and Mean Change (Δ) from Baseline in CGI-S**

LAST OBSERVATION CARRIED FORWARD ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
DUP SR 150 (I.)	120	4.4	113	-0.2	120	-0.6	120	-0.9	120	-1.1	120	-1.2	120	-1.2	120	-1.3	120	-1.4
DUP SR 300 (II)	113	4.4	113	-0.2	113	-0.5	113	-0.8	113	-0.9	113	-1.0	113	-1.2	113	-1.2	113	-1.4
Placebo (P)	117	4.4	116	-0.2	117	-0.4	117	-0.6	117	-0.7	117	-0.8	117	-0.9	117	-0.9	117	-1.0
2-sided p-values for pairwise comparisons																		
I. vs P	> 0.5		1.0		0.09		0.02		0.002		0.02		0.05		0.007		0.03	
II vs P	> 0.5		0.8		0.4		0.07		0.1		0.1		0.04		0.07		0.04	
OBSERVED CASES ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
DUP SR 150 (I.)	120	4.4	113	-0.2	109	-0.6	98	-1.0	89	-1.4	83	-1.4	70	-1.6	67	-1.8	64	-1.9
DUP SR 300 (II)	113	4.4	113	-0.2	100	-0.5	98	-0.9	87	-1.1	77	-1.2	74	-1.6	69	-1.6	62	-2.0
Placebo (P)	117	4.4	116	-0.2	112	-0.4	102	-0.7	91	-0.9	75	-1.1	69	-1.4	64	-1.5	56	-1.7
2-sided p-values for pairwise comparisons																		
I. vs P	> 0.5		1.0		0.05		0.03		0.002		0.02		0.4		0.1		0.3	
II vs P	> 0.5		0.8		0.3		0.1		0.2		0.3		0.3		0.4		0.2	

**Table 7**  
**Study 203**  
**Mean (X) CGI-I (Values less than four represent improvement)**

LAST OBSERVATION CARRIED FORWARD ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	X	N	X	N	X	N	X	N	X	N	X	N	X	N	X
IUP SR 150 (I.)	120	4.0	113	3.5	120	3.1	120	2.7	120	2.6	120	2.6	120	2.5	120	2.5	120	2.4
IUP SR 300 (II)	113	4.0	113	3.6	113	3.1	113	2.8	113	2.7	113	2.6	113	2.5	113	2.6	113	2.4
Placebo (P)	117	4.0	116	3.5	117	3.2	117	3.1	117	3.0	117	2.9	117	2.9	117	2.9	117	2.9
2-sided p-values for pairwise comparisons																		
I. vs P	*		1.0		0.2		0.01		0.006		0.01		0.04		0.01		0.009	
II vs P			0.7		0.3		0.09		0.08		0.07		0.03		0.05		0.009	
OBSERVED CASES ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	X	N	X	N	X	N	X	N	X	N	X	N	X	N	X
IUP SR 150 (I.)	120	4.0	113	3.5	109	3.0	98	2.6	89	2.4	83	2.2	70	2.1	67	1.9	64	1.8
IUP SR 300 (II)	113	4.0	113	3.6	100	3.0	98	2.7	87	2.6	77	2.4	74	2.1	69	2.1	62	1.8
Placebo (P)	117	4.0	116	3.5	112	3.2	102	3.0	91	2.8	75	2.6	69	2.2	64	2.1	56	2.1
2-sided p-values for pairwise comparisons																		
I. vs P	*		1.0		0.2		0.02		0.008		0.04		0.4		0.2		0.06	
II vs P			0.7		0.2		0.2		0.2		0.2		0.3		0.8		.006	

\* By definition, baseline scores are identical.

statistical significance between the 150 mg/d group and placebo and a significant difference (Yates  $X^2=5.32$ ,  $df=1$ ,  $p=0.021$ ) between the 300 mg/d group and placebo.

#### 7.2.1.4

#### Conclusions

(203)

The parametric analyses show inconsistent results across outcome measures, no clear evidence of an expected dose-response relationship, nor a consistency between LOCF and OC analyses. Had there been statistical correction for multiple-time-point or multiple-dose testing, then the data in favor of efficacy of either dose of bupropion sustained-release tested would be even weaker. Except for the CGI-I scale, the non-parametric analyses are not consistent across outcome measures, do not provide clear evidence of a dose-response relationship, and do not provide statistically significant evidence of the effect of bupropion sustained-release. The non-parametric analysis of the CGI-I scale alone does support the efficacy of 300 mg/d of bupropion sustained-release. On balance, although no specific standard of efficacy was established in the design of this study, the data from protocol 203 fail to show convincing evidence of the efficacy of either of the two doses of bupropion sustained-release that were tested.

#### 7.2.2 Study 205

##### 7.2.2.1 Investigators and Location

Eleven U.S.A. sites participated in this trial. The principal investigators were J. T. Apter at Princeton Biomedical Research, Princeton, NJ, R. J. Bielski at the Institute for the Study of Mood Disorders, Okemos, MI, J. L. Claghorn of Houston, TX, D. Dunner of Seattle, WA, J.M. Ferguson at Pharmacology Research Corporation, Murray, UT, J. W. Jefferson at Dean Foundation, Madison, WI, B. L. Kennedy at the University of Louisville, Louisville, KY, C. Merideth of San Diego, CA, R. K. Shrivastava at Eastside Comprehensive Medical Services of New York, NY, S. M. Stahl of San Diego, CA, and R. Weisler of Raleigh, NC.

##### 7.2.2.2 Study Plan

###### 7.2.2.2.1 Objectives/Rationale

The objective of this trial was to compare the safety and efficacy of four doses of bupropion sustained-release and placebo in the treatment of patients with major depression.

###### 7.2.2.2.2 Population

The following summarizes inclusion criteria for the study:

- Age greater than 17 years old
- Good physical health
- Meeting DSM-III-R criteria for Major Depressive Disorder, with a current Major Depressive Episode of between four weeks and two years duration
- Score of at least 20 on the first 17 items of the 28-item HAM-D at both time of screening and after one week of placebo washout, with a drop of not more than 20 per cent over the week of placebo washout.

Patients were excluded for the following:

- Predisposition to seizures, either by personal or family history, or by concurrent brain tumor or seizure-threshold-lowering medications
- Presence of a significant DSM-III-R Axis II diagnosis that would suggest non-responsiveness to pharmacotherapy for depression
- History of diagnosis of anorexia nervosa or bulimia
- Presence of medical disorder that would interfere with drug levels or with the accurate assessment of depression

statistical significance between the 150 mg/d group and placebo and a significant difference (Yates  $X^2=5.32$ ,  $df=1$ ,  $p=0.021$ ) between the 300 mg/d group and placebo.

#### 7.2.1.4

#### Conclusions

(203)

The parametric analyses show inconsistent results across outcome measures, no clear evidence of an expected dose-response relationship, nor a consistency between LOCF and OC analyses. Had there been statistical correction for multiple-time-point or multiple-dose testing, then the data in favor of efficacy of either dose of bupropion sustained-release tested would be even weaker. Except for the CGI-I scale, the non-parametric analyses are not consistent across outcome measures, do not provide clear evidence of a dose-response relationship, and do not provide statistically significant evidence of the effect of bupropion sustained-release. The non-parametric analysis of the CGI-I scale alone does support the efficacy of 300 mg/d of bupropion sustained-release. On balance, although no specific standard of efficacy was established in the design of this study, the data from protocol 203 fail to show convincing evidence of the efficacy of either of the two doses of bupropion sustained-release that were tested.

#### 7.2.2

#### Study 205

##### 7.2.2.1

##### Investigators and Location

Eleven U.S.A. sites participated in this trial. The principal investigators were J. T. Apter at Princeton Biomedical Research, Princeton, NJ, R. J. Bielski at the Institute for the Study of Mood Disorders, Okemos, MI, J. L. Claghorn of Houston, TX, D. Dunner of Seattle, WA, J.M. Ferguson at Pharmacology Research Corporation, Murray, UT, J. W. Jefferson at Dean Foundation, Madison, WI, B. L. Kennedy at the University of Louisville, Louisville, KY, C. Merideth of San Diego, CA, R. K. Shrivastava at Eastside Comprehensive Medical Services of New York, NY, S. M. Stahl of San Diego, CA, and R. Weisler of Raleigh, NC.

##### 7.2.2.2

##### Study Plan

###### 7.2.2.2.1

###### Objectives/Rationale

The objective of this trial was to compare the safety and efficacy of four doses of bupropion sustained-release and placebo in the treatment of patients with major depression.

###### 7.2.2.2.2

###### Population

The following summarizes inclusion criteria for the study:

- Age greater than 17 years old
- Good physical health
- Meeting DSM-III-R criteria for Major Depressive Disorder, with a current Major Depressive Episode of between four weeks and two years duration
- Score of at least 20 on the first 17 items of the 28-item HAM-D at both time of screening and after one week of placebo washout, with a drop of not more than 20 per cent over the week of placebo washout.

Patients were excluded for the following:

- Predisposition to seizures, either by personal or family history, or by concurrent brain tumor or seizure-threshold-lowering medications
- Presence of a significant DSM-III-R Axis II diagnosis that would suggest non-responsiveness to pharmacotherapy for depression
- History of diagnosis of anorexia nervosa or bulimia
- Presence of medical disorder that would interfere with drug levels or with the accurate assessment of depression

**Table 3**  
**Study 205: Mean (X) and Mean Change (Δ) from Baseline in 17-item HAM-D**

LAST OBSERVATION CARRIED FORWARD ANALYSIS																			
Treatment Week:		Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
Treatment Groups		N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
BUP SR 100 (VL)		112	23.6	107	-2.9	112	-5.0	112	-6.8	112	-8.2	112	-9.1	112	-9.7	112	-10.0	112	-10.5
BUP SR 200 (L)		114	23.2	106	-3.0	114	-4.3	114	-6.1	114	-7.2	114	-8.0	114	-9.0	114	-9.3	114	-9.6
BUP SR 300 (M)		111	23.6	106	-3.2	111	-4.9	111	-6.3	111	-7.6	111	-8.0	111	-8.5	111	-8.9	111	-9.0
BUP SR 400 (H)		111	24.2	108	-1.9	111	-4.2	111	-6.1	111	-7.4	111	-7.8	111	-8.3	111	-8.8	111	-9.3
Placebo (P)		116	23.4	109	-3.1	116	-4.8	116	-5.6	116	-6.8	116	-7.4	116	-8.0	116	-7.9	116	-8.3
VL vs P	2-sided p-values for pairwise compar- isons	> 0.5		0.59		0.84		0.12		0.10		0.061		0.082		0.042		0.035	
L vs P		> 0.5		0.81		0.46		0.51		0.61		0.52		0.29		0.18		0.22	
M vs P		> 0.5		0.96		0.91		0.44		0.39		0.57		0.66		0.42		0.53	
H vs P		> 0.05		0.018		0.34		0.50		0.47		0.64		0.74		0.41		0.30	
OBSERVED CASES ANALYSIS																			
Treatment Week:		Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
Treatment Groups		N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
BUP SR 100 (VL)		112	23.6	107	-2.9	103	-5.1	102	-7.2	89	-8.8	85	-9.9	86	-11.1	82	-11.5	76	-12.1
BUP SR 200 (L)		114	23.2	106	-3.0	100	-4.7	95	-6.6	90	-7.8	85	-9.0	83	-10.4	80	-11.1	74	-11.1
BUP SR 300 (M)		111	23.6	106	-3.2	98	-5.3	81	-7.4	80	-9.4	77	-10.2	71	-11.5	69	-11.9	66	-12.2
BUP SR 400 (H)		111	24.2	108	-1.9	94	-4.8	88	-7.2	83	-9.0	77	-9.8	74	-10.8	72	-11.6	70	-12.2
Placebo (P)		116	23.4	109	-3.1	107	-4.9	102	-5.9	90	-7.9	87	-8.8	83	-9.7	82	-9.5	75	-10.2
VL vs P	2-sided p-values for pairwise compar- isons	> 0.5		0.59		0.71		0.083		0.24		0.30		0.18		0.074		0.10	
L vs P		> 0.5		0.81		0.74		0.32		0.90		0.82		0.41		0.12		0.41	
M vs P		> 0.5		0.96		0.59		0.049		0.075		0.18		0.074		0.047		0.062	
H vs P		> 0.05		0.018		0.99		0.064		0.14		0.27		0.22		0.034		0.037	

FEB 17 1995

## Statistical Review and Evaluation

NDA#: 20-358/3-S

Sponsor: Burroughs-Wellcome

Name of Drug: Wellbutrin SR

Documents Reviewed: Vols 2.29, 2.46, Vol 11 dated 12/23/94

Medical Officer: Dan Oren, M.D., HFD-120

The sponsor has submitted 3 multidose, placebo controlled studies (203,205,212) of a sustained release formulation of Wellbutrin. Statistically significant results are scattered over various time points for several variables within each study. See Dr. Oren's review for study descriptions and a summary of results. No consistent or coherent evidence of efficacy emerges from this wealth of data. This reviewer performed a simple meta-analysis using these three studies in order to investigate whether strength of numbers would reveal a signal in the data.

This meta-analysis used the (change from baseline) HAMD 28 at 8 weeks for both observed cases and LOCF analyses. The treatment comparison was 300 mg vs PBO since 300 mg was near the high end and 300 mg was the dose common to all three trials. The 95% confidence intervals below are for the treatment difference between changes from baseline. All results are in the direction favorable for the drug.

	LOCF	OBSERVED CASES
<u>203</u> Spons' p-value	.051	.16
Conf Int	(-5.6, 0.14)	(-5.85, 1.31)
Post Hoc power	.46	.24
 <u>205</u> Spons' p-value	.39	.03
Conf Int	(-4.5, 1.5)	(-7.2, 0.04)
Post Hoc power	.16	.49
 <u>212</u> Spons' p-value	.25	.14
Conf Int	(-4.1, 1.0)	(-5.2, 0.7)
Post Hoc power	.21	.32

Phase 2-3 Studies: Placebo Controlled Trials

Protocol	Blind	Design	Centers	Length	Dosing	Setting	Diagnosis	Levels	Bupropion (po)	N*
203	Double	Parallel Group	6	8 weeks	Fixed	Outpatient	Major Depression	3	PBO am PBO pm	117
									150 mg am PBO pm	120
									150 mg am 150 mg pm	116
205	Double	Parallel Group	11	8 weeks	Fixed	Outpatient	Major Depression	5	PBO am PBO pm	118
									50 mg am 50 mg pm	115
									100 mg am 100 mg pm	115
									150 mg am 150 mg pm	113
									200 mg am 200 mg pm	114

\*Number of patients randomly assigned to treatment, after the exclusion of 9 patients from protocol 203 and 27 patients from protocol 205 for whom no treatment phase assessments were conducted.

Impression: We consider this to be a negative study that cannot provide support for the antidepressant efficacy of either the 150 or 300 mg/day bupropion SR doses.

### Study 205

#### (1) Unadjusted Results

The results in Table 2 were unadjusted for multiple comparisons, and even without such adjustment, these data did not suggest a consistent superiority for bupropion SR, at any of the 4 doses, over placebo.

The results were strongest for the 100 mg/day dose group, in particular for HAMD-28 total score and CGI Severity, but only for the LOCF analyses. There were virtually no positive findings for the OC analyses for the 100 mg/day dose group, and no consistently positive findings for either LOCF or OC analyses for any of the other higher dose groups.

#### (2) Adjusted Results

Given the four dose groups in this study, it was necessary to make an adjustment for multiple comparisons. One approach was to use Dunnett's test, which yielded a critical p-value of 0.012 for declaring any particular finding positive. Using this criterion p-value, there were only 3 significant pairwise comparisons, one for each of the higher three dose groups and all at week 7 in the OC analyses.

Impression: We consider this to be a negative study that cannot provide support for the antidepressant efficacy of any of the four dose groups.

### Study 212

#### (1) Unadjusted Results

The results in Table 3 were unadjusted for multiple comparisons, and even without such adjustment, these data did not suggest a consistent superiority for bupropion SR, at either dose, over placebo.

The results were strongest for the 150 mg/day dose group, in particular for HAMD-21, MADRS, and CGI Improvement. However, even for those variables, there was little support in the OC analyses. There was very little support on either the CGI Severity or the HAMD Item 1.

The results were very weak for the 300 mg/day dose group, with scattered positive findings at early time points and essentially no supportive findings later.

Enclosure 3

NDA 20-358

WELLBUTRIN SR (bupropion hydrochloride) Tablets

Table 2 Summary of Significance Levels <sup>1</sup> for Pairwise Comparisons (Bupropion SR vs Placebo) in Study 205				
Key Outcome Variables	Bupropion SR Dose Groups			
	100 mg	200 mg	300 mg	400 mg
	Week <sup>2</sup>	Week	Week	Week
	12345678	12345678	12345678	12345678
HAMD-17 LOCF OC	---t** ---t--t	----- -----	----- ---t-t*	*----- *-t---*
HAMD-28 LOCF OC	--t*** --t---t	----- -----t	----- ---t---	----- --t---*
HAMD Item 1 LOCF OC	---t*- -----	-t----- -----	----- --t-----	---t--- ---t-t*
CGI-S LOCF OC	--t*** --*-t--	----- -----	t----- t*-t--	----- -----t
CGI-I LOCF OC	--t-t** --t--t*	t--t** t---t*	t----- t--t**	----- --t--*

- 1      \* =  $p \leq 0.05$   
         t =  $p \leq 0.10$   
         - =  $p > 0.10$   
         \* =  $p \leq 0.012$  (criterion p-value for Dunnett's Test)

- 2      End of weeks 1-8

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- Females who were pregnant, breast-feeding, or unwilling to employ appropriate contraceptive methods during the study
- History within one year of alcohol or substance abuse
- Receipt of fluoxetine or an investigational drug within four weeks of the treatment phase, receipt of an MAOI drug or protriptyline within two weeks of the treatment phase, or receipt of any other psychoactive drug within one week of the treatment phase.
- History of treatment with bupropion
- Incapable of spontaneous conversation or activity
- Active suicidality.

#### 7.2.2.2.3 Planned Study Conduct/Dosing Plan

Following one week of single-blind b.i.d. placebo washout, this trial was an eight week, parallel, double blind study; patients were randomly assigned to receive placebo or one of four dose levels of bupropion sustained-release. Patients were randomized in blocks of five, with equal chances of receiving any of the five treatments. Medication consisted of identically-appearing tablets containing either placebo, 50 mg, or 150 mg bupropion sustained-release. Each patient received each week a carton with ten blister cards containing six tablets. They were instructed to take three tablets each morning and three each evening and to return the blister cards with all unused tablets. On this schedule, patients either received placebo b.i.d., 50 mg bupropion sustained-release b.i.d., 100 mg bupropion sustained-release b.i.d., 150 mg bupropion sustained-release b.i.d., or 200 mg bupropion sustained-release b.i.d.. Patients in the latter two groups were titrated to their study doses by the fourth and eighth days, respectively. Patients who experienced intolerable adverse effects from their assigned dose were to be discontinued from the trial. Except for chloral hydrate that was permitted as a supplement in the first two weeks of the study, concomitant medications intended for psychoactive purposes were not permissible during the study. Compliance was assessed by weekly review of the blister cards.

#### 7.2.2.2.4 Efficacy Assessments

The 17-item HAM-D, 28-item HAM-D, the CGI-S, and the CGI-I constituted the efficacy measures and were performed at each weekly visit. A screening visit occurred at the onset of placebo washout. A baseline (Day 0) visit occurred one week later at which time participating patients were randomly assigned to receive treatment. The remaining visits occurred at one week intervals over the following eight weeks.

#### 7.2.2.2.5 Safety Assessments

Safety assessments included physical examinations, clinical laboratory tests, electrocardiograms at the discretion of the individual investigators, and an adverse experience probe by investigators.

#### 7.2.2.2.6 Analysis/Plan

The sponsor designated the following *a priori* efficacy parameters: 17-item HAM-D score, 28-item HAM-D score, HAM-D depressed mood item #1, CGI-S rating, and CGI-I rating. The analyses were performed using observed scores and last observation carried forward scores. Parametric analysis and non-parametric "responder" analysis was specified for the data.

#### 7.2.2.3 Study Conduct/Outcome

##### 7.2.2.3.1 Patient Disposition

A total of 602 patients constituted the baseline sample and the intent-to-treat sample (those patients receiving at least one dose of their assigned medication and having at least one efficacy assessment after baseline) constituted

536 patients. The intent-to-treat sample consisted of 109 patients assigned to placebo, 107 patients assigned to 100 mg/d bupropion sustained-release, 106 patients assigned to 200 mg/d bupropion sustained-release, 106 patients assigned to 300 mg/d bupropion sustained-release, and 108 patients assigned to 400 mg/d bupropion sustained-release. Sixty-nine per cent of placebo patients, 71 per cent of 100 mg/d drug-treated, 70 per cent of 200 mg/d drug-treated, 62 per cent of 300 mg/d drug-treated, and 65 per cent of 400 mg/d drug-treated patients completed the study. Overall, 361 patients (67% of the intent-to-treat sample) completed the study. Appendix 7.2.2.3 shows the patient completion rates by week for each treatment group.

The highest proportion of dropouts occurred in the 300 and 400 mg/d bupropion sustained-release group and the lowest in the placebo and 100 mg/d drug groups. An ill-characterized category of "consent withdrawn" was the most common cause for early termination. Because some of the patients may have experienced adverse events before withdrawing consent to participate, the actual role of adverse experiences leading to premature study discontinuation may be larger than stated by the sponsor. Table 7.2.2.3.1 lists reasons for premature discontinuation by treatment group.

Table 7.2.2.3.1 Reasons for Premature Study Discontinuation from Protocol 205										
	Bupropion sustained-release Dosage Group:									
	100 mg/d N=119		200 mg/d N=120		300 mg/d N=120		400 mg/d N=119		Placebo N=124	
	#	% of N	#	% of N	#	% of N	#	% of N	#	% of N
Consent Withdrawn	17	14.3%	12	10.0%	13	10.8%	20	16.8%	15	12.1%
Inadequate Response/ Condition Deteriorated	8	6.7%	5	4.2%	6	5.0%	4	3.4%	5	4.0%
Adverse Experience	2	1.7%	9	7.5%	13	10.8%	12	10.1%	7	5.6%
Lost to Follow-up	6	5.0%	9	7.5%	14	11.7%	6	5.0%	9	7.3%
Protocol Violation	5	4.2%	7	5.8%	5	4.2%	1	0.8%	3	2.4%
Total	38	31.9%	42	35.0%	51	42.5%	43	36.1%	39	31.5%

#### 7.2.2.3.2 Demographic Characteristics

Appendix 7.2.2.3 presents the demographic characteristics of the patients enrolled. The majority were female, consistent with typical gender patterns for major depression. There were no appreciable differences between treatment groups on the basis of age, gender, or race. Seventy-eight per cent, 66 per cent, 67 per cent, 71 per cent, and 69 per cent, respectively, of patients in the 100 mg, 200 mg, 300 mg, 400 mg, and placebo groups were experiencing a recurrent episode of depression. The five groups were roughly comparable as to characterization of the present episode as agitated vs. retarded vs. uncomplicated, or typical vs. atypical depression.

#### 7.2.2.3.3 Baseline Illness Severity

Appendix 7.2.2.3 presents the baseline and follow-up measures of illness severity. Pairwise contrasts of baseline symptom scores on the efficacy measures across treatment groups based on means and standard deviations

supplied by the sponsor were performed using t-tests (cf: Stanton A. Glantz, *Primer of Biostatistics*, 1992, p. 81). No corrections were performed for multiple comparisons testing. The only statistically significant differences between drug groups and placebo groups at baseline were: the mean 28-item HAMD score was 1.6 points greater in the 400 mg/d group than in the placebo group ( $p < 0.05$ ); the mean item #1 of the HAMD score was 0.2 points lower in the 200 mg/d group than in the placebo group ( $p < 0.005$ ); the mean CGIS score was 0.2 points higher in the 300 mg/d and 400 mg/d groups than in the placebo group ( $p < 0.02$ ,  $p < 0.05$ , respectively). These differences appear to have little clinical significance.

#### 7.2.2.3.4 Dosing Information

The sponsor calculated mean daily dosages of medication intake as of the eighth day of the study (by which time patients had been titrated up to the full dosage level) through day of discontinuation. The mean daily dose of bupropion sustained-release ingested by the 100 mg/d group was 95 mg. The mean daily dose of bupropion sustained-release ingested by the 200 mg/d group was 191 mg. The mean daily dose of bupropion sustained-release ingested by the 300 mg/d group was 283 mg. The mean daily dose of bupropion sustained-release ingested by the 400 mg/d group was 375 mg.

#### 7.2.2.3.5 Concomitant Medications

Concomitant medication was administered to 87% of 100 mg/d patients, 83% of 200 mg/d patients, 86% of 300 mg/d patients, 82% of 400 mg/d patients, and 86% of placebo patients. The most commonly administered medications were non-narcotic analgesics, miscellaneous cold preparations or antihistamines, female hormones or birth control pills, antibiotic or antiviral agents, and vitamins or dietary supplements.

#### 7.2.2.3.6 Efficacy Results

As noted previously, the sponsor focused on the following as key efficacy variables: the 17-item HAMD, the 28-item HAMD, item #1 of the HAMD, the CGI-S, and the CGI-I. Appendix 7.2.2.3 presents the data for these key efficacy variables with both the observed case (OC) and the last observation carried forward (LOCF) analyses. Two-tailed t-tests were used to compare changes in each of these variables in the drug- vs. placebo-treated groups at each week of the study. In addition, chi square "responder analyses" were conducted to test for differences in the proportions of responders in the treatment groups. For the HAMD analyses, a patient whose total score was reduced by 50 per cent or more between baseline and discontinuation was considered a responder. For the CGI-I analysis, a patient who was rated as "very much improved" or "much improved" at discontinuation was considered a responder. The following is a brief summary of the findings.

Table 7.2.2.3.6 displays a summary of the statistical comparisons between placebo and both drug treatment groups for the outcome variables. The reader should note that these are not independent scales.

<p>Table 7.2.2.3.6</p> <p>Summary of Efficacy Variables in Study 205</p> <p>(?? = p≤ 0.10, ? = p≤ 0.05, p values were not corrected for multiple time-points or multiple dose-sizes comparisons testing)</p>											
Week	Daily Dose (mg)	17-HAMD		28-HAMD		HAMD-#1		CGI-S		CGI-I	
		LOCF	OC	LOCF	OC	LOCF	OC	LOCF	OC	LOCF	OC
1	100	?	?							??	??
	200										
	300										
	400										
2	100										
	200										
	300										
	400										
3	100		??		??			?	?	??	??
	200										
	300										
	400										
4	100			??						??	
	200										
	300										
	400										
5	100	??		?				??		??	
	200										
	300										
	400										
6	100	??		?	??	?		?	??	??	
	200										
	300										
	400										

Week	Daily Dose (mg)	17-HAMD		28-HAMD		HAMD-41		CGI-S		CGI-I	
		LOCF	OC	LOCF	OC	LOCF	OC	LOCF	OC	LOCF	OC
7	100	?	??	?	??			?	??	?	?
	200				??					?	?
	300		?		?				?		?
	400		?		?						?
8	100	?		?	??			?		?	??
	200									??	
	300		??		?						
	400		?		?		??				

#### 7.2.2.3.6.1 17-Item HAMD

The LOCF analyses showed p values of less than 0.05 favoring drug over placebo at seven and eight weeks for 100 mg/d, at no time for 200 mg/d or 300 mg/d, and at one week for 400 mg/d. The OC analysis showed p values of less than 0.05 favoring drug over placebo at no time for 100 mg/d or 200 mg/d, at three and seven weeks for 300 mg/d, and at one, seven, and eight weeks for 400 mg/d. Had the sponsor corrected their analysis for multiple-comparisons, no significant differences would have been demonstrated at any time point. Fifty-seven of 112 (51%) 100 mg/d patients, 45 of 114 (39%) 200 mg/d patients, 43 of 111 (39%) 300 mg/d patients, 47 of 111 (42%) 400 mg/d patients, and 38 of 116 (33%) placebo patients were considered treatment responders at time of discontinuation. Pearson chi-square analysis comparing the proportion of responders across the treatment groups showed a trend towards ( $\chi^2=8.22$ ,  $df=4$ ,  $p=0.084$ ), but no significant differences in response rates between the individual groups.

#### 7.2.2.3.6.2 28-Item HAMD

The LOCF analyses showed p values of less than 0.05 favoring drug over placebo at five through eight weeks for 100 mg/d, and at no times for 200, 300, or 400 mg/d. The OC analysis showed p values of less than 0.05 favoring drug over placebo at no times for 100 or 200 mg/d, at three and six through eight weeks for 300 mg/d and at seven and eight weeks for 400 mg/d. Had the sponsor corrected their analysis for multiple-comparisons, no significant differences would have been demonstrated at any time point. Fifty-six of 112 (50%) 100 mg/d patients, 47 of 114 (41%) 200 mg/d patients, 44 of 111 (40%) 300 mg/d patients, 47 of 111 (42%) 400 mg/d patients, and 39 of 116 (34%) placebo patients were considered treatment responders at time of discontinuation. Pearson chi-square analysis comparing the proportion of responders across the treatment groups showed no significant differences in response rates between the groups ( $\chi^2=6.49$ ,  $df=4$ ,  $p=0.165$ ).

#### 7.2.2.3.6.3 HAMD-Item #1

The LOCF analyses showed a p values of less than 0.05 favoring drug over placebo at six weeks for 100 mg/d and at no other times or dosages. The OC analysis showed a p values of less than 0.05 favoring drug over placebo at no times or dosages. Had the sponsor corrected their analysis for multiple-comparisons, no significant differences would have been demonstrated at any time point.

#### 7.2.2.3.6.4 CGI-S

The LOCF analyses showed p values of 0.05 or less favoring drug over placebo at three and six through eight weeks for 100 mg/d and at no other times or dosages. The OC analysis showed p values of less than 0.05 favoring drug over placebo at three weeks for 100 and 300 mg/d, at seven weeks for 300 mg/d and at no other times or dosages. Had the sponsor corrected their analysis for multiple-comparisons, no significant differences would have been demonstrated at any time point.

#### 7.2.2.3.6.5 CGI-I

The LOCF analyses showed p values less than 0.05 favoring drug over placebo at seven and eight weeks for 100 mg/d and at six and seven weeks for 200 mg/d and at no times for higher dosages. The OC analysis showed p values of less than 0.05 favoring drug over placebo at no time for 100 mg/d, at seven weeks for 200 mg/d, at three, six, and seven weeks for 300 mg/d, and at seven weeks for 400 mg/d. Had the sponsor corrected their analysis for multiple-comparisons, no significant differences would have been demonstrated at any time point. Sixty of 112 (54%) 100 mg/d patients, 57 of 114 (50%) 200 mg/d patients, 49 of 110 (45%) 300 mg/d patients, 49 of 111 (44%) 400 mg/d patients, and 48 of 116 (41%) placebo patients were considered treatment responders at time of discontinuation. Pearson chi-square analysis comparing the proportion of responders across the treatment groups showed no significant differences in response rates between the groups ( $\chi^2=4.44$ ,  $df=4$ ,  $p=0.35$ ).

#### 7.2.2.4 Conclusions

The parametric analyses show inconsistent results across outcome measures, no clear evidence of an expected dose-response relationship, nor a consistency between LOCF and OC analyses. Had there been statistical correction for multiple-time-point or multiple-dose testing, then the data in favor of efficacy of any dose of bupropion sustained-release tested would be even weaker. The non-parametric analyses are not consistent across outcome measures, do not provide clear evidence of a dose-response relationship, and do not provide statistically significant evidence of the effect of bupropion sustained-release. On balance, although no specific standard of efficacy was established in the design of this study, the data from protocol 205 fail to show convincing evidence of the efficacy of any of the doses of bupropion sustained-release that were tested.

#### 7.2.3 Other Studies

*not interested*  
Protocol 208 was an open multi-center trial of bupropion sustained-release in 3100 patients with the diagnosis of depression. For eight weeks patients were treated with the highest dose tolerable up to 300 mg/day. Beyond that time point, patients who chose to remain in the study were permitted to remain at any clinically appropriate dose. Clinical response was assessed by the CGI-S and the CGI-I, both of which demonstrated statistically significant improvement over baseline. Being that this was an uncontrolled study, these results cannot adequately demonstrate the efficacy of bupropion sustained-release.

### 7.3 Summary of Data Pertinent to Important Clinical Issues

#### 7.3.1 Predictors of Response

The sponsor did not report any particular predictors of response.

#### 7.3.2 Size of Treatment Effect

The relative effect of bupropion sustained-release as compared with placebo was slight. In both protocols 203 and 205 the mean decrease from baseline in 17-item HAM-D was 10 for bupropion sustained-release and 8 for placebo at endpoint. The baseline score of study 203 was 23 and in study 205 the baseline was 24.

Table 1 Study 205 Demographic Profile of Primary Study Sample (N=575)*								
Treatment Group	Age (Years)		Gender		Race		Mass (kg)	
	Mean	Range	Male N (%)	Female N (%)	White N (%)	Non-White N (%)	Mean	Range
Bupropion Sustained-Release 100 mg/d	39	18-79	48 (42%)	66 (58%)	100 (88%)	14 (12%)	79.5	45.4-133.3
Bupropion Sustained-Release 200 mg/d	41	20-82	38 (32%)	80 (68%)	106 (90%)	12 (10%)	79.4	47.6-155.1
Bupropion Sustained-Release 300 mg/d	40	20-76	38 (33%)	77 (67%)	106 (92%)	9 (8%)	79.0	49.9-167.8
Bupropion Sustained-Release 400 mg/d	40	20-63	50 (43%)	65 (57%)	98 (85%)	17 (15%)	78.7	44.0-150.1
Placebo	40	21-77	43 (38%)	70 (62%)	95 (84%)	18 (16%)	80.1	47.6-165.5

\*The sponsor excluded 27 of the 602 patients randomly assigned to a treatment condition at baseline from this table because no treatment phase assessments were available.

Table 2 Study 205 Patient Completion Rates										
Treatment Groups	Number Randomized	Intent-to-Treat Sample	Completers at Week [n (%)]							
			1	2	3	4	5	6	7	8
BLUP SR 100	119	107	107 (100%)	103 (96%)	102 (95%)	89 (83%)	85 (79%)	86 (80%)	82 (77%)	76 (71%)
BLUP SR 200	120	106	106 (100%)	100 (94%)	95 (90%)	90 (85%)	85 (80%)	83 (78%)	80 (75%)	74 (70%)
BLUP SR 300	120	106	106 (100%)	98 (92%)	81 (76%)	80 (75%)	77 (73%)	71 (67%)	69 (65%)	66 (62%)
BLUP SR 400	119	108	108 (100%)	94 (87%)	88 (81%)	83 (77%)	77 (71%)	75 (69%)	72 (67%)	70 (65%)
Placebo	124	109	109 (100%)	107 (98%)	102 (94%)	90 (83%)	87 (80%)	83 (76%)	82 (75%)	75 (69%)

**Table 4**  
**Study 205: Mean (X) and Mean Change (Δ) from Baseline in 28-item HAM-D**

LAST OBSERVATION CARRIED FORWARD ANALYSIS																			
Treatment Week:		Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
Treatment Groups		N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
DUP SR 100 (VI.)		112	34.3	107	-4.2	112	-7.1	112	-10.0	112	-12.0	112	-13.4	112	-14.1	112	-14.8	112	-15.6
DUP SR 200 (I.)		114	33.5	106	-4.7	114	-6.8	114	-9.1	114	-10.8	114	-11.9	114	-13.2	114	-13.7	114	-14.0
DUP SR 300 (M)		111	34.1	106	-5.0	111	-7.5	111	-9.3	111	-11.0	111	-11.8	111	-12.6	111	-13.3	111	-13.4
DUP SR 400 (II)		111	35.1	108	-3.4	111	-6.9	111	-9.3	111	-11.4	111	-11.7	111	-12.4	111	-13.1	111	-14.1
Placebo (P)		116	33.5	109	-4.2	116	-6.7	116	-8.0	116	-9.8	116	-10.5	116	-11.2	116	-11.4	116	-11.9
VI. vs P	2-sided p-values for pairwise compar- isons	> 0.2		0.88		0.58		0.10		0.085		0.033		0.041		0.021		0.018	
I. vs P		> 0.5		0.62		0.97		0.39		0.44		0.32		0.17		0.12		0.18	
M vs P		> 0.5		0.34		0.48		0.31		0.38		0.40		0.38		0.24		0.39	
II vs P		< 0.05		0.26		0.82		0.28		0.18		0.35		0.43		0.24		0.16	
OBSERVED CASES ANALYSIS																			
Treatment Week:		Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
Treatment Groups		N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
DUP SR 100 (VI.)		112	34.3	107	-4.2	103	-7.5	102	-10.6	89	-12.9	85	-14.5	86	-16.2	82	-17.1	76	-18.1
DUP SR 200 (I.)		114	33.5	106	-4.7	100	-7.4	95	-9.6	90	-11.8	85	-13.4	83	-15.4	80	-16.5	74	-16.5
DUP SR 300 (M)		111	34.1	106	-5.0	98	-8.0	81	-11.1	80	-13.6	77	-15.0	71	-17.1	69	-17.9	66	-18.5
DUP SR 400 (II)		111	35.1	108	-3.4	94	-7.9	88	-10.4	83	-13.4	77	-14.3	75	-15.4	72	-16.8	70	-18.0
Placebo (P)		116	33.5	109	-4.2	107	-6.9	102	-8.6	90	-11.3	87	-12.6	83	-13.7	82	-13.7	75	-14.9
VI. vs P	2-sided p-values for pairwise compar- isons	> 0.2		0.88		0.50		0.086		0.23		0.19		0.093		0.052		0.086	
I. vs P		> 0.5		0.62		0.57		0.37		0.74		0.59		0.22		0.087		0.40	
M vs P		> 0.5		0.34		0.25		0.038		0.078		0.11		0.026		0.015		0.032	
II vs P		< 0.05		0.26		0.28		0.093		0.08		0.20		0.17		0.045		0.036	

Table 5  
Study 205: Mean (X) and Mean Change (Δ) from Baseline in HAM-D Depressed Mood Item #1

		LAST OBSERVATION CARRIED FORWARD ANALYSIS															
Treatment Week	Baseline	WK 1		WK 2		WK 3		WK 4		WK 5		WK 6		WK 7		WK 8	
		N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Treatment Groups																	
IMP SR 100 (VL)	112	28	107	112	-0.3	112	-0.6	112	-0.8	112	-1.0	112	-1.2	112	-1.2	112	-1.2
IMP SR 200 (L)	114	27	106	114	-0.3	114	-0.5	114	-0.7	114	-0.8	114	-1.0	114	-1.0	114	-1.1
IMP SR 300 (M)	111	28	106	111	-0.4	111	-0.5	111	-0.7	111	-0.8	111	-0.9	111	-1.0	111	-1.0
IMP SR 400 (H)	111	28	108	111	-0.2	111	-0.6	111	-0.7	111	-1.0	111	-1.0	111	-1.0	111	-1.2
Placebo (P)	116	29	109	116	-0.3	116	-0.6	116	-0.7	116	-0.8	116	-0.9	116	-1.0	116	-1.0
VL vs P	> 0.05	0.9		0.9		0.4		0.2		0.1		0.04		0.1		0.2	
L vs P	< 0.005	0.8		0.1		0.9		0.8		1.0		0.4		0.8		0.6	
M vs P	> 0.05	0.7		0.4		0.8		0.7		0.8		0.9		0.9		0.8	
H vs P	> 0.1	0.2		0.6		0.6		0.1		0.3		0.4		0.6		0.3	

		OBSERVED CASES ANALYSIS															
Treatment Week	Baseline	WK 1		WK 2		WK 3		WK 4		WK 5		WK 6		WK 7		WK 8	
		N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Treatment Groups																	
IMP SR 100 (VL)	112	28	107	103	-0.3	102	-0.8	89	-1.0	85	-1.2	86	-1.3	82	-1.4	76	-1.4
IMP SR 200 (L)	114	27	106	100	-0.3	95	-0.7	90	-0.8	85	-1.0	83	-1.1	80	-1.2	74	-1.2
IMP SR 300 (M)	111	28	106	98	-0.4	81	-0.9	80	-1.1	77	-1.1	71	-1.2	69	-1.3	66	-1.3
IMP SR 400 (H)	111	28	108	94	-0.2	88	-0.8	83	-1.1	77	-1.2	75	-1.3	72	-1.4	70	-1.6
Placebo (P)	116	29	109	107	-0.3	102	-0.7	90	-1.0	87	-1.1	83	-1.1	82	-1.2	75	-1.3
VL vs P	> 0.05	0.9		0.8		0.2		0.5		0.7		0.2		0.3		0.3	
L vs P	< 0.005	0.8		0.2		0.7		0.3		0.3		0.8		0.9		0.7	
M vs P	> 0.05	0.7		0.7		0.1		0.2		0.8		0.6		0.6		0.7	
H vs P	> 0.1	0.2		0.9		0.2		0.07		0.2		0.1		0.2		0.05	

**Table 6**  
**Study 205: Mean (X) and Mean Change (Δ) from Baseline in CGI-S**

LAST OBSERVATION CARRIED FORWARD ANALYSIS																			
Treatment Week		Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
Treatment Groups		N	X	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A
HUP SR 100 (VI.)		112	4.5	106	-0.3	112	-0.6	112	-0.9	112	-1.1	112	-1.2	112	-1.4	112	-1.5	112	-1.5
HUP SR 200 (I.)		114	4.4	106	-0.3	114	-0.5	114	-0.8	114	-1.0	114	-1.1	114	-1.2	114	-1.3	114	-1.3
HUP SR 300 (M)		110	4.6	105	-0.4	110	-0.7	110	-0.8	111	-1.0	111	-1.2	111	-1.2	111	-1.4	111	-1.4
HUP SR 400 (II)		111	4.6	107	-0.2	111	-0.4	111	-0.8	111	-1.0	111	-1.1	111	-1.1	111	-1.2	111	-1.3
Placebo (P)		116	4.4	109	-0.2	116	-0.5	116	-0.7	116	-0.9	116	-1.0	116	-1.0	116	-1.1	116	-1.2
VI. vs P	2-sided p-values for pairwise compar- isons	> 0.2		0.8		0.4		0.05		0.1		0.06		0.03		0.04		0.05	
I. vs P		> 0.5		0.4		0.8		0.4		0.4		0.4		0.2		0.3		0.4	
M vs P		< 0.02		0.1		0.2		0.3		0.5		0.3		0.3		0.3		0.4	
II vs P		< 0.05		1.0		0.4		0.4		0.4		0.5		0.6		0.7		0.4	
OBSERVED CASES ANALYSIS																			
Treatment Week		Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
Treatment Groups		N	X	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A
HUP SR 100 (VI.)		112	4.5	106	-0.3	103	-0.6	102	-1.0	89	-1.1	85	-1.4	86	-1.7	82	-1.8	76	-1.8
HUP SR 200 (I.)		114	4.4	106	-0.3	100	-0.5	95	-0.8	90	-1.1	85	-1.2	83	-1.4	80	-1.6	74	-1.5
HUP SR 300 (M)		111	4.6	105	-0.4	98	-0.7	81	-1.0	80	-1.2	77	-1.5	71	-1.7	69	-1.9	66	-1.9
HUP SR 400 (II)		111	4.6	107	-0.2	94	-0.5	88	-0.9	83	-1.2	77	-1.4	75	-1.5	72	-1.7	70	-1.8
Placebo (P)		116	4.4	109	-0.2	107	-0.5	102	-0.7	90	-1.1	87	-1.2	83	-1.3	82	-1.4	75	-1.5
VI. vs P	2-sided p-values for pairwise compar- isons	> 0.2		0.8		0.2		0.04		0.5		0.1		0.07		0.06		0.2	
I. vs P		> 0.5		0.4		1.0		0.4		0.7		0.7		0.4		0.3		0.9	
M vs P		< 0.02		0.1		0.1		0.04		0.3		0.08		0.06		0.3		0.1	
II vs P		< 0.05		1.0		0.9		0.2		0.3		0.2		0.3		0.2		0.1	

**Table 7**  
**Study 205: Mean (X) CGI-I (Values less than four represent improvement)**

LAST OBSERVATION CARRIED FORWARD ANALYSIS																			
Treatment Week:		Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
Treatment Groups		N	X	N	X	N	X	N	X	N	X	N	X	N	X	N	X	N	X
NUP SR 100 (VI.)		112	4.0	106	3.5	112	3.3	112	3.0	112	2.9	112	2.7	112	2.6	112	2.5	112	2.5
NUP SR 200 (I.)		114	4.0	106	3.5	114	3.4	114	3.1	114	2.8	114	2.7	114	2.6	114	2.5	114	2.5
NUP SR 300 (M)		110	4.0	105	3.5	110	3.3	110	3.1	110	2.9	110	2.9	110	2.8	110	2.7	110	2.7
NUP SR 400 (II)		111	4.0	107	3.7	111	3.3	111	3.1	111	2.9	111	2.9	111	2.8	111	2.7	111	2.7
Placebo (P)		116	4.0	109	3.6	116	3.3	116	3.2	116	3.1	116	3.0	116	2.9	116	2.9	116	2.8
VI. vs P	2-sided p-values for pairwise compar- isons			0.2		0.6		0.08		0.2		0.09		0.06		0.03		0.04	
I. vs P				0.09		0.9		0.3		0.08		0.09		0.04		0.02		0.07	
M vs P				0.1		0.7		0.4		0.4		0.5		0.4		0.2		0.6	
II vs P				0.7		0.9		0.3		0.3		0.7		0.5		0.3		0.6	
OBSERVED CASES ANALYSIS																			
Treatment Week:		Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
Treatment Groups		N	X	N	X	N	X	N	X	N	X	N	X	N	X	N	X	N	X
NUP SR 100 (VI.)		112	4.0	106	3.5	103	3.2	102	2.9	89	2.8	85	2.6	86	2.4	82	2.3	76	2.2
NUP SR 200 (I.)		114	4.0	106	3.5	100	3.3	95	3.0	90	2.7	85	2.6	83	2.4	80	2.2	74	2.2
NUP SR 300 (M)		110	4.0	105	3.5	98	3.2	81	2.8	80	2.6	77	2.5	71	2.3	69	2.2	66	2.2
NUP SR 400 (II)		111	4.0	107	3.7	94	3.2	88	2.9	83	2.7	77	2.7	75	2.5	72	2.3	70	2.3
Placebo (P)		116	4.0	109	3.6	107	3.3	102	3.1	90	2.9	87	2.7	83	2.6	82	2.6	75	2.5
VI. vs P	2-sided p-values for pairwise compar- isons			0.2		0.4		0.08		0.4		0.2		0.1		0.03		0.1	
I. vs P				0.09		0.7		0.2		0.2		0.2		0.09		0.01		0.2	
M vs P				0.1		0.2		0.02		0.06		0.1		0.03		0.01		0.1	
II vs P				0.7		0.2		0.09		0.1		0.5		0.3		0.02		0.3	

\* By definition, baseline scores are identical.

FEB 17 1995

## Statistical Review and Evaluation

NDA#: 20-358/3-S

Sponsor: Burroughs-Wellcome

Name of Drug: Wellbutrin SR

Documents Reviewed: Vols 2.29, 2.46, Vol 11 dated 12/23/94

Medical Officer: Dan Oren, M.D., HFD-120

The sponsor has submitted 3 multidose, placebo controlled studies (203,205,212) of a sustained release formulation of Wellbutrin. Statistically significant results are scattered over various time points for several variables within each study. See Dr. Oren's review for study descriptions and a summary of results. No consistent or coherent evidence of efficacy emerges from this wealth of data. This reviewer performed a simple meta-analysis using these three studies in order to investigate whether strength of numbers would reveal a signal in the data.

This meta-analysis used the (change from baseline) HAMD 28 at 8 weeks for both observed cases and LOCF analyses. The treatment comparison was 300 mg vs PBO since 100 mg was near the high end and 300 mg was the dose common to all three trials. The 95% confidence intervals below are for the treatment difference between changes from baseline. All results are in the direction favorable for the drug.

	LOCF	OBSERVED CASES
Spons' p-value	.051	.16
<u>203</u> Conf Int	(-5.6, 0.14)	(-5.85, 1.31)
Post Hoc power	.46	.24
Spons' p-value	.39	.03
<u>205</u> Conf Int	(-4.5, 1.5)	(-7.2, 0.04)
Post Hoc power	.16	.49
Spons' p-value	.25	.14
<u>212</u> Conf Int	(-4.1, 1.0)	(-5.2, 0.7)
Post Hoc power	.21	.32

FEB 17 1995

# Statistical Review and Evaluation

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Name of Drug: Wellbutrin SR

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Post Hoc power	.16	.49
Spons' p-value	.25	.14
<u>212</u> Conf Int	(-4.1, 1.0)	(-5.2, 0.7)
Post Hoc power	.21	.32

Table AD3  
Study 212  
Mean (X) and Mean Change (Δ) from Baseline in 21-item HAM-D

LAST OBSERVATION CARRIED FORWARD ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
BUP SR 150 (L)	146	24.2	145	-4.3	146	-6.8	146	-8.5	146	-9.7	146	-10.3	146	-11.8	146	-12.2	146	-12.1
BUP SR 300 (H)	144	24.4	144	-3.1	144	-4.1	144	-6.9	144	-9.3	144	-9.7	144	-10.0	144	-10.8	144	-11.1
Placebo (P)	148	23.9	145	-3.4	148	-5.9	148	-8.0	148	-8.6	148	-9.6	148	-9.8	148	-9.9	148	-9.8
2-sided p-values for pairwise comparisons																		
L vs P	> 0.2		0.08		0.20		0.45		0.15		0.40		0.02		0.01		0.02	
H vs P	> 0.1		0.52		0.004		0.14		0.33		0.91		0.86		0.36		0.16	
OBSERVED CASES ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
BUP SR 150 (L)	146	24.2	145	-4.3	136	-6.9	133	-8.6	133	-10.1	122	-10.8	118	-12.8	117	-13.6	110	-13.7
BUP SR 300 (H)	144	24.4	144	-3.1	136	-4.3	131	-7.6	121	-10.6	111	-11.3	104	-11.8	104	-13.1	101	-13.4
Placebo (P)	148	23.9	145	-3.4	140	-6.0	132	-8.3	124	-9.2	117	-10.5	114	-11.2	107	-11.7	100	-11.6
2-sided p-values for pairwise comparisons																		
L vs P	> 0.2		.08		0.18		0.77		0.34		0.77		0.14		0.10		0.06	
H vs P	> 0.1		0.52		0.006		0.29		0.09		0.49		0.66		0.22		0.10	

**Impression:** We consider this to be a negative study that cannot provide support for the antidepressant efficacy of either the 150 or 300 mg/day bupropion SR doses.

### Study 205

#### (1) Unadjusted Results

The results in Table 2 were unadjusted for multiple comparisons, and even without such adjustment, these data did not suggest a consistent superiority for bupropion SR, at any of the 4 doses, over placebo.

The results were strongest for the 100 mg/day dose group, in particular for HAMD-28 total score and CGI Severity, but only for the LOCF analyses. There were virtually no positive findings for the OC analyses for the 100 mg/day dose group, and no consistently positive findings for either LOCF or OC analyses for any of the other higher dose groups.

#### (2) Adjusted Results

Given the four dose groups in this study, it was necessary to make an adjustment for multiple comparisons. One approach was to use Dunnett's test, which yielded a critical p-value of 0.012 for declaring any particular finding positive. Using this criterion p-value, there were only 3 significant pairwise comparisons, one for each of the higher three dose groups and all at week 7 in the OC analyses.

**Impression:** We consider this to be a negative study that cannot provide support for the antidepressant efficacy of any of the four dose groups.

### Study 212

#### (1) Unadjusted Results

The results in Table 3 were unadjusted for multiple comparisons, and even without such adjustment, these data did not suggest a consistent superiority for bupropion SR, at either dose, over placebo.

The results were strongest for the 150 mg/day dose group, in particular for HAMD-21, MADRS, and CGI Improvement. However, even for those variables, there was little support in the OC analyses. There was very little support on either the CGI Severity or the HAMD Item 1.

The results were very weak for the 300 mg/day dose group, with scattered positive findings at early time points and essentially no supportive findings later.

## (2) Adjusted Results

(212)

Given the two dose groups in this study, it was necessary to make an adjustment for multiple comparisons. One approach was to use Dunnett's test, which yielded a critical p-value of 0.025 for declaring any particular finding positive. Using this criterion p-value, the positive findings on the HAMD-21 and MADRS scores for the 150 mg dose group generally prevailed, but again, only for LOCF analyses.

Impression: We consider this to be a negative study that cannot provide support for the antidepressant efficacy of either the 150 or 300 mg/day bupropion SR doses.

Overall Conclusions Regarding Efficacy Data for Bupropion SR

In summary, none of these 3 studies provided evidence for the antidepressant efficacy of bupropion SR in the dose range being studied. The sample sizes for both studies should have been adequate, and on the basis of HAMD total scores at baseline, the study populations had depressive symptoms of sufficient severity to expect they might be responsive to drug treatment. While even apparently adequately designed studies of antidepressants often fail, there was, unfortunately, no active control arm to test the sensitivity of any of these trials for detecting a drug effect. The failure of the 300 and 400 mg doses to show clear effectiveness, despite their bid equivalency to IR doses of 300 or 400 mg suggests that it may be the study assay sensitivity that is the problem. Unfortunately, whatever the explanation is, the studies do not support the lower dose range for bupropion.

We note your conduct of a NONMEM analyses for studies 203, 205, and 212 combined, which you cite as providing supplementary evidence for the effectiveness of bupropion SR. As an alternative to your exploratory analysis, Dr. Hoberman from the Division of Biometrics performed a simple meta-analysis using all three studies to investigate whether or not insufficient power might in part be an explanation for the weak results for the individual trials. His analysis focused on the HAMD-28 total score, CGI-Severity, and HAMD-Depressed Mood Item at week 8 for the 300 mg vs placebo comparison. Given the greatly increased sample size, it is perhaps not surprising that significance was achieved for two of the three variables, i.e., HAMD-28 total score and CGI-Severity, both for LOCF and OC analyses, but importantly not for HAMD-Depressed Mood.

This analysis, showing effectiveness of an approved daily dose level, provides some support for the view that these studies were underpowered to detect the response to this formulation in this dose range and for this population being studied. While such an analysis has some explanatory value, it cannot support the effectiveness of the lower doses: (1) Whatever the outcome of the meta-analysis or the NONMEM analysis, neither was in the original analytical plan for this program, and thus, neither can be considered definitive in assessing the success or failure of the program. (2) The sample sizes involved in the meta-analysis, i.e., almost 400 for the 300 mg dose group and almost 500 for placebo, raise a concern about the possibility of having a sample size large enough to be able to achieve statistical significance for a treatment effect that is of marginal clinical significance. The point estimates of the effect sizes (Tables 4-6) seen in these studies are very small. Although similar estimates have been seen in some studies of active drugs, active drugs usually have larger estimated effects in some studies.

Enclosure 4

NDA 20-358

WELLBUTRIN SR (bupropion hydrochloride) Tablets

Table 3 Summary of Significance Levels <sup>1</sup> (2-sided) for Pairwise Comparisons (Bupropion SR vs Placebo) in Study 212																
Key Outcome Variables	150 mg vs Pbo								300 mg vs Pbo							
	Week <sup>2</sup>								Week							
	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8
HAMD-21																
LOCF	t	-	-	-	-	*	*	*	-	*	-	-	-	-	-	-
OC	t	-	-	-	-	-	t	t	-	*	-	t	-	-	-	t
MADRS																
LOCF	t	t	-	-	-	*	*	*	-	-	-	-	-	-	-	-
OC	t	t	-	-	-	-	t	*	-	-	-	t	-	-	-	t
HAMD Item 1																
LOCF	-	-	-	-	-	-	t	t	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-	-	*	-	-	-	-
CGI Severity																
LOCF	*	-	-	-	-	-	-	*	-	t	-	t	-	-	-	-
OC	*	-	-	-	-	-	-	-	-	*	-	*	-	-	-	t
CGI Improvement																
LOCF	-	-	-	-	-	*	*	*	*	*	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	t	*	t	-	*	-	-	-	t

- 1   \* =  $p \leq 0.05$   
      t =  $p \leq 0.10$   
      - =  $p > 0.10$   
      \* =  $p \leq 0.025$  (criterion p-value for Dunnett's Test)

- 2   End of weeks 1-8

**AD5.1.3****Extent of Exposure (dose/duration)**

Table AD5.1.3 shows the numbers of patients in protocol 212 according to mean daily bupropion sustained-release dose and duration of administration. The plurality of patients studied (48.4%) were treated with 150 mg/day. This trial represents 49 patient-years of exposure to bupropion sustained-release.

Table AD5.1.3 Number and Percentage of All Patients Receiving Bupropion Sustained-Release According to Mean Daily Dose* and Duration in Study 212**							
Duration (days)	100 mg	150 mg	200 mg	300 mg	400 mg	Total	Percentage
1-6	0	0	0	0	0	0	0%
7-13	1	4	1	6	0	12	4.1%
14-20	3	1	0	6	0	10	3.4%
21-27	1	5	3	6	0	15	5.2%
28-34	1	5	0	5	0	11	3.8%
35-41	1	4	0	9	0	14	4.8%
42-48	0	2	0	1	0	3	1.0%
49-55	0	20	1	20	0	41	14.1%
56	3	100	10	72	0	185	63.6%
Total	10	141	15	125	0	291	
Percentage	3.4%	48.4%	5.2%	43.0%	0%		100

\*Mean daily dose categories are based on the following dose ranges: 100 mg =  $\leq$  125 mg; 150 mg = 126-175 mg; 200 mg = 176-250 mg; 300 mg = 251-350 mg.

\*\*A total of 3 patients from Study 212 did not receive study medication beyond the initial titration period and were excluded from the above table.

**AD7.0****Efficacy Findings****AD7.1****Overview of Study 212**

Study 212 was intended to explore antidepressant efficacy of two intended dosing levels of bupropion sustained-release. It was a U.S. placebo-controlled fixed dose study.

**AD7.2.3****Study 212****AD7.2.3.1****Investigators and Location**

Six U.S.A. sites participated in this trial. The principal investigators were L. A. Cunningham at the Vine Street Clinic, Springfield, IL, D. Dunner at the University of Washington, Seattle, WA, L. F. Fabre at the Fabre Research Clinics, Houston, TX, C. Merideth of San Diego, CA, E. C. Settle, Jr. of Charleston, WV, and R. Weisler of Raleigh, NC.

## AD7.2.3.2

### Study Plan

## AD7.2.3.2.1

### Objectives/Rationale

The objective of this trial was to compare the safety and efficacy of two doses of bupropion sustained-release and placebo in the treatment of patients with major depression.

## AD7.2.3.2.2

### Population

The following summarizes inclusion criteria for the study:

- Age greater than 17 years old
- Meeting DSM-III-R criteria for Major Depressive Disorder, with a current Major Depressive Episode of between four weeks and two years duration
- Score of at least 20 on the 21-item Hamilton Depression Scale (HAMD) at both time of entry and after one week of placebo washout, with a drop of not more than 20 per cent over the week of placebo washout.
- Score at least 2 on the Depressed Mood item (#1) of the HAMD at both time of entry and after one week of placebo washout.

Patients were excluded for the following:

- Predisposition to seizures, either by personal or family history, or by concurrent brain tumor or seizure-threshold-lowering medications
- Presence of a significant DSM-III-R Axis II diagnosis that would suggest non-responsiveness to pharmacotherapy for depression
- History of diagnosis of anorexia nervosa or bulimia
- Presence of medical disorder that would interfere with drug levels or with the accurate assessment of depression.
- Females who were pregnant, breast-feeding, or unwilling to employ appropriate contraceptive methods during the study
- History within one year of alcohol or substance abuse
- Receipt of fluoxetine or an investigational drug within four weeks of the treatment phase, receipt of an MAOI drug or protriptyline within two weeks of the treatment phase, or receipt of any other psychoactive drug within one week of the treatment phase.
- History of treatment with bupropion
- Incapable of spontaneous conversation or activity
- Active suicidality.

## AD7.2.3.2.3

### Planned Study Conduct/Dosing Plan

Following one week of single-blind b.i.d. placebo washout, this trial was an eight week, parallel, double blind study; patients were randomly assigned to receive placebo, or one of two dose levels of bupropion sustained-release. Patients were randomized in blocks of six, with equal chances of receiving any of the three treatments. Medication consisted of identically-appearing tablets containing either placebo or 50 mg bupropion sustained-release. Each patient received a blister card containing a ten day supply of medication each week. After one week for increasing doses, patients were instructed to take three tablets in the morning and three each evening and to return the blister card with all unused tablets. On this schedule, patients either received placebo b.i.d., 150 mg bupropion sustained-release qam and placebo qpm, or 150 mg bupropion sustained-release b.i.d. The investigators were permitted to decrease the dose to a minimum of one tablet b.i.d. at any time if clinically indicated. Patients who experienced intolerable adverse effects from a minimum dose of 1 tablet b.i.d. were to be discontinued from the trial. Except for chloral hydrate that was permitted as a supplement in the first two weeks of the study, concomitant psychoactive medications were not permissible. Compliance was assessed by weekly review of the blister card.

#### AD7.2.3.2.4

#### Efficacy Assessments

The 21-item HAMD, the Clinical Global Impression for Severity of Illness (CGI-S), the Clinical Global Impression for Improvement of Illness (CGI-I), and the Montgomery-Asberg Depression Rating Scale (MADRS) constituted the efficacy measures and were performed at each weekly visit. A screening visit occurred at the onset of placebo washout. A baseline (Day 0) visit occurred one week later at which time participating patients were randomly assigned to receive treatment. The remaining visits occurred at one week intervals over the following eight weeks.

#### AD7.2.3.2.5

#### Safety Assessments

Safety assessments included assessment of vital signs at screening and baseline, and weight at screening, baseline, and discontinuation from treatment phase. An adverse experience probe was administered at each visit by investigators.

#### AD7.2.3.2.6

#### Analysis/Plan

The sponsor designated the following *a priori* efficacy parameters: 21-item HAMD score, HAMD depressed mood (item #1), MADRS total score, MADRS apparent sadness and reported sadness scores (items #1 and #2, separately and combined), CGI-S rating, and CGI-I rating. The analyses were performed using observed scores and last observation carried forward scores. Parametric analysis and non-parametric "responder" analysis was specified for the data.

#### AD7.2.3.3

#### Study Conduct/Outcome

##### AD7.2.3.3.1

##### Patient Disposition

A total of 456 patients constituted the baseline sample and the intent-to-treat sample (those patients receiving at least one dose of their assigned medication and having at least one efficacy assessment after baseline) constituted 434 patients. The intent-to-treat sample consisted of 145 patients assigned to placebo, 145 patients assigned to 150 mg/d bupropion sustained-release and 144 patients assigned to 300 mg/d bupropion sustained-release. Of the intent-to-treat sample, 69 per cent of placebo patients, 76 per cent of 150 mg/d drug-treated, and 70 per cent of 300 mg/d drug-treated patients completed the study. Overall, 311 patients (71% of the intent-to-treat sample) completed the study. Appendix AD7.2.3.3 shows the patient completion rates by week for each treatment group.

The highest proportion of dropouts occurred in the placebo group and the lowest in the 150 mg/d drug group. An ill-characterized category of "consent withdrawn" was the most common cause for early termination. Because some of the patients may have experienced adverse events before withdrawing consent to participate, the actual role of adverse experiences leading to premature study discontinuation may be larger than stated by the sponsor. Table AD7.2.3.3.1 lists reasons for premature discontinuation by treatment group.

Table AD7.2.3.3.1 Reasons for Premature Study Discontinuation from Protocol 212						
	Bupropion Sustained-Release Dosage Group					
	150 mg/d (N=152)		300 mg/d (N=150)		Placebo (N=154)	
	#	% of N	#	% of N	#	% of N
Inadequate Response/ Condition Deteriorated	5	3.3%	17	11.3%	13	8.4%
Adverse Experience	5	3.3%	7	4.7%	3	1.9%
Lost to Follow-up/Other	1	0.7%	2	1.3%	6	3.9%
Consent Withdrawn	15	9.9%	14	9.3%	17	11.0%
Protocol Violation	7	4.6%	7	4.7%	9	5.8%
Total	33	21.7%	47	31.3%	48	31.2%

#### AD7.2.3.3.2 Demographic Characteristics

Table AD5.1.2.2 above presents the demographic characteristics of the patients enrolled. The majority were female, consistent with typical gender patterns for major depression. There were no appreciable differences between treatment groups on the basis of age or race. Seventy-one per cent, 7 per cent, and 69 per cent, respectively, of patients in the 150 mg, 300 mg, and placebo groups were experiencing a recurrent episode of depression. The three groups were roughly comparable as to characterization of the present episode as agitated vs. retarded vs. uncomplicated depression.

#### AD7.2.3.3.3 Baseline Illness Severity

Appendix AD7.2.3.3 presents the baseline and follow-up measures of illness severity. Pairwise contrasts of baseline symptom scores on the efficacy measures across treatment groups based on means and standard deviations supplied by the sponsor were performed using t-tests (cf: Stanton A. Glantz, *Primer of Biostatistics*, 1992, p. 81). After correction for multiple comparisons testing, there were no statistically significant differences between groups.

#### AD7.2.3.3.4 Dosing Information

The sponsor calculated mean daily dosages of medication intake from the eighth day of the study (by which time patients had been titrated up to the full dosage level) through day of discontinuation. The mean daily dose of bupropion sustained-release ingested by the 150 mg/d group was 144 mg. The mean daily dose of bupropion sustained-release ingested by the 300 mg/d group was 276 mg.

#### AD7.2.3.3.5 Concomitant Medications

Concomitant medication was administered to 70% of 150 mg/d patients, 75% of 300 mg/d patients, and 67% of placebo patients. The most commonly administered medications were non-narcotic analgesics, miscellaneous cold preparations or antihistamines, female hormones or birth control pills, and antibiotic or antiviral agents.

## AD7.2.3.3.6

## Efficacy Results

This analysis focuses upon the following commonly-used key efficacy variables: the 21-item HAMD, item #1 of the HAMD, the MADRS, the Clinical Global Impression for Severity of Illness (CGI-S), and the Clinical Global Impression for Improvement of Illness (CGI-I). Appendix AD7.2.3.3 presents the data for these key efficacy variables with both the observed case (OC) and the last observation carried forward (LOCF) analyses. Two-tailed t-tests were used to compare changes in each of these variables in the drug- vs. placebo-treated groups at each week of the study. In addition, chi square "responder analyses" were conducted to test for differences in the proportions of responders in the treatment groups. For the HAMD and MADRS analyses, a patient whose total score was reduced by 50 per cent or more between baseline and discontinuation was considered a responder. For the CGI-I analysis, a patient who was rated as "very much improved" or "much improved" at discontinuation was considered a responder. The following sections are a brief summary of the findings.

Table AD7.2.3.3.6 displays a summary of the statistical comparisons between placebo and both drug treatment groups for the outcome variables. The reader should note that these are not independent scales.

<p>Table AD7.2.3.3.6            Summary of Efficacy Variables in Study 203. L=LOCF analysis, O=OC analysis            (?? = 0.05 &lt; p ≤ 0.10, ? = p ≤ 0.05, + = p ≤ 0.01 favoring drug over placebo;            X = p ≤ 0.10 favoring placebo over drug.            p values were not corrected for multiple time-points or multiple dose-sizes comparisons testing)</p>											
Week	Daily Dose (mg)	21-HAMD		HAMD-#1		MADRS		CGI-S		CGI-I	
		L	O	L	O	L	O	L	O	L	O
1	150	??	??			??	??	?	?		
	300									X	X
2	150					??	??				
	300	X	X					X	X	X	X
3	150										
	300										
4	150										
	300		??		?		??	??	?		?
5	150										
	300										
6	150	?				?				??	
	300										
7	150	?	??	??		?	??			?	
	300										
8	150	?	??	??		?	??	??		?	??
	300						??	??	??		??

**AD7.2.3.3.6.1****21-Item HAM-D**

The LOCF analyses showed p values of less than 0.05 favoring drug over placebo at six, seven, and eight weeks for 150 mg/d and favored placebo over drug at two weeks for 300 mg/d. The OC analysis showed p values of less than 0.05 favoring drug over placebo at no time. The only robust differences were seen in the LOCF and OC analyses at two weeks when placebo favored 300 mg/d drug. Seventy-six of 146 (52%) 150 mg/d patients, 74 of 144 (51%) 300 mg/d patients, and 59 of 148 (40%) placebo patients were considered treatment responders at time of discontinuation. A Pearson chi-square analysis comparing the proportion of responders across the treatment groups showed a trend toward a difference between the three treatment groups ( $X^2=5.54$ ,  $df=2$ ,  $p=0.063$ ).

**AD7.2.3.3.6.3****HAMD-Item #1**

The LOCF analyses showed p values of less than 0.05 favoring drug over placebo at no time for 150 mg/d or 300 mg/d. The OC analysis showed p values of less than 0.05 favoring drug over placebo at no time for 150 mg/d and at four weeks for 300 mg/d. Had the sponsor corrected their analysis for multiple-comparisons, no significant differences would have been demonstrated at any time point.

**AD7.2.3.3.6.4****CGI-S**

The LOCF analyses showed p values of 0.05 or less favoring drug over placebo at one week for 150 mg/d and at no time for 300 mg/d. The OC analysis showed p values of 0.05 or less favoring drug over placebo at one week for 150 mg/d and at four weeks for 300 mg/d. At two weeks the OC analysis showed placebo favoring 300 mg/d drug. Had the sponsor corrected their analysis for multiple-comparisons, no significant differences would have been demonstrated at any time point.

**AD7.2.3.3.6.5****CGI-I**

The LOCF analyses showed p values of 0.05 or less favoring drug over placebo at seven and eight weeks for 150 mg/d. At one and two weeks the LOCF analysis showed placebo favoring 300 mg/d drug. The OC analysis showed p values of less than 0.05 favoring drug over placebo at no time for 150 mg/d and at four weeks for 300 mg/d. At one week the OC analysis showed placebo favoring 300 mg/d drug. Had the sponsor corrected their analysis for multiple-time point comparisons, no significant differences would have been demonstrated at any time point. Seventy-seven of 146 (53%) 150 mg/d patients, 72 of 144 (50%) 300 mg/d patients, and 61 of 148 (41%) placebo patients were considered treatment responders at time of discontinuation. A Pearson chi-square analysis comparing the proportion of responders across the treatment groups showed no significant differences between the groups ( $X^2=4.27$ ,  $df=2$ ,  $p=0.118$ ).

**AD7.2.3.3.6.6****MADRS**

The LOCF analyses showed p values of less than 0.05 favoring drug over placebo at six, seven, and eight weeks for 150 mg/d and at no time for 300 mg/d. The OC analysis showed p values of less than 0.05 favoring drug over placebo at no time for 150 mg/d or 300 mg/d. Seventy-five of 146 (51%) 150 mg/d patients, 76 of 144 (53%) 300 mg/d patients, and 59 of 148 (40%) placebo patients were considered treatment responders at time of discontinuation. A Pearson chi-square analysis comparing the proportion of responders across the treatment groups showed a trend toward a difference between the three treatment groups ( $X^2=5.90$ ,  $df=2$ ,  $p=0.052$ ).

**AD7.2.3.4****Conclusions**

The parametric analyses show inconsistent results across outcome measures and no clear evidence of an expected dose-response relationship. Had there been statistical correction for multiple-time-point or multiple-dose testing, then the data in favor of efficacy of either dose of bupropion sustained-release tested would be even weaker.

relationship, and do not provide statistically significant evidence of the effect of bupropion sustained-release. On balance, although no specific standard of efficacy was established in the design of this study, the data from protocol 212 fail to show convincing evidence of the efficacy of either of the two doses of bupropion sustained-release that were tested.

#### AD7.3.2 Size of Treatment Effect

The relative effect of bupropion sustained-release as compared with placebo was slight. In protocol 212 the mean decrease from baseline in 21-item HAMD was 14 for bupropion sustained-release and 12 for placebo at endpoint. The baseline score of study 212 was 24.

#### AD8.0 Safety Findings

##### AD8.1 Methods

Safety assessments from study 212 were derived from 302 patients who were exposed to bupropion sustained-release, with the exception of 8 patients for whom no treatment phase assessments were available.

Safety issues were evaluated on the basis of these data sets and case report forms. Uncommon, severe adverse events were assessed using premature discontinuations from clinical trials and "serious" adverse events (as defined below), while more common but less grave adverse reactions were identified through routinely collected safety data. Section AD8.6 contains a discussion of those adverse events deemed both significant and potentially drug-related.

##### AD8.2 Deaths

None were reported.

#### AD8.3 Assessment of Dropouts

##### AD8.3.1 Overall Pattern of Dropouts

Table AD8.3.1 summarizes reasons for premature discontinuation among patients who were randomly assigned to receive treatment under protocol 212. This table was compiled by reviewing the reasons assigned by the individual investigators for each subject who dropped out. In several cases where "Consent Withdrawn" was assigned by the investigator as a reason for withdrawal, but where the case reports or narrative case summaries suggested to this reviewer that "Lack of Efficacy" or "Adverse Experiences" better captured the reason for dropping out, one of the latter two explanations was used in the table.

Appendix AD7.2.3.3 Efficacy Data for Study 212

Table AD2 Study 212 Patient Completion Rates										
Treatment Groups	Number Randomized	Intent-to-Treat Sample	Completers at Week (N (%))							
			1	2	3	4	5	6	7	8
BUP SR 150	146	145	145 (100%)	136 (94%)	133 (92%)	133 (92%)	122 (84%)	118 (81%)	117 (81%)	110 (76%)
BUP SR 300	144	144	144 (100%)	136 (94%)	131 (91%)	121 (84%)	111 (77%)	104 (72%)	104 (72%)	101 (70%)
Placebo	148	145	145 (100%)	140 (97%)	132 (91%)	124 (86%)	117 (81%)	114 (79%)	107 (74%)	100 (69%)

Table AD5  
Study 212  
Mean (X) and Mean Change (Δ) from HAMD Depressed Mood Item #1

LAST OBSERVATION CARRIED FORWARD ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A
BUP SR 150 (L)	146	2.8	145	-0.4	146	-0.7	146	-0.9	146	-1.0	146	-1.2	146	-1.3	146	-1.3	146	-1.4
BUP SR 300 (II)	144	2.8	144	-0.3	144	-0.5	144	-0.9	144	-1.1	144	-1.1	144	-1.1	144	-1.3	144	-1.3
Placebo (P)	148	2.9	145	-0.3	148	-0.6	148	-0.9	148	-1.0	148	-1.1	148	-1.1	148	-1.1	148	-1.1
2-sided p-values for pairwise comparisons																		
I. vs P	> 0.6		0.46		0.48		0.61		0.59		0.50		0.14		0.07		0.10	
II vs P	> 0.4		0.57		0.28		0.99		0.12		0.98		0.53		0.26		0.29	
OBSERVED CASES ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	A	N	A	N	A	N	A	N	A	N	A	N	A	N	A
BUP SR 150 (L)	146	2.8	145	-0.4	136	-0.7	133	-1.0	133	-1.1	122	-1.3	118	-1.4	117	-1.5	110	-1.6
BUP SR 300 (II)	144	2.8	144	-0.3	136	-0.5	131	-1.0	121	-1.3	111	-1.3	104	-1.2	104	-1.5	101	-1.6
Placebo (P)	148	2.9	145	-0.3	140	-0.6	132	-0.9	124	-1.0	117	-1.2	114	-1.3	107	-1.3	100	-1.4
2-sided p-values for pairwise comparisons																		
I. vs P	> 0.6		0.46		0.46		0.70		0.80		0.66		0.37		0.23		0.21	
II vs P	> 0.4		0.57		0.32		0.62		0.03		0.71		0.65		0.12		0.14	

Table AD6  
Study 212  
Mean (X) and Mean Change (Δ) from Baseline in CGI-S

LAST OBSERVATION CARRIED FORWARD ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
BUP SR 150 (I)	146	4.3	145	-0.4	146	-0.7	146	-0.9	146	-1.0	146	-1.2	146	-1.4	146	-1.5	146	-1.5
BUP SR 300 (II)	144	4.3	144	-0.3	144	-0.4	144	-0.8	144	-1.1	144	-1.1	144	-1.1	144	-1.3	144	-1.4
Placebo (P)	148	4.3	145	-0.3	148	-0.6	148	-0.9	148	-0.9	148	-1.1	148	-1.2	148	-1.2	148	-1.2
2-sided p-values for pairwise comparisons																		
I vs P	> 0.8		0.04		0.17		0.86		0.43		0.38		0.11		0.12		0.05	
II vs P	> 0.4		0.81		0.06		0.26		0.09		0.99		0.70		0.53		0.15	
OBSERVED CASES ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
BUP SR 150 (I)	146	4.3	145	-0.4	136	-0.7	133	-0.9	133	-1.1	122	-1.4	118	-1.6	117	-1.6	110	-1.7
BUP SR 300 (II)	144	4.3	144	-0.3	136	-0.4	131	-0.8	121	-1.3	111	-1.3	104	-1.4	104	-1.7	101	-1.8
Placebo (P)	148	4.3	145	-0.3	140	-0.6	132	-0.9	124	-1.0	117	-1.2	114	-1.4	107	-1.5	100	-1.4
2-sided p-values for pairwise comparisons																		
I vs P	> 0.8		0.04		0.15		0.88		0.76		0.59		0.26		0.39		0.12	
II vs P	> 0.4		0.81		0.05		0.34		0.04		0.66		0.91		0.30		0.07	

Table AD7  
Study 212  
Mean (X) CGI-I (Values less than four represent improvement relative to time of screening)

LAST OBSERVATION CARRIED FORWARD ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
BUP SR 150 (L)	146	4.0	145	3.4	146	3.1	146	2.8	146	2.7	146	2.6	146	2.5	146	2.4	146	2.4
BUP SR 300 (H)	144	3.9	144	3.7	144	3.4	144	3.0	144	2.7	144	2.7	144	2.7	144	2.6	144	2.5
Placebo (P)	148	3.9	145	3.5	148	3.2	148	2.9	148	2.9	148	2.8	148	2.7	148	2.7	148	2.7
2-sided p-values for pairwise comparisons																		
L vs P	0.03		0.36		0.35		0.49		0.20		0.15		0.05		0.04		0.02	
H vs P	> 0.6		0.02		0.02		0.29		0.21		0.70		0.67		0.39		0.26	
OBSERVED CASES ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
BUP SR 150 (L)	146	4.0	145	3.4	136	3.1	133	2.8	133	2.6	122	2.5	118	2.3	117	2.3	110	2.2
BUP SR 300 (H)	144	3.9	144	3.7	136	3.4	131	2.9	121	2.6	111	2.5	104	2.4	104	2.2	101	2.2
Placebo (P)	148	3.9	145	3.5	140	3.2	132	2.9	124	2.8	117	2.7	114	2.5	107	2.5	100	2.4
2-sided p-values for pairwise comparisons																		
L vs P	0.03		0.36		0.20		0.59		0.27		0.27		0.16		0.24		0.06	
H vs P	> 0.6		0.02		0.06		0.74		0.93		0.28		0.35		0.13		0.06	

Table AD8  
Study 212  
Mean (X) and Mean Change (Δ) from Baseline in MADRS Total Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
BUP SR 150 (L)	146	27.8	145	-4.3	146	-7.4	146	-9.3	146	-10.4	146	-11.8	146	-13.4	146	-13.9	146	-14.0
BUP SR 300 (H)	144	28.2	144	-3.2	144	-5.0	144	-8.2	144	-10.8	144	-11.1	144	-11.2	144	-12.6	144	-13.2
Placebo (P)	148	27.2	145	-3.2	148	-6.0	148	-8.6	148	-9.4	148	-10.4	148	-11.0	148	-11.1	148	-11.2
2-sided p-values for pairwise comparisons																		
L vs P	> 0.3		0.07		0.08		0.50		0.34		0.20		0.03		0.01		0.62	
H vs P	> 0.1		0.88		0.17		0.54		0.16		0.56		0.88		0.21		0.11	
OBSERVED CASES ANALYSIS																		
Treatment Groups	Treatment Week																	
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6		Wk 7		Wk 8	
	N	X	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
BUP SR 150 (L)	146	27.8	145	-4.3	136	-7.5	133	-9.4	133	-10.8	122	-12.5	118	-14.8	117	-15.6	110	-16.2
BUP SR 300 (H)	144	28.2	144	-3.2	136	-5.1	131	-9.0	121	-12.3	111	-13.0	104	-13.6	104	-15.6	101	-16.3
Placebo (P)	148	27.2	145	-3.2	140	-6.1	132	-9.0	124	-10.0	117	-11.6	114	-12.8	107	-13.2	100	-13.5
2-sided p-values for pairwise comparisons																		
L vs P	> 0.3		0.07		0.10		0.86		0.67		0.52		0.17		0.19		0.05	
H vs P	> 0.1		0.88		0.18		0.80		0.06		0.42		0.76		0.12		0.06	

**Appendix AD8.7****Summary of Serious Adverse Events Occurring in Protocol 212 Considered to be Unlikely to be Related to Bupropion Sustained-Release**

Patient #	Age	Gender	Dose (mg/d)	Duration (days)	Adverse Event
20128	51	M	Placebo	1	Excision of pre-existing basal cell carcinoma
11033	37	F	300	Prolonged	Cervical carcinoma in situ
50376	36	F	150	1	Excision of pre-existing basal cell carcinoma and benign intradermal nevus
40540	31	F	300	1	Spontaneous abortion eight days after discontinuation from study

NDA 20-358

MAY 25 1995

Burroughs Wellcome Company  
Attention: Donald A. Knight  
Vice President, Drug Regulatory Affairs  
3030 Cornwallis Road  
Research Triangle Park, North Carolina 27709

Dear Mr. Knight:

Please refer to your resubmitted New Drug Application (NDA) dated and received February 28, 1994, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Wellbutrin® (Bupropion Hydrochloride) 50, 100, and 150 mg Sustained Release Tablets, NDA 20-358, for the treatment of depression.

We also acknowledge receipt of your additional communications (see Enclosure 1).

We have completed our review of your application, and it is not approvable. Under section 505(d) of the Act and 21 CFR 314.125(b)(5) of the FDA implementing regulations, you have failed to provide substantial evidence consisting of adequate and well-controlled studies, as defined in 21 CFR 314.126, that Wellbutrin SR® will have the effect it is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Please note that we have additionally included a list of environmental assessment and chemistry and manufacturing concerns to convey all of the deficiencies in this application.

#### **Overview of Basis for Non-Approvable Decision**

Before providing a detailed explanation for our views on why your clinical program failed to support the antidepressant effectiveness of Wellbutrin SR in the dose range proposed, we felt it would be useful to briefly summarize our views on what the critical issues are for this NDA and to give our historical perspective on how these issues unfolded.

In your December 23, 1994 letter, you acknowledged that your primary motivation for the Wellbutrin SR program was to develop a formulation that would be safer with regard to the risk of seizures than the immediate release (IR) formulation. You hypothesized that seizure risk was linked to peak plasma levels, and on this basis, you sought to develop a formulation that would decrease the peak plasma level and the peak to trough fluctuation for bupropion and its metabolites, while maintaining an equivalent extent of absorption. Although it is true that you obtained FDA's general prior agreement that a bioequivalence approach as outlined above would suffice, along with adequate safety data for the new formulation, it was not apparent at that time that you also sought to substantially change the recommended dosing range for this drug.

Since a second goal of your program, beyond developing a sustained release formulation that you hoped would be associated with a lower seizure risk, was to support a change in the recommended dose range from the currently recommended range of 300-450 mg/day to a lower range, i.e., 150-300 mg/day, you launched a series of clinical trials. While you recognized the need for clinical efficacy trials to support such a change, you unfortunately embarked on this program without sufficiently alerting us to your intentions and without seeking our input.

A third goal of your program, and a corollary to your primary motivation of developing a less seizurogenic formulation, was to provide the support needed to modify labeling with regard to seizure risk. Your large open study designed to provide an estimate of seizure risk with the new formulation, although described as a study of the new formulation, was importantly also an examination of seizure risk associated with a lower dose range.

We consider your bioequivalence program to have been successful in achieving the goals stated above for that program. In fact, under steady state conditions at the 300 mg/day dose, we believe that you have shown equivalence for parent drug with regard to both rate and extent of absorption (i.e., for bupropion SR 150 mg bid vs bupropion IR 100 mg tid). For the major metabolites, which appear to be the predominant active species for this drug, there is no question about your having met the test of equivalence with regard to both rate and extent of absorption under steady state conditions at the 300 mg/day dose. Although the IR and SR products are not bioequivalent during the interval prior to attainment of steady state, we do not believe this would bar a conclusion of overall bioequivalence for a chronically administered product, such as an antidepressant. We would therefore be prepared to approve the sustained release tablets at a dose of 300-400 mg per day.

Your open seizure trial, i.e., study 208, established a cumulative seizure rate at 8 weeks of roughly 0.1% for bupropion SR in a 100-300 mg/day dose range, compared to the 4-fold higher rate of roughly 0.4% for bupropion IR in a 300-450 mg/day range. Unfortunately, there is no way to tell whether this was due to the change in dosage form or the lower dose. Given the very similar bioavailability of the IR and SR forms, it seems most likely that the lower seizure rate resulted from the lower dose range.

In the absence of additional studies that demonstrate the effectiveness of bupropion SR in the 150-300 mg/day dose range, it would not be possible to approve the SR formulation in the proposed dose range. For the reasons detailed below, we do not believe you have shown bupropion sustained release tablets to be effective at these doses.

#### **Deficiencies in the Efficacy Data**

We examined studies 203, 205, and 212, i.e., your randomized, placebo-controlled trials in depressed outpatients utilizing bupropion SR doses ranging from 100 to 400 mg/day, focusing on the following variables as key measures of an antidepressant effect: HAMD-17, HAMD-21, and HAMD-28 Total Scores; MADRS Total Score; HAMD Depressed Mood Item (Item 1); CGI-Severity; and CGI-Improvement. We considered both last-observation-carried-forward (LOCF) or observed-cases (OC) analyses.

The critical issue here is not whether or not bupropion works, or whether or not the SR formulation works, but rather, what is the effective dose range that should be recommended to clinicians. The data from the early bupropion immediate release studies supported the effectiveness and acceptable safety of the currently recommended bupropion dose range of 300 to 450 mg/day, albeit with the recognized problem of a fairly steep dose response curve for seizures. The clinical data for the SR formulation fail overall to support the 150-300 mg/day range, although we believe our meta-analysis provides some additional support for the view that the approved dose of 300 mg/day is at the low end of the effective dose range.

#### **Deficiencies in the Chemistry and Manufacturing**

1. The stability data for the drug product are insufficient to support the proposed 24 month expiry date, and additional data at 30°C is needed that includes 24 month data. An expiry data of 18 months is suggested until further confirmatory data is available. In addition, the label storage statement "Store at 15°C-30°C (59°F-86°F)" is acceptable only for expiry dates of less than 24 months.
2. The proposed "individual unidentified compound" specification for the drug product of 0.2% should be lowered to 0.1%.

#### **Deficiencies in the Environmental Assessment**

##### **Item 4, description of the proposed action:**

- a. Requested Approval: The description of the request should mention the NDA number.
- b. Need for Action: The added benefit of sustained-release tablets over the presently marketed immediate-release tablets should be stated.
- c. Production Locations:
  - i. Proprietary Intermediates: It should be confirmed that none of the input materials are proprietary intermediates that are manufactured at another location. If proprietary intermediates are used, information about their manufacture must be provided.
  - ii. The exact addresses for the facilities used in production of the drug substance and drug product should be provided.
  - iii. Disposal Locations: The license number of the off-site incineration facility used by The Wellcome Foundation Limited, and the dates of expiration for the licenses of the incineration facility and the landfill site, should be given. In addition, the application should state that disposition of drug product in a landfill is appropriate based on the toxicity of the drug substance.

	LOCF	OBSERVED CASES
Meta p-value	.02	.01
Meta Conf Int	(-3.5, -0.3)	(-4.6, -0.7)
Meta power	.64	.75

In addition, the average change from baseline for drop outs was calculated:

		# Drop outs	mean change from baseline
<u>203</u>	300mg	51	7.5
	PBO	61	6.1
<u>205</u>	300mg	45	5.9
	PBO	41	6.4
<u>212</u>	300mg	41	7.5
	PBO	48	8.3

Overall, there does not appear to be an appreciable difference either in the percentage or condition of drop outs between the two groups.

Of the 6 p-values for CGI-Severity (3 studies X 2 analyses), there was only 1 statistically significant result. Nevertheless, the meta-analysis produced statistically significant results for both LOCF and observed cases. The confidence intervals for change from baseline were (-.46, -.06) and (-.59, -.11) respectively.

Results are negative with respect to the Depressed Mood item of the HAM-D. Neither the observed case nor the LOCF meta-analysis produces a statistically significant result. Of the 6 analyses, only 1 was statistically significant.

Studies 203 and 205 were designed to detect a 3 point difference assuming a standard deviation of 7 in each group. Study 212 used a difference of 2.5 with a standard deviation of 7. In fact, the design of 212 was based on the results of 203 and 205. This was clearly a mistake as we see from the very low post hoc powers for

each of the studies. That is, the probabilities of getting statistically significant results if the true situations were the actual treatment differences and standard deviations found in the trials, were uniformly low.

In fact, the actual standard deviations in all 3 trials were between 10-12, certainly not around 7. In addition, the average treatment differences of studies 203 and 205 were -2.75 and -1.5, respectively. The sponsor was unjustifiably optimistic to detect a difference of -2.5 in study 212 under these circumstances. Even if the treatment difference were realistic, the sponsor presumably knew that studies 203 and 205 produced standard deviations which would have required double the sample size as that required if assuming a standard deviation of 7. However, it is possible that they mistakenly used underestimates of standard deviations based on administrative interim analyses. In any case, study 212 was not adequately designed.

#### Discussion

Ironically, the only variable of the three major ones not to be statistically significant in the meta-analysis was the Depressed Mood item. This result must be seen in the light of the actual designs which were based on the total HAMD score, a composite endpoint which may be more sensitive than just one item. Ultimately, this submission may represent 3 nearly identically designed trials which appear underpowered to detect a small difference from placebo.



David Hoberman, Ph.D.  
Mathematical Statistician

Concur: Dr. Nevius *SEN 2-14-95*

Dr. Dubey *62-2-17-95*

Enclosure 5

NDA 20-358

WELLBUTRIN SR (bupropion hydrochloride) Tablets

Table 4 Size of Treatment Effect in Study 203 (Difference Between Bupropion SR and Placebo in Mean Change from Baseline for HAMD-17 Total Score at Week 8 (LOCF))			
Groups	Baseline <sup>1</sup>	Baseline-Wk8 <sup>2</sup>	Difference <sup>3</sup>
Placebo	23.2	-8.1	
Bup.SR 150 mg	23.1	-10.2	2.1
Bup.SR 300 mg	23.4	-10.2	2.1

Table 5 Size of Treatment Effect in Study 205 (Difference Between Bupropion SR and Placebo in Mean Change from Baseline for HAMD-17 Total Score at Week 8 (LOCF))			
Groups	Baseline <sup>1</sup>	Baseline-Wk8 <sup>2</sup>	Difference <sup>3</sup>
Placebo	23.4	-8.3	
Bup.SR 100 mg	23.6	-10.5	2.2
Bup.SR 200 mg	23.2	-9.6	1.3
Bup.SR 300 mg	23.6	-9.0	0.7
Bup.SR 400 mg	24.2	-9.3	1.0

Table 6 Size of Treatment Effect in Study 212 (Difference Between Bupropion SR and Placebo in Mean Change from Baseline for HAMD-21 Total Score at Week 8 (LOCF))			
Groups	Baseline <sup>1</sup>	Baseline-Wk8 <sup>2</sup>	Difference <sup>3</sup>
Placebo	27.2	-11.2	
Bup.SR 150 mg	27.8	-14.0	2.8
Bup.SR 300 mg	28.2	-13.2	2.0

- 1 Baseline mean HAMD Total Score
- 2 Change from baseline to week 8 (LOCF)
- 3 Difference between bupropion SR and placebo in mean change from baseline to week 8 (LOCF) for HAMD Total Score

Table 8.3.1.2, supplied by the sponsor, summarizes reasons for premature discontinuation among patients who were assigned to receive treatment under protocol 208. Because 67 patients assigned to receive treatment dropped out between point of randomization and first ingestion of medication, the total number of subjects in this table is larger by 67 than the number of subjects in the demographics table of section 5.1.2.

Table 8.3.1.1 Incidence of Dropout by Treatment Group and Reason in Protocols 203 and 205		
Reason for Dropout	Bupropion Sustained-Release (N=719)	Placebo (N=245)
Lack of Efficacy	7.5%	14.7%
Adverse Experiences	10.2%	5.7%
Unknown	5.8%	6.1%
Consent Withdrawn	12.2%	12.2%
Protocol Violation	3.5%	1.6%
Total Dropouts	39.2%	40.4%

Table 8.3.1.2 Incidence of Dropout by Treatment Group and Reason in Protocol 208	
Reason for Dropout	Bupropion Sustained-Release (N=3167)
Lack of Efficacy	6.9%
Adverse Experiences	11.4%
Unknown Other	0.7%
Consent Withdrawn	11.0%
Protocol Violation	5.0%
Total Dropouts	35.0%

### 8.3.2 Adverse Events Associated with Dropout

As noted in Table 8.3.1, 10.2% of the bupropion sustained-release-assigned patients in the integrated Phase 2-3 safety database withdrew because of an adverse experience, as compared with 5.7% of placebo-assigned patients.

The following table lists all those categories of adverse experiences leading to dropout that were associated with at least 0.3% of the 693 subjects who were randomly assigned to receive bupropion sustained-release in protocols 203 and 205 who received some of the medication. Placebo rates for the same adverse experiences are shown for comparison. In those cases where the individual investigators did not designate a specific adverse event resulting in discontinuation, this reviewer assigned the specific adverse event or events based on the case report listings or narrative case summaries.

9.0

### Labeling Review

A labeling review is not included because this review recommends non-approval.

10.0

### Conclusions

The data supplied in this NDA does not make a convincing case for the efficacy of bupropion sustained-release as an antidepressant at any of the dosages employed. The presented trials suggest that when used as indicated in the protocols bupropion sustained-release is a reasonably safe medication. The absence of a clearly-defined benefit from bupropion sustained-release, however, argues against its approvability for the treatment of depression.

11.0

### Recommendations

On the basis of the data set available, this application does not meet criteria for approvability for the treatment of depression.



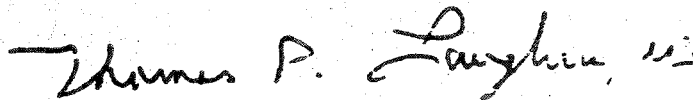
Dan A. Oren, M.D.  
Division of Neuropharmacologic Drug Products

NDA 20-358

HFD-120: TLaughren GDubitsky DOren PDavid

4-3-95

While I believe the sponsor has demonstrated bioequivalence for the Wellbutrin IR and SR formulations, I agree that they have not provided clinical evidence to justify the proposed change in dosing recommendations for this drug. Consequently, I agree that the application, as submitted with proposed labeling, is not approvable. My memo to the file provides my more detailed discussion of the pertinent issues.



61, PDP

AD10.0

Conclusions

The data supplied in the protocol 212 supplement to the NDA does not make a convincing case for the efficacy of bupropion sustained-release, nor does it materially affect the conclusions of the main Clinical Review of this NDA regarding efficacy and safety of the drug.



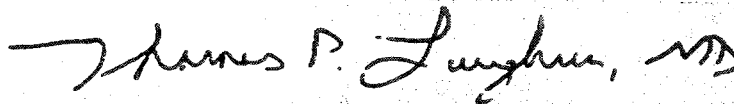
Dan A. Oren, M.D.  
Division of Neuropharmacologic Drug Products

NDA 20-358 Addendum  
HFD-120: TLaughren/GDubitsky/DOren/PDavid

1040 - Received 2-2-95 7P

4-3-95

I agree that this additional study does not alter the problem of insufficient clinical data to justify the change in dosing recommendations proposed for Wellbutrin SR. My memo to the file provides my more detailed discussion of the pertinent issues.



GL, PDA

## (2) Adjusted Results

(212)

Given the two dose groups in this study, it was necessary to make an adjustment for multiple comparisons. One approach was to use Dunnett's test, which yielded a critical p-value of 0.025 for declaring any particular finding positive. Using this criterion p-value, the positive findings on the HAMD-21 and MADRS scores for the 150 mg dose group generally prevailed, but again, only for LOCF analyses.

Impression: We consider this to be a negative study that cannot provide support for the antidepressant efficacy of either the 150 or 300 mg/day bupropion SR doses.

Overall Conclusions Regarding Efficacy Data for Bupropion SR

In summary, none of these 3 studies provided evidence for the antidepressant efficacy of bupropion SR in the dose range being studied. The sample sizes for both studies should have been adequate, and on the basis of HAMD total scores at baseline, the study populations had depressive symptoms of sufficient severity to expect they might be responsive to drug treatment. While even apparently adequately designed studies of antidepressants often fail, there was, unfortunately, no active control arm to test the sensitivity of any of these trials for detecting a drug effect. The failure of the 300 and 400 mg doses to show clear effectiveness, despite their bid equivalency to IR doses of 300 or 400 mg suggests that it may be the study assay sensitivity that is the problem. Unfortunately, whatever the explanation is, the studies do not support the lower dose range for bupropion.

We note your conduct of a NONMEM analyses for studies 203, 205, and 212 combined, which you cite as providing supplementary evidence for the effectiveness of bupropion SR. As an alternative to your exploratory analysis, Dr. Hoberman from the Division of Biometrics performed a simple meta-analysis using all three studies to investigate whether or not insufficient power might in part be an explanation for the weak results for the individual trials. His analysis focused on the HAMD-28 total score, CGI-Severity, and HAMD-Depressed Mood Item at week 8 for the 300 mg vs placebo comparison. Given the greatly increased sample size, it is perhaps not surprising that significance was achieved for two of the three variables, i.e., HAMD-28 total score and CGI-Severity, both for LOCF and OC analyses, but importantly not for HAMD-Depressed Mood.

This analysis, showing effectiveness of an approved daily dose level, provides some support for the view that these studies were underpowered to detect the response to this formulation in this dose range and for this population being studied. While such an analysis has some explanatory value, it cannot support the effectiveness of the lower doses: (1) Whatever the outcome of the meta-analysis or the NONMEM analysis, neither was in the original analytical plan for this program, and thus, neither can be considered definitive in assessing the success or failure of the program. (2) The sample sizes involved in the meta-analysis, i.e., almost 400 for the 300 mg dose group and almost 500 for placebo, raise a concern about the possibility of having a sample size large enough to be able to achieve statistical significance for a treatment effect that is of marginal clinical significance. The point estimates of the effect sizes (Tables 4-6) seen in these studies are very small. Although similar estimates have been seen in some studies of active drugs, active drugs usually have larger estimated effects in some studies.

20358

Wellb.

SR

MEMORANDUM

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

DATE: February 8, 1996

FROM: Thomas P. Laughren, M.D. *TPL*  
Group Leader, Psychiatric Drug Products  
Division of Neuropharmacological Drug Products  
HFD-120

SUBJECT: Recommendation for Approvable Action for Wellbutrin  
(bupropion) SR

TO: File NDA 20-358  
[Note: This memo should be filed with the 9-22-95 re-  
submission of the NDA.]

1.0 BACKGROUND

I refer to my 4-4-95 memo for a more complete background on this NDA. In summary, this NDA is for a sustained release formulation of bupropion, a drug which is currently approved in an immediate release formulation for the treatment of depression (NDA 18-644). NDA 20-358 was originally submitted 4-13-93. The NDA was not filed due to chemistry and pharmacology deficiencies. After the repair of these deficiencies, the NDA was re-submitted 2-28-94. The program included both clinical and bioequivalence trials. The labeling submitted with the application proposed dosing in a range of 150-300 mg/day, i.e., a lower dose range than that recommended for the currently available SR product. Unfortunately, the clinical trials failed to demonstrate effectiveness for the SR product in the lower dose range studied, and a non-approvable letter was issued 5-25-95. However, in that letter, we acknowledged that the sponsor had demonstrated in their PK studies the bioequivalence of the SR and IR formulations (when dosed bid for the SR vs tid for the IR), with regard to both extent and rate of absorption. In fact, we indicated that we would be willing to approve the SR formulation in a dose range of 300-400 mg/day, providing the sponsor submitted labeling consistent with this recommendation.

The 9-22-95 re-submission of this NDA responds to the issues raised in our 5-25-95 non-approvable letter. From a clinical standpoint, the sponsor is now recommending for Wellbutrin SR a maximum dose of 400 mg/day, i.e., a dose close to the currently recommended maximum dose of 450 mg/day. It was decided internally that, given this dosing recommendation, we could rely on the IR/SR bioequivalence

data for establishing an effectiveness link between the IR effectiveness data and the SR formulation.

There was also the question of whether or not the sponsor would need to conduct an additional bioequivalence study at the maximum recommended dose, since equivalence for the IR and SR formulations had been established only at 300 mg/day. However, given the linear kinetics for the IR formulation between 300 and 450 mg/day, there was an internal consensus that no additional biopharmaceutics studies would be needed to support this approval.

Two chemistry deficiencies were noted in our 5-25-95 non-approvable letter, i.e., regarding stability data and environmental assessment, and these issues have been adequately addressed in the 9-22-95 re-submission.

To my knowledge, there are no other outstanding issues that would preclude the approvability of this NDA.

## 2.0 LABELING REVISIONS

The draft labeling included in the 9-22-95 resubmission of this NDA was substantially deficient, primarily regarding the clinical sections. The major difficulty in my view was the failure in the revised labeling to adequately emphasize the dose-relatedness for certain important adverse events and to include in labeling incidence data for these events at bupropion doses that are being recommended. It is again important to note that the SR program failed to demonstrate the effectiveness of bupropion SR, and consequently, we are relying on the IR data, generally at higher doses than those used in the SR program, for our judgement about the effectiveness of the SR formulation.

In the draft of labeling accompanying the approvable letter, I have substantially re-written much of the clinical sections, and in other cases, I have embedded requests for the sponsor to make revisions on the basis of data that they can readily access. The draft labeling contains numerous embedded comments explaining in detail why we are proposing changes in their labeling, and I will comment more briefly here on some of the key issues that were subject to revision.

## CLINICAL PHARMACOLOGY

### Pharmacodynamics

The sponsor added language suggesting a mechanism for the antidepressant action of bupropion. Such language is not present in currently approved labeling and its addition is contrary to what has in recent years been our general approach in this section, namely, to neutrally describe the pharmacology of a drug and simply

acknowledge truthfully that we don't know the mechanism of action. Consequently, I have deleted this language and replaced it with a more neutral description of bupropion's pharmacology. I have also deleted some animal toxicology data suggestive of a difference between the IR and SR formulations, however, at doses far in excess of those relevant to human experience.

#### Pharmacokinetics

The sponsor's proposed PK section heavily emphasized the PK for bupropion SR, but failed, in my view, to adequately compare the PK for the SR and IR formulations. Since we are basing our efficacy judgement solely on the bioequivalence of these 2 formulations, I felt it was important to describe the steady state findings for these different formulations. The other reason for emphasizing the bioequivalence of the SR and IR is to justify the inclusion in later sections of adverse event data for the IR, often occurring at somewhat higher doses than used in the SR program, but at doses that are necessarily recommended for the SR, considering the clinical trials upon which efficacy is based.

#### Clinical Trials

In recent years, we have added clinical trials subsections to provide some detail on the clinical trials supporting the effectiveness of a drug, and I felt that was particularly important here. The subsection I have added describes the 2 relevant IR studies, and also notes truthfully that the effectiveness of the SR is based on a link to these IR studies through the bioequivalence of these products, and not on independent data.

#### INDICATIONS AND USAGE

The sponsor had deleted the cautionary statement about seizures that is in current labeling, based on the lower seizure incidence observed in the SR study involving patients dosed in a bupropion range of 100-300 mg/day. Of course, we are recommending a dosing range of 300-400 mg/day, a range for which bupropion IR has been shown to have a seizure risk about 4-fold higher than that seen in this lower dose range. Given the bioequivalence of these formulations, I consider the seizure caution equally pertinent to the SR labeling, and I have added it back in.

#### WARNINGS

The sponsor's proposed Warnings section significantly de-emphasizes the risk of seizure with Wellbutrin SR, and adds, mostly as an afterthought, the IR data at the higher doses still being recommended for the SR product. In the absence of any directly relevant data in this higher dose range for the SR product, coupled with the demonstrated bioequivalence for these products, I think it is essential to more strongly emphasize the dose relatedness for

this event and minimize the implication that the formulation change results in a lower and more acceptable seizure rate.

#### PRECAUTIONS

The most significant changes I have made here are in the General Precautions subsection. The sponsor has minimized several of the adverse findings noted in this section: agitation and insomnia; psychosis, etc., and appetite and weight changes. Again, the difficulty is that the SR data are based on a generally lower dosage strategy than that used in the IR program. I have proposed modifications in this section that illustrate more clearly the dose-relatedness for these findings and their equal relevance for the IR and SR formulations.

#### REVERSE REACTIONS

The general problem with this section was the same as in the earlier sections, a failure to distinguish between the different doses of cypripion used in the IR and SR programs. I have asked the sponsor to redo this section, focusing on the 2 pertinent fixed doses used in the SR program, i.e., 300 and 400 mg/day.

#### DOSE AND ADMINISTRATION

I have added back in the "General Dosing Considerations" statement that is in current labeling, since I feel it is as relevant for the SR as for the IR. I have also modified dosing instructions to clarify that 100 mg/day, and not 150 mg/day, is the initial target dose for Wellbutrin SR.

#### CONCLUSIONS AND RECOMMENDATIONS

Given that the sponsor is now willing to recommend a dosing range for cypripion SR that is comparable to the range currently recommended for bupropion IR, I think we can consider this application approvable. However, major work is still needed to develop labeling that will adequately inform clinicians about the risks and benefits of this drug, and I have proposed comments for a letter that emphasizes the discrepancy between the labeling they have proposed and what is needed.

WHD:NEA 20 358

HFD:12 DivFile

HFD:12 Tlaughren/Pleher/PAndreason/GDubitsky/PDavid

HFD:12 RTemple

XXX MEMBERS AE1

**ADDENDUM TO:**

**Review and Evaluation of Clinical Data  
NDA 20,358**

**Sponsor:** Glaxo Wellcome  
**Drug:** Wellbutrin SR (bupropion hydrochloride sustained release tablets)  
**Indication:** Depression  
**Material Submitted:** Response to Approvable Letter  
**Correspondence Date:** May 14, 1996  
**Date Received:** May 15, 1996

**I. Background**

NDA 20,358 was submitted on February 28, 1994. The clinical review was completed on November 14, 1994, and it was declared non-approvable in a letter dated May 25, 1995, because the sponsor failed to provide adequate evidence of clinical efficacy. Subsequently, based on a meeting with the firm on August 2, 1995, and further consultation within the agency, it was decided to consider approvability based on bioequivalence with the approved immediate-release formulation with the provision that Wellbutrin SR be labeled with essentially the same safety statements as found in the labeling for the approved product. The sponsor responded with a September 22, 1995, submission that included proposed labeling based on prior discussions. In turn, we issued an approvable letter dated March 12, 1996, and included, from a clinical perspective, a request for revised labeling, a safety update, a foreign regulatory update, and launch promotional material. The current submission comprises the sponsor's response.

**II. Safety Update**

**A. Database**

This update consists of safety data from seven studies:

- continuation phase of Study 208 (depression),
- Study 209 (depression),
- Studies 403, 404, 405, 406, and 407 (smoking cessation).

A total of 1577 patients from Study 208, who were reported previously in the NDA and for whom longer-term safety data

Line listings of all patients and volunteers with serious adverse events and with adverse events leading to premature study discontinuation are presented by study. In addition, narrative summaries are provided for all serious adverse events and for adverse dropouts in Studies 209, 403, and 407, which are completed studies.

## Methodology

## Serious Adverse Events

**Table 1: Serious AE's Not Previously Reported**

[illegible]

<sup>1</sup>This number is approximate since Studies 209, 404, and 405 are still blinded.

The narrative summaries for these cases were reviewed and, with the exception of Patient 403/3227, the adverse events were not felt to be reasonably attributable to the study drug. Patient 403/3227 experienced dyspnea, blue lips, hand and foot swelling, periorbital and perioral edema, and extremity petechiae after taking a dose of verapamil, which she took chronically for hypertension, with a peanut butter sandwich on Day 25 of treatment with Wellbutrin SR 300 mg/day. She was treated in the local emergency room with parenteral Benadryl, steroids, and epinephrine and recovered. She was discharged on tapering doses of oral steroids. However, even in this case, a causal link to Wellbutrin SR is difficult to assess because verapamil and peanut butter were felt to be equally likely etiologies of this anaphylactic reaction.

#### Adverse Events Leading to Premature Discontinuation

Only three non-serious adverse events resulting in dropout were not observed in previous databases: chickenpox, anorgasmia, and tongue blisters. Each was reported in one patient. The case of chickenpox was felt to be unlikely to be drug related. The 53 year old male with anorgasmia experienced this event after taking Wellbutrin SR 300 mg/day for 106 days; no other information was available. The patient with tongue blisters (403/1023) was a 41 year old Indian male who experienced this event after 30 days of treatment with Wellbutrin SR 300 mg/day; he apparently continued treatment for another 11 days before stopping treatment. This event may have been related to Wellbutrin SR.

#### **C. Conclusions**

None of the data contained in this safety update changes previous conclusions regarding the overall safety profile of Wellbutrin SR.

### **III. Foreign Regulatory Actions**

Neither the immediate-release nor sustained release formulations of bupropion are marketed outside the United States. Applications to market Wellbutrin Tablets were submitted to Canada (1981) and the U.K. (1983); after deficiency letters were issued by both agencies (1986 and 1983, respectively), these applications were withdrawn.

A clinical trial exemption (CTX) to investigate Wellbutrin SR Tablets as an aid to smoking cessation was submitted to the U.K. in January 1996 and was rejected the following month related to several safety issues, many of which were cited in the 1983 deficiency letter (including seizures, potential carcinogenicity and liver toxicity in animals,

lack of studies on addictive potential, and questions regarding the adequacy of animal studies). This plan for investigation in the U.K. has not been pursued.

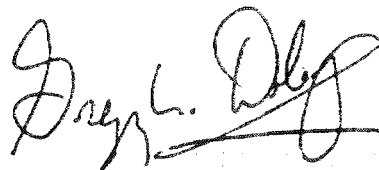
In sum, it seems that none of the foreign concerns are new; most, if not all, emerged prior to U.S. approval of Wellbutrin.

#### IV. Introductory Promotional Materials

No promotional materials were submitted at this time. These will be drafted and submitted to the agency after consensus on labeling but prior to market introduction.

#### V. Labeling

Product labeling proposed by the sponsor was reviewed and edited. However, since labeling will require further modification, the edited version is not included as part of this review but will be forwarded to the Team Leader under separate cover.



Gregory M. Dubitsky, M.D.  
August 9, 1996

cc: NDA 20,358  
HFD-120  
HFD-120/GDubitsky  
PAndreason  
TLaughren  
PDavid

-96

I agree that this NDA  
can now be approved  
we still need to get agreement  
with GW on final labeling,  
and also expiration date &  
disinfectant spec. See mem.  
to file for more detailed

~~response~~

Page 4

shrewsb. Laughren 11/92  
TL, PDP

SEP 11 1996

**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS**

Review of Chemistry, Manufacturing, and Controls

**NDA #:** 20-358

**CHEMISTRY REVIEW #:** 4

**DATE REVIEWED:** 28-AUG-96

**SUBMISSION TYPE**

**DOCUMENT DATE**

**CDER DATE**

**ASSIGNED DATE**

AMENDMENT

14-MAY-96

15-MAY-96

20-MAY-96

**NAME & ADDRESS OF APPLICANT:**

GLAXO WELLCOME INC  
Five Moore Drive  
Research Triangle Park, NC 27709

**DRUG PRODUCT NAME**

Proprietary:

WELLBUTRIN® SR

Nonproprietary/Established/USAN:

Bupropion hydrochloride

Code Name/#:

Chem. Type/Ther. Class:

**PHARMACOLOGICAL CATEGORY/INDICATION:** ANTIDEPRESSANT/DEPRESSION

**DOSAGE FORM:**

TABLETS

**STRENGTHS:**

50, 100 and 150mg

**ROUTE OF ADMINISTRATION:**

Oral

**DISPENSED:**

XX Rx \_\_\_ OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

(±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride(USAN)

CAS #: 31677-93-7; 34911-55-2 (bupropion base)

C<sub>13</sub>H<sub>18</sub>ClNO . HCl Mol.Wt: 276.21

**CONCLUSIONS & RECOMMENDATIONS:**

Based on review of the Chemistry and Manufacturing Controls Section, we recommend that the the label storage statement revisions and the addition of a cap liner to the container system be APPROVED; we do not recommend approval of a 24 month expiration date at this time or revision of the original dissolution specifications. Methods Validation is still in progress.  
cc:

Org. NDA 20-358

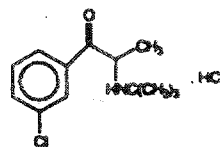
HFD-120/Division File

HFD-120/CBParisek/8/28/96

HFD-120/David

HFD-120/SBlum

R/D Init by: SBLUM



WELLBUTRIN (bupropion hydrochloride)

*Charles B. Parisek 8/29/96*

Charles B. Parisek, Ph.D., Review Chemist

filename: N020358a.004

**Enclosure 1**

**NDA 20-358**

**WELLBUTRIN SR (bupropion hydrochloride) Tablets**

**Amendments and Correspondence submitted to NDA since original resubmission:**

March 11, 1994	May 27, 1994	June 29, 1994 (2)
July 14, 1994	July 22, 1994	July 29, 1994
August 1, 1994 (2)	August 2, 1994	August 18, 1994
August 30, 1994	September 12, 1994	September 30, 1994
October 21, 1994	November 11, 1994	December 23, 1994
January 10, 1995	January 25, 1995	February 2, 1995
February 21, 1995	February 23, 1995	March 7, 1995
March 30, 1995		



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 18-644

MAR 25 1991

Burroughs-Wellcome Company  
Attention: Michael J. Dalton, Pharm.D.  
Head, Department of Pharmaceutical Products  
Drug Regulatory Affairs  
3030 Cornwallis Road  
Research Triangle Park, North Carolina 27709

Dear Dr. Dalton:

Please refer to your New Drug Application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Wellbutrin<sup>®</sup> (bupropion hydrochloride) tablets.

We acknowledge receipt of your amendment dated November 20, 1990, requesting our opinion whether your proposal would support a labeling change to permit bid dosing of Wellbutrin<sup>®</sup> at 300 mg/day.

Reference is also made to telephone conversations on November 14 and 28, 1990, between Dr. Loren Miller of your firm and Dr. Thomas Laughren of this Agency, regarding what data would be required to gain approval of a sustained release formulation of Wellbutrin<sup>®</sup>.

We have completed our review of your requests and have the following recommendations:

We agree that a clinical study demonstrating the safety and effectiveness of the 150 mg bid dosing would not be necessary. However, given the limited data available about the steady-state pharmacokinetics of bupropion, and particularly the morpholinol metabolite, we are not prepared to rely on simulations alone. Therefore, we would want to see data from actual studies comparing the pharmacokinetics of bupropion and the morpholinol metabolite in 100 mg tid and 150 mg bid dosing.

Regarding your more informal request for advice about what studies might be needed to support a sustained release form of Wellbutrin<sup>®</sup>, we again feel that it would not be necessary to demonstrate the safety and effectiveness of such a product in a clinical study. However, you would, at a minimum, need to demonstrate that such a product, when given at a total dose of 300 mg/day, resulted in steady-state plasma levels of bupropion and the morpholinol metabolite that fell within the time-concentration windows for these entities seen with 100 mg tid dosing with the immediate release form.

Should you have any questions concerning this NDA, please contact Mr. Paul David, Consumer Safety Officer, at (301) 443-3504.

Sincerely yours,

Paul Leber, M.D.  
Director  
Division of Neuropharmacological  
Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Review and Evaluation of Clinical Data  
NDA #20,358

Sponsor:	Burroughs Wellcome Co.
Drug:	Wellbutrin (Bupropion HCl) SR
Material Submitted:	Revised labeling
Correspondence Date:	September 22, 1995
Date Received:	September 25, 1995
Related NDAs	18644

**I. Description of Compound**

A. Generic Name:	Bupropion HCl
B. Drug Category:	
C. Formulation:	Sustained release tablets

**II. Background**

Wellbutrin SR is the trade name for bupropion HCl sustained release formulation (BSR) made by Burroughs Wellcome Co.. Wellbutrin immediate release tablets are currently marketed. The sponsor received a non-approvable letter for BSR because three placebo controlled studies failed to show that the drug was effective at the proposed dose of 300 mg/day (150 mg po BID). The sponsor was informed that approval of the drug would be considered if they applied for approval based on bioequivalence of BSR to the immediate release formulation of bupropion (BIR). This would require the sponsor to submit new labeling that would change the recommended dose range to the existing bioequivalent range (300-450 mg/day), supply safety data for the BSR proposed dose range, and include the information on adverse events associated with the BIR and BSR in the labeling.

**III. Data Reviewed-Proposed labeling for Wellbutrin SR**

**Description Section:** The proposed labeling is uniquely for the sustained release formulation, Wellbutrin SR. The description section, therefore, deletes the description of Wellbutrin and describes Wellbutrin SR. Further references to "Wellbutrin" immediate release formulation is changed to the generic bupropion immediate release throughout the proposed labeling.

**Clinical Pharmacology Section:** New information is added to this section regarding basic science findings that shed light on the proposed mechanism of action of bupropion. A reference is made to an animal tox/path study that examines the seizure thresholds of

mice with equal doses of BSR and BIR. The sponsor states, "When administered to mice in equal doses, a sustained release formulation of bupropion produces significantly fewer convulsions than an immediate release aqueous formulation." This is animal data that implies that BSR is less likely to cause seizures in humans and might therefore be safer to use than BIR with respect to seizures. The large body of human data is for the 300 mg/day dose level which is at the lowest end of the recommended dose range of 300-400 mg/day.

**Absorption, Distribution, Pharmacokinetics, and Elimination Section:** This section removes the information for BIR and inserts the data for BSR.

**Indications and Usage Section:** This section removes the specific seizure incidence information and refers the prescriber to the Warnings section.

**Contraindications Section:** The contraindications remain for patients with a seizure disorder and patients with bulimia or anorexia nervosa.

**Warnings Section:**

**Seizures:** A review of the extended treatment protocol (study 208) is presented and clearly states what the seizure incidence is for doses of 300 mg/day. The BIR seizure incidence data is presented after this.

**Hepatotoxicity warnings remain unchanged.**

**Precautions Section:** This section is amended to present the safety data of BSR with respect to agitation and insomnia. Precautions against psychosis, confusion and other neuropsychiatric phenomena have subsumed the terms delusions, paranoia, and psychotic episodes under the term psychosis. The section discussing altered appetite and weight was amended to reflect the sponsors experience with BSR and still reports data from comparison studies with BIR and TCAs.

**Information to patients section:** This section was changed to reflect the use of Wellbutrin SR in the place of Wellbutrin. Changes in the dosing schedule, and most importantly, the reference to seizure risks and precautions has been removed.

**Drug Interactions, Carcinogenesis-Mutagenesis-Impairment-of-Fertility, Pregnancy, and Pediatric Use sections** are essentially unchanged. Data on use of BSR in the elderly was added based on experience from the extended safety study (208).

**Adverse Events section:** This section reflects tabular results of adverse events encountered by the 987 patients who were involved in the controlled clinical trials groups. This is somewhat misleading in that only half of the patients (487) received BSR in the

proposed dose range of 300-400 mg/day. As all of the lower dose patients were included in the 1% and 5% ADR tables, this creates an artificially inflated denominator.

The narrative section reflects the experience with BSR as opposed to BIR. The narrative states that 4320 patients were exposed to Wellbutrin SR; however, 4202 patients can only be accounted for in the data that was submitted for review.

### III. Conclusions and Recommendations

The newly proposed labeling submitted by the sponsor is accurate in-so-far as what is presented. The sponsors do not mention the efficacy study results for BSR, (which were not encouraging) and they do not mention that the BSR formulation was approved on bioequivalence alone. The safety section removes most of the repeated warnings regarding seizures and merely refers the reader to the "Warnings" section. The only reference to seizure risk in the patient information section was removed.

One should consider presenting the data for the patients in the recommended dose range in the ADR tables instead of including the patients in the lower dose ranges. The current presentation artificially inflates the denominator and produces lower AE rates than those that would represent the recommended use.

  
Paul J. Andreason, M.D.

cc: NDA#20,358  
HFD-120  
HFD-120/PAndreason  
Dubitsky  
TLaughren  
PDavid

2-1-76

I agree that the labeling needs much work, and I have developed a draft of labeling that is substantially different than what sponsor has proposed. See draft labeling & my memo & file for details.  
— Thomas P. Laughren, MD  
GL, PDP

8 / 8  
Part 120.1

## REVIEW AND EVALUATION OF CLINICAL DATA

### Application Information

NDA # 20-358

Sponsor: Burroughs Wellcome Co.

Clock Date: March 7, 1994

### Drug Name

Generic Name: Bupropion hydrochloride

Proposed Trade Name: Wellbutrin SR (rejected)

### Drug Characterization

Pharmacological Category: Antidepressant

Proposed Indication: Treatment of depressive disorders

NDA Classification: 3S

Dosage Forms, Strengths, and Routes of Administration:  
Oral tablets in 50, 100, and 150 milligram strengths

### Reviewer Information:

Clinical Reviewer: Dan A. Oren, M.D.

Review Completion Date: November 14, 1994

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**1.0 Material Utilized in Review**

**1.1 Material from NDA**

The following is a list of specific items reviewed:

Volume	Submission Date	Material
2.13	Feb. 28, 1994	Summary of Phase 2 trial #203
2.14-2.19	Feb. 28, 1994	Study reports for trial #203
2.20	Feb. 28, 1994	Summary of Phase 2 trial #205
2.21-2.28	Feb. 28, 1994	Study reports for trial #205
2.29, 2.46	Feb. 28, 1994	Integrated summary of effectiveness
2.29, 2.46	Feb. 28, 1994	Integrated summary of safety
2.47-2.59	Feb. 28, 1994	Case report forms
	June 6, 1994	Response to request for additional efficacy data
	June 29, 1994	Additional case report forms submitted
	June 29, 1994	Response to request for demographic and exposure data
5.2	July 14, 1994	Revised labeling
5.1, 5.3, 5.8-5.11	July 14, 1994	Study report for Phase 3 trial #208
	July 29, 1994	Narrative summaries of premature discontinuation
	August 1, 1994	Response to request for adverse effect data
	August 2, 1994	Response to request for relative risk data
	August 18, 1994	Additional case report forms submitted
	September 9, 1994	Response to request for additional demographic data
	September 12, 1994	Worldwide marketing and application history submitted

Safety issues were addressed primarily via the integrated summary of safety, supplemented by examination of individual study reports and case report forms.

**1.2 Related Reviews**

The division files for IND's (Burroughs Wellcome's commercial IND's for Wellbutrin and bupropion sustained-release tablets) were consulted during the course of this review.

## 2.0 Background

### 2.1 Indication

There are almost 20 drugs approved as antidepressant medications in the U.S.A. Most of the antidepressants marketed are thought to have their therapeutic action by inhibition of re-uptake of norepinephrine or serotonin or by inhibition of monoamine oxidase. Approximately 75 per cent of depressed patients who are treated with an antidepressant medication have good clinical responses to the treatments. Rigorous dietary restrictions associated with monoamine oxidase inhibitors and significant levels of unwelcome side effects associated with most of the tricyclic and tetracyclic antidepressants and with serotonin-selective reuptake inhibitors limit the range of usefulness of these medications. Bupropion is an aminoketone in a class by itself among the antidepressants, though it is structurally related to the anorectic agent diethylpropion, a sympathomimetic with stimulant properties. Bupropion is capable of reducing firing rates of noradrenergic neurons in the locus ceruleus and, with one exception, demonstrates a mild side effect profile. Clinical use of the drug is limited, primarily, by the occurrence of seizures, particularly associated with high serum levels of the substance and with patients with a predilection to seizures or with histories of anorexia or bulimia. To reduce the risk of seizures, bupropion is currently labeled for prescription on a t.i.d. schedule that reduces the risk of seizure but also makes compliance with medication intake difficult. Development of a sustained-release form of bupropion is expected to allow for reduction of peak levels of bupropion and, therefore, reduce the risk of seizures being induced by the medication. Provision of the medication on a b.i.d. instead of a t.i.d. basis may allow for increased compliance with the treatment.

### 2.2 Related INDs and NDAs

See section 1.2 above.

### 2.3 Administrative History

The original IND for bupropion sustained-release was submitted 7/17/86. In a letter dated 3/25/91, the Division went on record as stating that a clinical study demonstrating the safety and efficacy of a sustained-release formulation of bupropion would not be required. Data comparing the pharmacokinetics of bupropion sustained-release and its active metabolites, however, was still required.

At a meeting with representatives of the firm on 1/28/1992, the Division stated that any change in labeling regarding the incidence of seizure while on bupropion sustained-release could only be considered if the sustained-release formulation decreased  $C_{max}$ , demonstrated bioequivalency, and if the firm could demonstrate convincingly that seizure incidence is directly correlated with  $C_{max}$ . In a letter to the sponsor dated 3/16/93, the Division stated that transfer of labeling regarding seizures from the Warnings to the Precautions section could only be considered if the sponsor conducted a large enough study to conclude reasonably that the incidence of seizure was less than 0.3%. If the firm could not demonstrate improved or equivalent bioavailability, they would need to conduct two adequate and well controlled clinical trials to support approval of the formulation.

### 2.4 Proposed Directions for Use

In the proposed labeling, specified contraindications are seizure disorder, current or past history of bulimia or anorexia nervosa, intake within the prior two weeks of a monoamine oxidase inhibitor, or history of hypersensitivity to the sustained-release or immediate release formulations of the compound. To reduce the potential risk of seizures further, the proposed labeling encourages prescription of a maximum of 300 mg/day of the sustained-release formulation, avoiding single doses of the compound that exceed 150 mg, and very gradual incrementation of dose. The labeling further discourages the use of the compound in patients who might be at higher risk of seizure. Such patients might have a history of seizure or cranial trauma, concurrent receipt of other psychoactive medications that might reduce the seizure threshold, recent history of abrupt discontinuation of benzodiazepine treatment, or other predispositions toward seizure. When used as recommended by the sponsor, the incidence of seizure with the

sustained-release formulation is substantially less than that of the immediate-release formulation, and comparable to that of other commercially-marketed antidepressants.

The proposed labeling states that limited clinical data suggests a higher incidence of adverse experiences in patient receiving concurrent administration of immediate-release bupropion and levodopa and advises caution in prescribing the sustained-release formulation along with levodopa. Physicians are also advised to exercise caution when co-administering drugs that affect hepatic drug-metabolizing enzyme systems (e.g., carbamazepine, cimetidine, phenobarbital, and phenytoin).

Caution is urged in patients with known cardiovascular, hepatic, or renal disease.

The drug is classified as belonging to Pregnancy Category B. Because of the potential for serious adverse reactions in infants who might receive bupropion through mother's milk, the physician is advised to use clinical judgment in deciding whether to recommend that a mother discontinue breast feeding, or alternatively, discontinue bupropion.

Regarding special populations, it is stated that safety and effectiveness in children has not been established. For geriatric use, the sponsor notes that exposure of elderly patients to sustained-release bupropion is limited, but that one study has demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects.

Although the sponsor has limited experience with sustained-release bupropion in overdose, the proposed labeling does address overdoses with the immediate release formulation of the substance. The manufacturer recommends hospitalization and general supportive measures along with EKG and EEG monitoring for 48 hours after suspected overdoses.

The recommended initial dosage is 150 mg daily, titrated up to a maximum daily dose of 300 mg, with dose increases occurring at intervals of at least one week. The sponsor recommends administering individual doses of no greater than 150 mg, with daily doses greater than 150 mg being given b.i.d. with at least eight hours between successive doses.

## 2.5 Foreign Marketing

Neither bupropion immediate-release nor bupropion sustained-release has ever been marketed outside the U.S.A. Applications to market the immediate-release form of bupropion in the United Kingdom and Canada were withdrawn in 1984 and 1986, respectively, following deficiency that each country's regulatory agency found in the applications. No applications for the marketing of bupropion sustained-release have been made outside of the U.S.A.

## 3.0 Chemistry

The chemistry has been reviewed separately. An environmental assessment is still pending. The stability of the sustained-release formulation has not yet been adequately reported to the satisfaction of the agency. There are no other outstanding chemistry concerns of clinical relevance.

## 4.0 Animal Pharmacology

The animal pharmacology is reviewed separately, and only a brief summary is presented here.

Nonclinical pharmacology studies suggest that bupropion may inhibit the reuptake of both norepinephrine and dopamine. It spares central and peripheral  $\alpha_1$  and  $\alpha_2$  adrenergic receptors,  $H_1$  histamine receptors, muscarinic (cholinergic) receptors, and  $D_2$  dopaminergic receptors.

In studies of bupropion sustained-release, acute toxicity was tested in rats and mice. The LD50 in mice was 544 mg/kg for males and 636 mg/kg for females. In rats the LD50 was 607 mg/kg for males and 482 mg/kg for females. Signs of acute toxicity included labored breathing, salivation, arched back, ptosis, ataxia, and convulsions.

A multidose toxicity studies of bupropion sustained-release involved three month administration to rats of both degraded and undegraded compound. Findings included dose-related salivation and increases in liver and thyroid weights due to reversible microsomal enzyme induction. The findings in this study did not differ in any significant way from the findings in previous studies of bupropion immediate-release.

Lifetime carcinogenicity studies with bupropion immediate-release were performed in rats and mice at doses up to 300 and 150 mg/kg/day respectively. There was an increase in nodular proliferative lesions at doses of 100 to 300 mg/kg/day in the rat. Similar lesions were seen in the mouse. No increase in malignant tumors of the liver and other organs was seen in either study.

The immediate release formulation produced a borderline positive response (two to three times control mutation rate) in some strains in the Ames bacterial mutagenicity test, and a high oral dose (300, but not 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. A similar response on the Ames test was seen with the bupropion sustained-release formulation. Bupropion sustained-release did not induce chromosomal aberrations in rats during cytogenicity studies.

No evidence of impairment of fertility due to bupropion immediate-release at oral doses up to 300 mg/kg/day. In the sponsor's opinion, teratogenicity studies of both the immediate-release and sustained-release formulations were negative.

## 5.1.2

## Demographics

Table 5.1.2.1 presents the demographic information for patients studied in Phase 1 trials. These subjects were all male, predominantly white, and age 40 or under. Table 5.1.2.2 provides the demographic profile for the primary efficacy study population: all patients exposed to bupropion sustained-release or placebo in the clinical efficacy phase 2-3 trials, with the exception of 36 patients for whom no treatment phase assessments were available. Table 5.1.2.3 provides the demographic profile for all patients known to have received study medication in the Phase 3 seizure incidence trial. Patients were mainly white females under age 60. Bupropion sustained-release was administered to no patients under 18 years of age. The demographic profiles for the bupropion sustained-release and placebo groups in the integrated efficacy and safety data sets are similar, as the tables illustrate.

Table 5.1.2.1 Demographic Profile of Bupropion sustained-release for Phase 1 Studies (N=132)		
Parameter		Value
Age (Years)	Mean	25
	Range	18-40
Gender	Male	100%
	Female	0%
Race	White	73%
	Non-White	27%
Mass (kg)	Mean	73.6
	Range	58.5-88.9

Table 5.1.2.2 Demographic Profile for Phase 2 and 3 Clinical Efficacy Studies			
Parameter		Bupropion (N=693)	Placebo (N=235)
Age (years)	Mean	39	40
	Range	18-79	19-82
Gender	Male	34%	37%
	Female	66%	63%
Race	White	86%	88%
	Non-White	14%	12%
Mass (kg)	Mean	78.3	79.1
	Range	44.0-167.8	47.6-155.1

Table 5.1.2.3 Demographic Profile for Phase 3 Seizure Incidence Study		
Parameter		Bupropion (N=3100)
Age (years)	Mean	42
	Standard Deviation	12
	Range	18-86
Gender	Male	37.6%
	Female	62.4%
Race	White	89.5%
	Black	7.0%
	Other	3.5%

### 5.1.3 Extent of Exposure (dose/duration)

Table 5.1.3.1 shows the numbers of patients in Phase I trials according to mean daily bupropion sustained-release dose and duration of administration. A majority of patients (55.3%) were exposed to 300 mg/day dosing. The mean daily dose and duration of bupropion sustained-release treatment for patients in Phase 2 and 3 trials is shown in Table 5.1.3.2. The majority of patients studied (53.9%) were treated with 300 mg/day. The three Phase 2-3 trials represent 439 patient-years of exposure to bupropion sustained-release.

Table 5.1.3.1 Number and Percentage of All Volunteers Receiving Bupropion Sustained-Release According to Mean Daily Dose and Duration in Phase I Clinical Pharmacology Studies					
Duration (days)	100 mg	150 mg	300 mg	Total	Percentage
1	2	0	1	3	2.3%
2	21	36	1	58	43.9%
3	0	0	37	37	28.0%
14	0	0	34	34	25.8%
Total	23	36	73	132	
Percentage	17.4%	27.3%	55.3%		100%

### 7.3.3

#### Choice of Dose

None of the doses studied in protocols 203 and 205 was unequivocally an effective treatment based on the parametric analyses of the individual studies. (The largest data base on any individual dosage of bupropion sustained-release is that based on the subjects who received 300 mg/day of the medication—the approved standard daily dosage for bupropion immediate-release.)

### 7.3.4

#### Duration of Treatment

Both studies 203 and 205 suggest that periods of four weeks or less are inadequate to demonstrate efficacy of bupropion sustained-release with the sample sizes used.

### 7.4

#### Conclusions Regarding Efficacy Data

Protocols 203 and 205 both fail to show unequivocal evidence of the efficacy of the doses of bupropion sustained-release that were tested.

## **8.0 Safety Findings**

### **8.1 Methods**

The bupropion sustained-release NDA integrated safety summary provided the foundation for the safety assessment which follows. The Burroughs-Wellcome integrated safety database included data from Phase 2 and Phase 3 studies; the Phase 1 safety findings were considered separately. The Phase 1 Clinical Pharmacology trials involved 131 subjects who received bupropion sustained-release. The sponsor's pooled Phase 2-3 integrated summary of safety database incorporates data from 928 patients who were exposed to bupropion sustained-release or placebo in studies 203 and 205, with the exception of 36 patients for whom no treatment phase assessments were available. Of this group, 693 patients received bupropion sustained-release and 235 patients received placebo. In addition, the sponsor performed a phase 3 study (Protocol 208) designed to measure seizure incidence. This study consisted of an open-label trial of bupropion sustained-release in 3100 patients in a treatment phase for eight weeks, and in an optional continuation phase extending indefinitely beyond the eight weeks.

Safety issues were evaluated on the basis of these data sets and case report forms. Uncommon, severe adverse events were assessed using premature discontinuations from clinical trials and "serious" adverse events (as defined below), while more common but less grave adverse reactions were identified through routinely collected safety data. Treatment emergent changes in vital signs and clinical laboratory tests were examined and are described in Section 8.5. Section 8.6 contains a discussion of those adverse events deemed both significant and potentially drug-related.

### **8.2 Deaths**

None were reported from the pooled safety database from the placebo-controlled trials 203 and 205. Six deaths did occur during the open trial (208): three due to suicide, one due to homicide, and two due to cardiac illness. None of these deaths were considered attributable to bupropion sustained-release. Patient 021-016 was a 75-year-old female who died of cardiac arrest 45 days after starting bupropion sustained-release. She had a history of hypertension. Patient 034-021 was a 39-year-old male who killed himself with a gun 11 days after discontinuing bupropion sustained-release prematurely, after having taken the medication for nine days total. Patient 053-028 was a 32-year-old male who died of a multiple drug overdose, without ever having taken a single dose of bupropion sustained-release. As of July 14, 1994, three patients had died in the continuation phase of the study. Patient 045-015 was a 36-year-old female who killed herself with a gun after approximately three months of bupropion sustained-release intake. Patient 074-013 was a 32-year-old male who was killed by a gunshot following an argument at his workplace after approximately twelve weeks of bupropion sustained-release intake. Patient 078-006 was a 66-year-old male with a history of hypertension and hyperlipidemia who died of a presumed myocardial infarction after 130 days of bupropion sustained-release intake. He had complained of chest pain to his primary physician six weeks before death.

### **8.3 Assessment of Dropouts**

#### **8.3.1 Overall Pattern of Dropouts**

Table 8.3.1.1 summarizes reasons for premature discontinuation among patients who were randomly assigned to receive treatment under protocols 203 and 205. Because 36 patients assigned to receive treatment dropped out between point of randomization and first ingestion of medication, the total number of subjects in this table is larger by 36 than the number of subjects in the integrated summary of safety database. This table was compiled by reviewing the reasons assigned by the individual investigators for each subject who dropped out. In several cases where "Consent Withdrawn" was assigned by the investigator as a reason for withdrawal, but where the case reports or narrative case summaries suggested to this reviewer that "Lack of Efficacy" or "Adverse Experiences" better captured the reason for dropping out, one of the latter two explanations was used in the table.

Table 8.3.2.1 Incidence of Premature Termination Due to Specific Adverse Events in Protocols 203 and 205		
Reason	Bupropion SR (N=693)	Placebo (N=235)
Allergic (including rash, pruritus, urticaria)	2.6%	0.9%
Headache	1.3%	0.9%
Nausea/Vomiting	1.2%	0.4%
Anxiety/Nervousness/Panic Attack	0.9%	0.0%
Cardiac (including palpitations, tachycardia, hypertension, chest pain, myocardial infarction)	0.7%	0.9%
Insomnia	0.6%	0.4%
Agitation	0.6%	0.4%
Dizziness	0.3%	0.0%
Hallucinations	0.3%	0.0%

The following table lists all those categories of adverse experiences leading to dropout that were associated with at least 0.5% of the 3100 subjects who received bupropion sustained-release in protocol 208.

Table 8.3.2.2 Incidence of Premature Termination Due to Specific Adverse Events in Protocol 208	
Reason	Bupropion SR (N=3100)
Allergic (including rash, pruritus, urticaria)	1.4%
Headache	1.1%
Nausea/Vomiting	1.1%
Anxiety/Nervousness/Panic Attack	1.5%
Cardiac (including palpitations, arrhythmias, syncope, chest pain, myocardial infarction)	0.5%
Insomnia	1.0%
Agitation	0.7%
Dizziness	0.5%
Irritability	0.5%
Somnolence	0.4%
Impotence	0.3% (of 1167 males)

In the placebo-controlled studies, there was a dose-dependent association between medication-intake and risk of allergic event causing discontinuation: allergic events occurred in 1 of 115 patients (0.9%) who received 100 mg/d bupropion sustained-release, in 4 of 235 patients (1.7%) who received 150 to 200 mg/d of bupropion sustained-release, and in 13 of 343 (3.8%) patients who received 300 mg/d or more of bupropion sustained-release.

It should be noted that the above profile of adverse events leading to study discontinuation is similar to that established in the initial product development of bupropion immediate-release. In that form of the drug, the more common events causing discontinuation were neuropsychiatric disturbances (3.0%) (primarily agitation and abnormal mental status), digestive tract disorders (2.1%) (primarily nausea and vomiting), neurological disturbances (1.7%) (primarily seizures, headaches, and sleep disturbances), and dermatologic problems (1.4%) (primarily rashes). The similar profiles are seen despite use of lower total levels of drug and, presumably, fewer fluctuations of blood level of bupropion in the bupropion sustained-release trials.

#### 8.4 Safety Findings Discovered with Other Specific Search Strategies/ Search for Serious Events

The sponsor conducted a manual search of the available clinical data from the two Phase 2-3 placebo-controlled studies for events that it considered "serious." The criteria for "serious" were fatal, life-threatening, permanently disabling, requiring or prolonging hospitalization, congenital abnormality, overdose, cancer, other—as determined by the investigators. Six such events were identified in the placebo-controlled trials. Four of these occurred in subjects who received bupropion sustained-release and two occurred in subjects receiving placebo. Attribution of cause of serious events was left at the discretion of the individual investigators. None of the adverse events was attributed to the medication by the sponsor. In patient #2043 of protocol 205, however, the development of a severe "stomach flu" with nausea, vomiting, diarrhea, and dehydration requiring hospitalization within six days of commencing intake of bupropion sustained-release—which is associated with nausea and vomiting—in this reviewer's opinion may have been associated with the drug. In patient #2045, "cramp-like" chest pain began within two days after commencing intake of bupropion sustained-release and persisted for three days. An EKG the day after the pain resolved was negative. Chest pain did not recur until six weeks further into the study; at that time it evolved into a myocardial infarction. Although the case report form for this subject makes no mention of underlying disease, the summary table in the sponsor's integrated safety summary records that coronary artery disease was found to be present in this patient at post-MI catheterization. No patient taking the medication overdosed or attempted suicide during the course of the controlled studies. Although seizure incidence was a major concern with the immediate-release form of bupropion, no patient experienced a seizure during the course of the placebo-controlled studies of bupropion sustained-release.

An additional 55 serious events were noted as of July 14, 1994 as having occurred during the course of open bupropion sustained-release trial 208. Seven of these were considered by the sponsor as being possibly or reasonably attributable to bupropion sustained-release: three patients experienced seizures, two patients experienced panic attacks, one patient experienced facial edema consistent with an allergic response, and one patient experienced severe somnolence. Ten patients experienced serious suicidal ideation, overdosed, or otherwise attempted suicide. Eight patients experienced angina pectoris or a myocardial infarction.

All events that the sponsor categorized as serious that were thought by the sponsor or this reviewer as being possibly or reasonably attributable to bupropion sustained-release are listed in Appendix 8.4.

## 8.5

## Other Safety Findings

## 8.5.1

## ADE Incidence Tables

Treatment emergent adverse experiences were considered adverse experiences that emerged or worsened following the beginning of the treatment phase. All investigator terms were converted by the sponsor to COSTART terms.

<b>Table 8.5.1.1</b> <b>Treatment Emergent Adverse Experiences in Placebo-Controlled Phase 2-3 Trials</b> <b>(Reported by at least 1% of Patients Treated with Bupropion Sustained-Release)</b>			
BODY SYSTEM / ADVERSE EXPERIENCE	Bupropion sustained-release Dosing Group		
	100-200 mg/d (N=350)	300-400 mg/d (N=343)	Placebo (N=235)
<b>Psychiatric Disorders</b>			
Insomnia	9.7%	14.0%	7.2%
Agitation	2.6%	5.0%	1.7%
Anxiety	4.6%	5.2%	3.4%
Nervousness	3.4%	3.2%	2.1%
Somnolence	2.6%	1.5%	1.7%
Irritability	4.0%	2.9%	0.4%
Abnormal Dreams*	2.6%	1.5%	2.1%
CNS Stimulation	0%	2.0%	0.9%
<b>Other Nervous System Disorders</b>			
Dizziness	9.4%	7.9%	5.1%
Tremor	3.7%	6.1%	0.4%
Hypertonia	1.4%	0.6%	0.4%
<b>Digestive Tract Disorders</b>			
Dry Mouth	12.9%	19.5%	5.5%
Nausea	10.3%	13.7%	7.2%
Diarrhea	5.1%	5.8%	6.0%
Constipation	8.5%	9.0%	7.2%

\*This category primarily represents nightmares, but also includes vivid dreams, and other changes in dream patterns.

BODY SYSTEM / ADVERSE EXPERIENCE	Bupropion sustained-release Dosing Group		
	100-200 mg/d (N=350)	300-400 mg/d (N=343)	Placebo (N=235)
Vomiting	2.9%	2.9%	1.3%
Toothache/Tooth Abscess	2.0%	1.7%	3.0%
Flatulence	3.7%	1.5%	1.7%
Body (General)			
Headache	30.3%	25.7%	26.8%
Chest Pain	1.4%	2.9%	0.9%
Asthenia	1.4%	2.3%	1.7%
Back Pain	3.7%	3.2%	3.4%
Fever	1.1%	2.3%	0%
Neck Pain	2.3%	1.5%	1.7%
Accidental Injury	1.7%	1.5%	2.1%
Respiratory System Disorders			
Pharyngitis	1.7%	5.2%	1.7%
Rhinitis	10.6%	5.5%	8.5%
Sinusitis	1.1%	5.5%	1.7%
Respiratory Complaints	1.7%	1.1%	1.7%
Skin and Appendages Disorders			
Sweating	2.9%	6.1%	1.3%
Rash	2.6%	5.2%	0.9%
Pruritus	2.3%	3.8%	1.7%
Urticaria	0.6%	1.5%	0%
Cardiovascular			
Palpitations	2.3%	2.9%	1.7%
Migraine	1.7%	1.7%	1.3%
Hot Flashes	1.4%	1.5%	1.3%
Hypertension	1.7%	1.2%	0.9%
Tachycardia	1.4%	0.9%	0.9%

BODY SYSTEM / ADVERSE EXPERIENCE	Bupropion sustained-release Dosing Group		
	100-200 mg/d (N=350)	300-400 mg/d (N=343)	Placebo (N=235)
<b>Infections</b>			
Upper Respiratory Infection	7.7%	7.9%	7.2%
Flu Syndrome	4.3%	2.6%	2.6%
<b>Special Senses</b>			
Tinnitus	3.4%	5.2%	1.7%
Taste Perversion	1.1%	2.0%	0%
Blurred Vision	2.6%	2.0%	2.6%
<b>Musculoskeletal</b>			
Arthralgia	2.3%	2.0%	0.9%
Myalgia	3.4%	4.4%	3.4%
<b>Urinary System Disorders</b>			
Urinary Tract Infection	1.4%	0.9%	0.4%
Urinary Frequency	1.7%	3.5%	1.7%
<b>Reproductive Disorders, Male</b> (percentage based on # male patients (BUP SR 100-200=122, BUP SR 300-400=115))			
Impotence	1.6%	0.9%	0%
<b>Reproductive Disorders, Female</b> (percentage based on # female patients (BUP SR 100-200=228, BUP SR 300-400=228))			
Dysmenorrhea	1.8%	2.6%	4.7%

#### Common, Drug-Related Adverse Events

The following adverse events occurred at a rate greater than five per cent in at least one bupropion sustained-release dose group, and were seen at least twice as frequently in one or more bupropion sustained-release dose groups as among placebo patients:

- Agitation
- Dry Mouth
- Pharyngitis
- Rash
- Sinusitis
- Sweating
- Tinnitus
- Tremor

Bupropion immediate-release use was also associated with tremor at a rate more than twice as frequently as placebo. Other adverse experiences reported more frequently by bupropion immediate-release patients than those on placebo included agitation, dry mouth, rash, and excessive sweating.

#### *Dose Response for Common, Drug-Related Adverse Events*

Visual inspection of rates in Table 8.5.1.1 for the following adverse events (repeated in Table 8.5.1.2) suggested that the following adverse experiences demonstrated a dose dependency: Agitation, dry mouth, pharyngitis, rash, sweating, tinnitus, and tremor.

Table 8.5.1.2 Treatment Emergent Adverse Experiences in Placebo-Controlled Phase 2-3 Trials (Reported by at least 1% of Patients Treated with Bupropion Sustained-Release with Dose Dependency Apparent)			
ADVERSE EXPERIENCE	Bupropion sustained-release Dosing Group		
	100-200 mg/d (N=350)	300-400 mg/d (N=343)	Placebo (N=235)
Agitation	2.6%	5.0%	1.7%
Dry Mouth	12.9%	19.5%	5.5%
Pharyngitis	1.7%	5.2%	1.7%
Rash	2.6%	5.2%	0.9%
Sweating	2.9%	6.1%	1.3%
Tinnitus	3.4%	5.2%	1.7%
Tremor	3.7%	6.1%	0.4%

## 8.5.2 Laboratory Findings

Clinical laboratory tests were obtained on all patients in the two major placebo-controlled studies 203 and 205, and the findings for chemistry, hematology, and urinalysis will be described below.

### 8.5.2.1 Serum Chemistry

Appendix 8.5.2.1 lists the bounds that the sponsor provided for consideration of abnormal chemistry values as being of potential clinical significance.

The following table displays the proportions of patients meeting those criteria in placebo-controlled trials 203 and 205. Patients were counted if they exceeded a laboratory value at the point of discontinuation from the study. The denominator from which the percentages are calculated is the number of patients in that dosing group, excluding those who had lab values beyond the bounds specified before and after the study.

**Table 8.5.2.1.1**  
**Proportions of Patients Having Potentially Clinically Significant Changes in Serum Chemistry Variables in**  
**Protocols 203 and 205**

Serum Chemistry Variables	Bupropion sustained-release			Placebo		
	Total Patients	Abnormal		Total Patients	Abnormal	
	#	#	%	#	#	%
Total Bilirubin--High	693	1	0.1%	235	0	0%
Alkaline Phosphatase	693	0	0%	235	0	0%
ALT (SGPT)--High	692	2	0.3%	235	1	0.4%
AST (SGOT)--High	692	2	0.3%	235	0	0%
Creatinine--High	693	2	0.3%	235	0	0%
Creatinine--Low	693	1	0.1%	235	0	0%
Glucose--High	692	4	0.6%	234	0	0%
Glucose--Low	692	3	0.4%	235	0	0%
Albumin	693	0	0%	235	0	0%
Sodium	693	0	0%	235	0	0%
Potassium--Low	693	1	0.1%	235	0	0%
Potassium--High	693	0	0%	235	0	0%
Bicarbonate--Low	691	2	0.3%	234	3	1.3%

The number of patients exceeding the bounds of normal laboratory values was not large enough to draw any significant statistical inferences about different effects of drug versus placebo in causing extreme laboratory values. Mean changes from baseline to last visit in serum chemistry parameters were compared by the sponsor across treatment groups with Wilcoxon rank sum analysis (Table 8.5.2.1.2). Although there were some statistically significant differences, none were felt to be clinically important for the group as a whole. One patient (205-2004) with a prior history of elevated creatinine levels had a creatinine level of 1.9 mg/dL and urinalysis protein value of 3+ at screening. After five weeks of 200 mg/d bupropion sustained-release, serum creatinine level was 2.1 mg/dL and urine protein was unchanged. The patient was then discontinued from protocol 205 because of the increase in creatinine. No other patients were discontinued due to abnormal serum chemistries.

**Table 8.5.2.1.2**  
**Wilcoxon Rank Sum Analysis of Clinical Chemistry Change Scores**  
**in Protocols 203 and 205**

Clinical Chemistry and Direction of Statistically Significant Change	p Values for Treatment vs. Placebo: • = <0.05; + = <0.01					
	Protocol 203		Protocol 205			
	150 mg/d	300 mg/d	100 mg/d	200 mg/d	300 mg/d	400 mg/d
Albumin (↓)						•
Alk. Phosphatase (↑)	+				•	•
ALT						
AST						
Bicarbonate						
Bilirubin						
Creatinine (↑)	+	+	+	+	-	+
Glucose (↓)	•					
Potassium						
Sodium (↑)	•					

#### 8.5.2.2 Hematology

Appendix 8.5.2.2 lists the bounds that the sponsor provided for consideration of abnormal chemistry values as being-of potential clinical significance.

The following table displays the proportions of patients meeting those criteria in placebo-controlled trials 203 and 205. Patients were counted if they exceeded a laboratory value at the point of discontinuation from the study. The denominator from which the percentages are calculated is the number of patients in that dosing group, excluding those who had lab values beyond the bounds specified before and after the study.

**Table 8.5.2.2.1**  
**Proportions of Patients Having Potentially Clinically Significant Changes in Hematology Variables in**  
**Protocols 203 and 205**

Hematology Variables	Bupropion sustained-release			Placebo		
	Total Patients	Abnormal		Total Patients	Abnormal	
	#	#	%	#	#	%
Hemoglobin--Low	693	0	0%	235	1	0.4%
Hemoglobin--High	693	0	0%	235	0	0%
MCV--Low	691	1	0.1%	235	1	0.4%
MCV--High	691	0	0%	235	0	0%
WBC--Low	693	2	0.3%	235	1	0.4%
WBC--High	692	1	0.1%	235	0	0%
Neutrophils--High	693	2	0.3%	235	0	0%
Lymphocytes--High	693	0	0%	235	1	0.4%
Monocytes--High	693	0	0%	235	0	0%
Eosinophils--High	692	1	0.1%	235	0	0%
Basophils--High	693	0	0%	235	0	0%
Platelets--Low	693	0	0%	235	1	0.4%
Platelets--High	693	0	0%	235	0	0%

The number of patients exceeding the bounds of normal hematology values was not large enough to draw any significant statistical inferences about different effects of drug versus placebo upon these hematology values. Mean changes from baseline to last visit in serum chemistry parameters were compared by the sponsor across treatment groups with Wilcoxon rank sum analysis (Table 8.5.2.1.2). Although there were some statistically significant differences, none were felt to be clinically important. No patients were discontinued because of hematological findings.

Table 8.5.2.2 Wilcoxon Rank Sum Analysis of Hematology Change Scores in Protocols 203 and 205						
Hematology and Direction of Statistically Significant Change	p Values for Treatment vs. Placebo: * = <0.05; + = <0.01					
	Protocol 203		Protocol 205			
	150 mg/d	300 mg/d	100 mg/d	200 mg/d	300 mg/d	400 mg/d
Hemoglobin (↑)	+					+
MCV						
Platelets						
WBC						
Neutrophils (↑)	-	+				+
Lymphocytes (↓)	+	+			*	-
Monocytes (↑)					+	+
Eosinophils						
Basophils						

### 8.5.2.3 Urinalysis

The sponsor considered dipstick urinalysis blood or protein values of greater than two as being of potential clinical significance.

The following table displays the proportions of patients meeting those criteria in placebo-controlled trials 203 and 205. Patients were counted if they exceeded a laboratory value at the point of discontinuation from the study. The denominator from which the percentages are calculated is the number of patients in that dosing group, excluding those who had lab values beyond the bounds specified before and after the study.

Table 8.5.2.3 Proportions of Patients Having Potentially Clinically Significant Changes in Urinalysis Variables in Placebo-Controlled Studies 203 and 205						
Urinalysis Findings	Bupropion sustained-release			Placebo		
	Total Patients	Abnormal		Total Patients	Abnormal	
	#	#	%	#	#	%
Hematuria	691	12	1.7%	235	2	0.9%
Proteinuria	693	0	0%	254	1	0.4%

The low incidence of hematuria that was observed overall in this study pool made the power to detect a one percentage point statistically significant difference between the observed incidence of hematuria in drug versus placebo-treated patients less than 20 per cent. Although a Fisher Exact Test comparing the incidence of hematuria in drug-treated vs. placebo-treated groups does not reach statistical significance ( $p=0.54$ ), the

**Table 8.5.3**  
**Differences in Effect of Bupropion Sustained-Release vs. Placebo on Vital Signs**  
(S=Systolic BP, D=Diastolic BP, P=Pulse, W=Weight)  
(↑=Increase in Parameter, ↓=Decrease in Parameter)  
(\* =  $p \leq 0.05$ , + =  $p \leq 0.01$ )

Week	Protocol 203 Dosage		Protocol 205 Dosage			
	150 mg/d	300 mg/d	100 mg/d	200 mg/d	300 mg/d	400 mg/d
1	↑D+, ↓W+	↓W+	↑P-	↑P+, ↓W*	↑P*, ↓W+	↑P*, ↓W+
2		↓W+		↑S*, ↓W+	↓W+	↓W+
3	↓W+	↓W+		↓W+	↓W+	↓W+
4	↑P+	↓W+		↑D+, ↓W+	↑P*, ↓W*	↓W+
5	↓W+	↓W+			↓W*	↓W+
6	↓W+	↓W+		↑D*	↑P*, ↓W*	↓W+
7		↓W+			↓W*	↓W+
8		↑S*, ↓W+			↑D*	↑P*, ↓W+

#### 8.5.4 Electrocardiograms

Electrocardiograms were not systematically obtained in the phase 2-3 trials presented. Electrocardiograms were obtained on 164 subjects at screening whose history of physical examination suggested to investigators the potential value of an EKG. Sixteen subjects had EKG's during the treatment phase of the protocol and 156 subjects had EKG's at discontinuation from the protocols. In the opinion of the individual investigators, there were no clinically important drug-related alterations in electrocardiograms. Nevertheless, one 63-year-old white female (Patient 5058, protocol 205) who dropped out of the study due to an anxiety attack while being treated with bupropion sustained-release 400 mg/d was noted at a discontinuation EKG to have atrial enlargement and negative precordial T-waves that were thought to be changes consistent with increased anxiety.

#### 8.5.5 Special Studies

Protocol 208 was conducted specifically to assess the cumulative incidence of seizures and other adverse events occurring during an eight week period of intake of 100-300 mg/day bupropion sustained-release. This study was an open trial of bupropion sustained-release conducted in 109 centers nationwide that enrolled 3167 patients. Of these, 48 did not receive study medication, and it is unknown whether another 19 ingested study medication. These 67 patients were excluded from all further summaries. Six patients were excluded from seizure incidence summaries because they were found to have had a prior history of treatment with bupropion. A "100-300 mg cohort" was defined as patients who during their participation in the treatment phase received at least one daily dose of 100 mg and a minimum of 90% of the total cumulative dose required for a 100 mg/day regimen. This cohort was made up of 2958 patients, more than two-thirds of whom were at the 300 mg/day dosing level. The number of patients at each dosing level at each week of the protocol is listed in Table 8.5.5. below. The treatment setting and population was intended to represent a general treatment population. To be included in the study patients were required to be at least age 18, have a diagnosis of depression, and be considered appropriate for treatment with bupropion sustained-release. Exclusion criteria were as follows:

**Table 8.5.3**  
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(↑=Increase in Parameter, ↓=Decrease in Parameter)  
(\* =  $p \leq 0.05$ , + =  $p \leq 0.01$ )

Week	Protocol 203 Dosage		Protocol 205 Dosage			
	150 mg/d	300 mg/d	100 mg/d	200 mg/d	300 mg/d	400 mg/d
1	↑D+, ↓W+	↓W+	↑P-	↑P+, ↓W*	↑P*, ↓W+	↑P*, ↓W+
2		↓W+		↑S*, ↓W+	↓W+	↓W+
3	↓W+	↓W+		↓W+	↓W+	↓W+
4	↑P+	↓W+		↑D+, ↓W+	↑P*, ↓W*	↓W+
5	↓W+	↓W+			↓W*	↓W+
6	↓W+	↓W+		↑D*	↑P*, ↓W*	↓W+
7		↓W+			↓W*	↓W+
8		↑S*, ↓W+			↑D*	↑P*, ↓W+

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- Prior treatment with any form of bupropion;
- History or current diagnosis of bulimia or anorexia nervosa;
- Known predisposition to seizure (e.g., history of seizure, significant head trauma, family history of idiopathic seizure disorder, concurrent treatment with medication that lowered seizure threshold, or clinical history of alcohol or substance abuse within the last year);
- Receipt of any neuroleptic or antidepressant within one week of the treatment phase (two weeks for MAOI's, clomipramine, maprotiline, or protriptyline, and four weeks for fluoxetine);
- Unstable medical disorder or a disorder that would interfere with the pharmacokinetics of bupropion, or interfere with the accurate assessment of depression;
- Pregnancy, lactation, or unwillingness to employ contraceptive methods acceptable to the investigator during the study (females only);
- Active suicidality.

Table 8.5.5 Number of Patients in Cohort by Treatment Day of Protocol 208			
Treatment Day	100 mg/day	200 mg/day	300 mg/day
1	101	777	2080
7	54	745	2080
14	47	638	1979
21	41	584	1847
28	40	562	1775
35	39	517	1684
42	35	493	1621
49	34	471	1578
56	34	457	1546

During the eight-week treatment phase of the study, bupropion sustained-release in doses up to 300 mg/day was associated with an observed seizure rate of 0.06% (2/3094) with an upper one-sided 95% confidence limit of 0.14%. Including patients who remained in the continuation phase of the study beyond the eight-week standard treatment period, bupropion sustained-release in doses up to 300 mg/day was associated with an observed seizure rate of 0.10% (3/3094) with an upper one-sided 95% confidence limit of 0.19%. A survival analysis of the 2958 patients in the 100-300 mg cohort population yielded a cumulative seizure rate of 0.08% with an upper one-sided 95% confidence limit of 0.18% for the treatment phase.

Fifty-one of the 2958 patients in the 100-300 mg cohort experienced an adverse event that the sponsor termed "serious," of which seven were considered to be possibly attributable or reasonably attributable to bupropion sustained-release: three patients had generalized convulsive seizures, two patients experienced panic attacks, one patient experienced hypersomnolence, and one patient experienced facial edema consistent with an allergic reaction. All three of the patients who had seizures possibly or reasonably attributable to bupropion sustained-release were males between the ages of 43 and 49 years old: patient 011-004 had a history of alcohol dependence and had been drinking alcohol prior to a seizure on the 54th day of treatment; patient 073-024 had a past history of alcohol abuse and experienced a seizure on the third day of treatment at 100 mg/day; and patient 054-004 was

noted to have a small arachnoid cyst on MRI and a history of six alcoholic drinks per day after he experienced a seizure on the 66th day of treatment. In addition, three patients experienced seizures as sequelae following overdoses with bupropion sustained-release: patient 036-004 had ingested her last bupropion sustained-release prior to a period of three days of intermittent cocaine abuse that culminated in an overdose with over 500 mg chlordiazepoxide and phencyclidine; after "hoarding tablets" for some time, patient 081-011 took an overdose of a "handful" of 150 mg tablets of bupropion sustained-release; and patient 090-022 ingested 600 mg of bupropion sustained-release over a 24-hour period to "catch up" on previously missed doses. Two patients experienced seizures that were considered unrelated to bupropion sustained-release intake: patient 008-004 experienced a seizure on the first day of the study before taking her first dose of medication and patient 022-032 experienced a seizure 39 days after discontinuing the study after one dose of bupropion sustained-release. No other seizures were reported.

Six patients died during the protocol: three patients committed suicide, two patients died of cardiac disease, and one patient was murdered. None of the deaths were considered to be attributable to bupropion sustained-release. A total of 2572 patients (83% of 3100) were assessed as having either no side effects or side effects which did not significantly interfere with their functioning.

#### 8.5.6 Withdrawal Phenomena/Abuse Potential

The sponsor reports no instances of bupropion sustained-release abuse or dependence. Withdrawal phenomena were not formally assessed after patients discontinued bupropion sustained-release. In the development of bupropion immediate-release, the sponsor noted that a dose of 400 mg produced a modest elevation over placebo responses on the morphine benzedrine group subscale of the Addiction Research Center Index, and a score intermediate between amphetamine and placebo on the Liking Scale of the Addiction Research Center Index.

#### 8.5.7 Human Reproduction Data

Human reproduction data is lacking from both the clinical use of bupropion immediate-release and bupropion sustained-release. The sponsor does not report any pregnancies during bupropion sustained-release clinical trials.

#### 8.5.8 Overdose Experience

There is very limited experience with overdoses of bupropion sustained-release. There were no overdoses of active medication in the controlled clinical trials. There were three overdoses with bupropion sustained-release in protocol 208. Patient 004-019, a 37-year-old male, ingested three grams of medication and two beers. He vomited quickly afterwards and reported lightheadedness and blurred vision. He was released after evaluation. Patient 081-011, a 34-year-old female, ingested a "handful" of bupropion sustained-release 150 mg tablets. She vomited quickly afterwards, and then appeared lethargic and confused. In the emergency room she experienced a generalized convulsive seizure. After gastric lavage and treatment with charcoal and magnesium sulfate, the patient was released. Patient 090-022, a 35-year-old male, took an extra 300 mg over the course of 24 hours in order to "catch up" on missed doses. He experienced a generalized convulsive seizure approximately six hours after the last dose of medication.

The manufacturer reports that bupropion immediate-release overdoses of up to 17.5 grams have been reported. Seizure was reported in approximately one-third of all cases. Other serious reactions reported with overdoses of the compound included hallucinations, loss of consciousness, and tachycardia. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported when the drug was part of a multi drug overdose.

A three-year multi-center retrospective analysis of overdoses of bupropion immediate-release reported to six regional poison control centers (Spiller *et al*, *Am J Emerg Med* (1994) 12:43-45) reported that sinus tachycardia occurred in 25 of 58 patients (43%) but no other arrhythmias or conduction defects were found. Seizures occurred in 12 patients (21%). The mean ingestion of patients experiencing seizures was 3078 mg, whereas the mean ingestion of patients not experiencing seizures was 2148 mg. Time to onset of seizures ranged from one to eight hours (mean=4 hours). Multiple seizures occurred in two of these patients. In five cases where electrolytes were reported, three patients were documented to have hypokalemia. The significance and prevalence of this hypokalemia is unknown. Benzodiazepines were effective in stopping the convulsions in seven of eight cases when they were used. In the eighth case, follow-up use of diphenylhydantoin successfully terminated the seizure. Lethargy and tremors were also seen frequently following overdose. Other CNS effects seen in overdose were confusion, lightheadedness, hallucinations, and paresthesias. Coma was observed in two of nine patients who ingested both bupropion and a benzodiazepine. The only patient in the series who experienced hypotension required a two-hour dopamine infusion and intubation. All of this group of patients recovered without physical sequelae.

In the only case of bupropion immediate-release overdose detailed in the emergency medicine literature, an 18-year-old female took nine grams of bupropion without concomitant medications or substances. This produced combativeness, and sinus tachycardia without conduction abnormality, followed by a 45 second tonic-clonic seizure that abated with administration of 10 mg of intravenous diazepam. She was further treated with oral intubation, gastric lavage, activated charcoal, and sorbitol. The patient was extubated in 24 hours and her tachycardia resolved after 48 hours. There was no further seizure activity. Two fatal overdose cases (a 37-year-old male and a 60-year-old female) in which bupropion immediate-release was the major toxicology finding were reported to have followed overdoses of less than ten grams bupropion. In both cases blood levels of 4.0 mg/L—more than forty times the expected plasma concentrations in patients—were found.

## 8.6 Summary of Important Adverse Events Considered Drug Related

### 8.6.1 Seizures

Although the sponsor reported no seizures as having occurred during the testing of bupropion sustained-release in protocols 203 and 205, seizures did arise in open trial 208. As noted in section 8.5.5, in protocol 208 bupropion sustained-release was associated with an observed seizure rate of 0.10% with an upper 95% confidence limit of 0.19%. The incidence of seizure with bupropion sustained-release doses of up to 300 mg/day, when administered to subjects without known risk-factors that might increase seizure incidence, appears to be similar to that of other commercially-available antidepressants.

By contrast, the immediate-release formulation of bupropion has been well described as being associated with seizures. The immediate-release compound has been associated with seizures in approximately 0.4 per cent of patients treated at doses up to 450 mg/day. This incidence may be two to four times greater than that of other marketed antidepressants. The estimated seizure risk increases almost tenfold at doses between 450 and 600 mg/day. The risk of seizure from immediate-release bupropion appears to be strongly associated with dose and the presence of predisposing factors, including history of head trauma or seizure, central nervous system tumor, history of bulimia or anorexia nervosa, or concomitant intake of medications known to lower the seizure threshold. Sudden and large increases in doses were thought to contribute to increased risk of seizure.

### 8.6.2 Allergic Phenomena

Eighteen patients (2.6% of 693 total bupropion sustained-release-treated patients) in protocols 203 and 205 discontinued bupropion sustained-release due to rash, pruritus, or urticaria. In protocol 208's eight-week treatment phase, 44 patients (1.4% of 3100 bupropion sustained-release-treated patients) discontinued due to these allergic phenomena. Only two out of 245 (0.9%) patients in the placebo-treated groups of protocols 203 and 205

discontinued participation because of an allergic reaction. The divergence between incidence of allergic phenomena in drug- vs. placebo-treated controls, and the previous description of allergic phenomena in bupropion immediate-release-treated patients makes it likely that these adverse events are directly related to bupropion sustained-release.

#### 8.6.3 Anxious States

Six patients (0.9% of 693 total bupropion sustained-release-treated patients) in protocols 203 and 205 discontinued bupropion sustained-release due to anxious phenomena, including agitation, nervousness, anxiety, and panic attacks. In protocol 208, 43 patients (1.4% of 3100 bupropion sustained-release-treated patients) discontinued due to these anxious phenomena. None of the 245 patients in the placebo-treated groups of protocols 203 and 205 discontinued participation because of an anxious state. Panic attacks were also clearly associated as an adverse event with higher doses of bupropion sustained-release. None of the patients treated with placebo or doses of bupropion sustained-release less than 200 mg/day experienced a panic attack in protocols 203 and 205. In contrast, the relative proportions of 200 mg/day, 300 mg/day, and 400 mg/day bupropion sustained-release-treated patients experiencing panic attacks were 0.9% (1 of 115), 1.3% (3 of 229), and 1.8% (2 of 114), respectively. Panic attacks in patients taking bupropion sustained-release in protocols 203 and 205 all occurred between the 5th and 18th days of treatment and were likely associated with increasing drug levels. (Two patients in protocol 208 experienced panic attacks: one patient was on 100 mg/day bupropion sustained-release and experienced the attack on the 4th day of treatment, the other was on 200 mg/day bupropion sustained-release and experienced the attack on the 22nd day of treatment). The divergence between incidence of anxious phenomena in drug- vs. placebo-treated controls, and the previous description of similar phenomena in bupropion immediate-release-treated patients makes it likely that these adverse events are directly related to bupropion sustained-release.

#### 8.6.4 Theoretical Risk of Treatment-Emergent Mania

Although mania was not reported as a treatment-emergent adverse effect of bupropion sustained-release in any of the three protocols considered in this review, antidepressants are considered to pose theoretical risks of inducing mania. In the data concerning bupropion immediate-release that supported NDA 18,644, "manic reaction" was noted as an adverse event affecting 0.23% (3 of 1315) patients in the safety database for that formulation. Placebo-treated patients were noted as experiencing a similarly low rate (0 of 140 patients) of treatment-emergent mania in that NDA. A recent report on the use of bupropion immediate-release in 11 patients with bipolar disorder (Fogelson, Bystritsky, and Pasmun, *J Clin Psychiatry* (1992) 53:443-446) noted that 6 of the patients experienced manic or hypomanic episodes that necessitated discontinuation of the medication.

#### 8.7 Summary of Important Adverse Events Considered Not Drug Related

During clinical trials involving significant numbers of patients, serious untoward events may occur incidentally. No deaths occurred in the course of the controlled clinical trials for bupropion sustained-release; six deaths that were probably not drug-related in protocol 208 were described in section 8.2. Three serious events that were probably not drug-related occurred in protocols 203 and 205 to subjects taking bupropion sustained-release: urinary tract infection with prostatitis, cholelithiasis, and myocardial infarction. The conclusion of lack of causality between the myocardial infarction and bupropion sustained-release treatment (patient 2045) is predicated upon the sponsor's statement that post-infarction catheterization documented the existence of pre-existing coronary artery disease. In protocol 208 non-drug-related important events included nine patients with suicide attempts or overdoses, eight patients with cardiac disease or events, six patients with coincidental surgeries, four patients with infections, and three patients with cerebrovascular disease or events. Two patients (008-004 and 022-032) who experienced seizures not considered drug-related are referred to above in section 8.5.5. All treatment-emergent serious events from protocols 203, 205, and 208 that are considered to be unlikely to be related to bupropion sustained-release are listed in Appendix 8.7.

## 8.8 Summary of Drug Interactions

### 8.8.1 Drug-Demographic Interactions

Effects of gender, age, and race on the incidence of the common, drug-related adverse events (see section 8.5.1) of agitation, dry mouth, pharyngitis, rash, sinusitis, sweating, tinnitus, and tremor were explored in the following manner. Combining data from the two placebo-controlled trials (203 and 205), relative risks for males and females were calculated for each of the adverse events considered:

$$RR_m = \text{Bupropion sustained-release rate in males} + \text{Placebo rate in males}$$
$$RR_f = \text{Bupropion sustained-release rate in females} + \text{Placebo rate in females}$$

The ratio of these relative risks was then calculated:  $RR_f / RR_m$ . To determine confidence intervals for the relative risk ratios, odds ratios for males and females were determined along with a common odds ratio (Mantel-Haenszel method). Homogeneity of the odds ratios so obtained was then assessed with the Breslow-Day test. Similar methods were applied for age (< 60 years old vs. ≥ 60 years old) and for race (white vs. non-white).

With these methods, dry mouth ( $p=0.04$ ) and tinnitus ( $p=0.025$ ) were both identified as more frequently apparent drug-related adverse events in females than in males. Because these demographic findings arose out of multiple comparisons, however, their value should be interpreted cautiously. No other adverse events were significantly linked to other demographic factors.

### 8.8.2 Drug-Disease Interactions

The sponsor has not studied interactions of bupropion sustained-release with other diseases beyond depression in humans. A detailed study of bupropion immediate-release in patients with heart disease has been published, however (Roose *et al*, *Am J Psychiatry* (1991) 148:512-516). In patients with depression and preexisting left ventricular dysfunction, ventricular arrhythmias, and/or conduction disease who were taking a mean of 442 mg/day bupropion immediate-release, over three weeks the medicine caused a slight rise in supine blood pressure, but did not exacerbate ventricular arrhythmias or affect pulse rate. It caused a low rate of orthostatic hypotension and was discontinued in 14% of the patients because of adverse effects, including exacerbation of baseline hypertension.

### 8.8.3 Drug-Drug Interactions

The sponsor has not studied interactions of bupropion sustained-release with other drugs in humans. One report in the medical literature notes that bupropion immediate-release causes an increased risk of increased agitation, confusion, hallucinations, and nausea and vomiting when administered with levodopa.

BODY SYSTEM / ADVERSE EXPERIENCE	Bupropion sustained-release Dosing Group		
	150 mg/d (N=147)	300 mg/d (N=147)	Placebo (N=150)
<b>Cardiovascular</b>			
Palpitations	3.4%	3.4%	1.3%
Migraine	0.7%	0.7%	0.7%
Hot Flashes	1.4%	0.7%	0%
Hypertension	0%	0%	2.0%
Tachycardia	1.4%	0%	0%
<b>Infections</b>			
Upper Respiratory Infection	2.7%	7.5%	4.7%
Flu Syndrome	8.8%	1.4%	4.0%
<b>Special Senses</b>			
Tinnitus	4.8%	6.8%	2.0%
Taste Perversion	0%	2.7%	0.7%
Blurred Vision	2.7%	3.4%	0.7%
<b>Musculoskeletal</b>			
Arthralgia	2.7%	0%	0%
Myalgia	0.7%	2.7%	2.0%
Leg Cramps	2.0%	0%	1.3%
Twitch	1.4%	1.4%	0%
<b>Urinary System Disorders</b>			
Urinary Tract Infection	2.0%	1.4%	0%
Urinary Frequency	2.0%	1.4%	1.3%
<b>Reproductive Disorders, Male</b> (percentage based on # male patients (BUP SR 150=57, BUP SR 300=49, PLACEBO=51))			
Impotence	1.8%	0%	0%
<b>Reproductive Disorders, Female</b> (percentage based on # female patients (BUP SR 150=90, BUP SR 300=98, PLACEBO=99))			
Dysmenorrhea	1.1%	1.0%	2.0%

None of the adverse events listed above occurred at a rate greater than five per cent in at least one bupropion

None of the adverse events listed above occurred at a rate greater than five per cent in at least one bupropion sustained-release dose group, and were seen at least twice as frequently in one or more bupropion sustained-release groups as among placebo patients.

#### **AD8.5.3 Weight**

No patient treated with bupropion sustained-release in study 212 had to discontinue the drug because of changes in weight. Among the 359 patients for whom discontinuation weight data was available, the mean weight change at discontinuation for the placebo, bupropion sustained-release 150 mg, and bupropion sustained-release 300 mg groups was a decrease of 0.3, 1.0, and 1.7 pounds, respectively. The difference between the effect on the 300 mg group and the placebo groups was significant at  $p < 0.01$ . The difference between the 150 mg group and the placebo group was not significant.

#### **AD8.6 Summary of Important Adverse Events Considered Drug Related**

Although the incidence of drug-related important adverse events was small, these sections are identified to complement the data summarized already in the main text of this review.

##### **AD8.6.1 Seizures**

The sponsor reported no seizures as having occurred during the testing of bupropion sustained-release in protocol 212.

##### **AD8.6.2 Allergic Phenomena**

Three patients (1.0% of 302 total bupropion sustained-release-treated patients) in protocol 212 discontinued bupropion sustained-release due to rash, pruritus, or urticaria. Zero out of 154 patients in the placebo-treated group of protocol 212 discontinued participation because of an allergic reaction.

##### **AD8.6.3 Anxious States**

Three patients (1.0% of 302 total bupropion sustained-release-treated patients) in protocol 212 discontinued bupropion sustained-release due to anxious phenomena, including agitation, nervousness, anxiety, and panic attacks. One (0.6%) of the 154 patients in the placebo-treated group of protocol 212 discontinued participation because of an anxious state. In protocol 212, panic attacks not seen in the medication-treated patients.

##### **AD8.6.4 Theoretical Risk of Treatment-Emergent Mania**

Mania was not reported as a treatment-emergent adverse effect of bupropion sustained-release in protocol 212.

#### **AD8.7 Summary of Important Adverse Events Considered Not Drug Related**

No deaths occurred in the course of protocol 212. Three serious events that were probably not drug-related occurred to subjects taking bupropion sustained-release in protocol 212: diagnosis of cervical carcinoma, excision of a pre-existing papillary basal cell carcinoma, and spontaneous abortion in one subject eight days after discontinuation from the study. All treatment-emergent serious events from protocol 212 that are considered to be unlikely to be related to bupropion sustained-release are listed in Appendix AD8.7.

**Phase 3 Study: Seizure Incidence Study**

Protocol	Blind	Design	Centers	Length	Dosing	Setting	Diagnosis	Levels	Bupropion (po)	N*
208	None	Fixed Dose	109	8 weeks and ongoing	Fixed	Inpatient and Outpatient	Depression	1	150 mg am 150 mg pm	3100

\*Number of patients studied, with the exclusion of 67 patients excluded from all analyses except premature discontinuation because they never received or it is unknown if they received study medication.

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