TITLE PAGE

Division: Worldwide Development
Information Type: Worldwide Epidemiology Study Protocol

Title:	Assessment of Bupropion Misuse and Abuse 2004-2011

Compound Number:	GR67205
Development Phase	N/A
Effective Date:	11-DEC-2013

Subject: Drug Abuse, Epidemiology, Bupropion

Author(s): [redacted]

PASS information

Title	Assessment of Bupropion Misuse and Abuse 2004-2011.
Protocol version identifier	01
Date of last version of protocol	NA
EU PAS register number	Study not registered in the EU PAS Register yet.
Active substance	Bupropion
Medicinal product	Wellbutrin, Wellbutrin XL, Wellbutrin SR, Zyban
Product reference	[Reference number(s) of centrally authorised products and/or, if possible, of nationally authorised products subject to the study]
Procedure number	[If applicable, Agency or national procedure number(s), e.g. EMA/X/X/XXX]
Marketing authorisation holder(s)	[Marketing authorisation holder(s) which initiate(s), manage(s) or finance(s) the study]
Joint PASS	No

Research question and objectives	The objective of this study is to examine the degree of misuse and abuse of bupropion using the Drug Abuse Warning Network Database. Objectives are as follows: 1. To examine the number of bupropion reports over time within the DAWN databse and to draw a comparison against the number of all DAWN reports for prescription drugs. 2. To examine the number of reports for bupropion, stratfified by demographics, route of administration, and disposition of the patient.
Country(-ies) of study	Unites States
Author	[redacted], PhD, MSPH Worldwide Epidemiology, GlaxoSmithKline Five Moore Dr 17.2110 Research Triangle Park, NC 27709

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	[Name, address and contact details of the marketing authorisation holder(s).]
MAH contact person	[Contact person for this PASS protocol submission (if this a joint PASS, only one person should be mentioned)]

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
AERS	Adverse Event Reporting System
AMA	Against Medical Advice
ED	Emergency Department
GSK	GlaxoSmithKline

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

2. RESPONSIBLE PARTIES

Responsible parties are listed in a standalone document in Annex 1.

SPONSOR SIGNATORY:

[redacted] December 17, 2013

Primary Author/ Project officer **Date**

[redacted] 17/12/2013

Therapy Area Leader **Date**

SPONSOR INFORMATION PAGE

WWEpi Project Identifier: PRJ2215

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Sponsor Medical Monitor Contact Information:

Regulatory Agency Identifying Number(s):

3. ABSTRACT

***Title** Assessment of Bupropion Misuse and Abuse 2004-2011

*Rationale and background

Bupropion hydrochloride was first approved on 30 December 1985 in United States for depression and is currently approved in 80 countries. Bupropion has also subsequently been approved for smoking cessation and for seasonal affective disorder.

The main trade names for bupropion hydrochloride are Wellbutrin, Wellbutrin SR and Wellbutrin XL/XR for the treatment of depression, and Zyban for use in smoking cessation. Cumulative exposure to bupropion is estimated at approximately 97.3 million patient exposures up to 31 December 2012.

Bupropion hydrochloride is is a weak catecholamine reuptake inhibitor predominantly affecting serotonin, norepinephrine and dopamine. With its clinical profile, its mechanism of action and its structural similarities to diethylpropion, amphetamines, and cocaine, bupropion resembles stimulants in many respects, leading to concerns about potential abuse of the product.

In early preclinical studies, bupropion showed amphetamine-like effects in animals. Drug discrimination studies in rodents and primates indicate that the subjective experience (stimulus cue) elicited by bupropion is generalized to stimulants such as d-amphetamine, cocaine, and methylphenidate. [de la Garza 1987; Bergman, 1989; Kamien, 1989; Lamb, 1990]

Despite the evidence for stimulant effects in animals suggesting a relevant abuse potential, several clinical studies in humans indicated that oral intake of bupropion had lower abuse liability than amphetamine, methylphenidate, and even caffeine. Accordingly, it was concluded that bupropion did not exhibit amphetamine-like characteristics in humans, and the drug has been classified as a substance of low abuse potential. [Miller, 1983; Griffith, 1983; Rush, 1998; Zernig, 2004]

Abuse potential had been part of the Benefit Risk Management Plan for bupropion up until 2003 and at that point, had no longer been regarded as a potential risk that required additional/further evaluation outside standard pharmacovigilance monitoring. The current European Risk Management Plan also states that standard pharmacovigilance monitoring applies to abuse potential. Monitoring has shown a recent increase in the number of spontaneous reports from the Adverse Event reporting System (AERS) of drug abuse and this was recently discussed by the Safety Review Team (SRT).

SRT agreed that although the numbers of abuse reports was small relative to the total number of reports for bupropion in OCEANS, there was sufficient information in AERS to warrant investigation of the potential effect on public health.

To investigate the degree of misuse and abuse of bupropion (including non-oral routes of administration) in the United States, the Drug Abuse Warning Network will be used to examine the study period 2004-2011.

*Research question and Objective(s)

There are two primary objectives to the study, which are as follows:

1. To examine the number of bupropion reports over time within the DAWN databse and to describe the number of all DAWN reports for prescription drugs. This is analogous to the disproportionality analysis conducted within GCSP for the evaluation of safety signals.

2. To examine the number of reports for bupropion, stratfified by demographics, route of administration, and disposition of the patient.

Secondary objective:

1. If sample size permits, an evaluation of the disposition of the patients exposed to only bupropion at the time of Emergency Department (ED) visit will be conducted.

*Study Design

DAWN is a public health surveillance system that reports on drug-related visits to hospital Emergency Departments (ED). DAWN is used to monitor trends in drug misuse and abuse, identify the emergence of new substances and drug combinations, assess health hazards associated with drug use and abuse, and estimate the impact of drug use, misuse, and abuse on the United States' health care system.

DAWN's target sample frame consists of all non-Federal, short-stay, general medical and surgical hospitals in the United States that have one or more EDs open 24 hours a day. DAWN employs a multistage sampling design for the selection of EDs for analysis. Stratified simple random sampling with oversampling in selected metropolitan areas is used to select the hospitals.

A DAWN case is any ED visit involving recent drug use. DAWN cases are identified through the review of ED medical records in participating hospitals. DAWN captures both ED visits that are directly caused by drugs and those in which drugs are a contributing factor but not the direct cause of the ED visit. These criteria encompass all types of drug-related events, including accidental ingestion and adverse reaction, as well as drug misuse or abuse. Within each hospital, 50 percent to 100 percent of the days of the month are systematically selected, and a census of ED visits is selected for review for these days.

DAWN collects data on all types of drugs—illegal drugs, prescription and over-the-counter medications, dietary supplements, and both pharmaceutical and nonpharmaceutical inhalants. DAWN notes whether alcohol is involved in addition to drug(s) for patients of all ages. Because alcohol is considered an illicit drug for minors,

alcohol abuse without the involvement of other drugs is considered a drug-related ED visit for patients under the age of 21. DAWN does not report current medications (i.e., medications and pharmaceuticals taken regularly by the patient as prescribed or indicated) that are deemed by the ED medical staff to be unrelated to the ED visit.

DAWN classifies drugs using a modified version of the Multum Lexicon, © 2012, a drug vocabulary and classification tool originated by Multum Information Services, Inc. DAWN has adapted the Lexicon to allow for the inclusion of illegal drugs, inhalants, and alternative medicines that are reported to DAWN.

*Population

The study population includes patients of all ages presenting to emergency departments for drug-related causes. The DAWN visit eligibility criteria are intended to be broad and inclusive and to have few exceptions. They take into account the fact that documentation in medical records varies in clarity and completeness across hospitals and among clinicians within hospitals. The criteria are designed to minimize the potential for DAWN Reporter judgments that could cause data to vary systematically and unexpectedly across different data collectors and hospitals. In addition, the criteria allow for the capture of a diverse set of drug-related visits that can be aggregated or disaggregated to serve a variety of analytical purposes and the interests of multiple audiences.

There are a few clearly delineated exceptions to the DAWN eligibility criteria. An ED visit is *not* a DAWN visit if

- there is no evidence of recent drug use;
- the patient left the ED without being treated;
- the patient consumed a nonpharmaceutical substance but did not inhale it;
- the patient has a history of drug use but no recent use;
- alcohol is the only substance involved, and the patient is an adult (aged 21 or older);
- all the drugs mentioned in the ED record are not related to the ED visit (e.g., list of current medications);
- drugs identified in toxicology testing are not related to the visit, and the medical record does not contain any additional drug-related information that would make the visit a DAWN case; or
- the patient is being treated as a consequence of undermedication (i.e., taking too little of a drug).

*Variables

There are few variables within the DAWN dataset. For this analysis, variables of interest can be grouped into the following categories:

Year of visit
Demographic: Age, Sex, Race
Case Type: Reason for presentation to the Emergency Department
Drug Mentions: Drug, Route of Administration, Toxicology Confirmed
Patient Disposition: Result of Treatment in ED

*Data sources

The Drug Abuse Warning Network datasets from 2004-2011 will be used for the proposed analyses.

*Study size

There are no a priori specified hypotheses for this study which would drive sample size calculations. All eligible DAWN cases will be included in this analysis.

*Data analysis

This study is descriptive in nature and will be comprised only of univariate analyses.

*Milestones
TBD

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned date
Start of data collection	December 2013
End of data collection	January 2014
<Registration in the EU PAS register>	December 2013
Final report of study results	February 2014

6. RATIONALE AND BACKGROUND

6.1. Background

Bupropion hydrochloride was first approved on 30 December 1985 in United States for depression and is currently approved in 80 countries. Bupropion has also subsequently been approved for smoking cessation and for seasonal affective disorder.

The main trade names for bupropion hydrochloride are Wellbutrin, Wellbutrin SR and Wellbutrin XL/XR for the treatment of depression, and Zyban for use in smoking

cessation. Cumulative exposure to bupropion is estimated at approximately 97.3 million patient exposures up to 31 December 2012.

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In early preclinical studies, bupropion showed amphetamine-like effects in animals. Drug discrimination studies in rodents and primates indicate that the subjective experience (stimulus cue) elicited by bupropion is generalized to stimulants such as d-amphetamine, cocaine, and methylphenidate. [de la Garza 1987; Bergman, 1989; Kamien, 1989; Lamb, 1990]

Despite the evidence for stimulant effects in animals suggesting a relevant abuse potential, several clinical studies in humans indicated that oral intake of bupropion had lower abuse liability than amphetamine, methylphenidate, and even caffeine. Accordingly, it was concluded that bupropion did not exhibit amphetamine-like characteristics in humans, and the drug has been classified as a substance of low abuse potential. [Miller, 1983; Griffith, 1983; Rush, 1998; Zernig, 2004]

In post marketing surveillance intended to assess any signals of abuse or dependence on bupropion since the introduction of Zyban in the USA **(**TNRS/95/008/003 - Study 100900**)**, data from the American Association of Poison Control Centres (AAPCC) showed that the reporting rate for bupropion between 1991 and 1999 was much the same range as most other antidepressants, but was lower than diazepam and alprazolam, which are known to be associated with abuse, misuse and dependence. Data from the Drug Abuse Warning Network (DAWN) from the same time period reported rates of abuse, misuse and/or dependence for bupropion that were statistically significantly less when compared to the reference medications, fluoxetine or amitriptyline. For both data sources, no increase in the reporting rate of abuse or misuse of bupropion was seen during the period after Zyban was launched in the USA.

Clinical studies and post marketing surveillance described above have been for the oral formulation, the only marketed form of bupropion. More recently, during routine pharmacovigilance, an increasing number of spontaneous cases reporting attempts to abuse bupropion by nasal insufflation (snorting) or injection (predominantly intravenous) have been noted.

After oral administration, approximately 95% of a bupropion dose undergoes extensive first pass metabolism before being distributed throughout the rest of the body. However, nasal insufflation bypasses first-pass metabolism, resulting in more rapid, higher plasma concentrations and stronger stimulant-like effects.[Graff, 2005]

Abuse potential had been part of the Benefit Risk Management Plan for bupropion since 2003 and at that point, had no longer been regarded as a potential risk that required additional/further evaluation outside standard pharmacovigilance monitoring. The

current European Risk Management Plan also states that standard pharmacovigilance monitoring applies to abuse potential. Monitoring has shown a recent increase in the number of spontaneous reports from the AERS database of drug abuse and this was recently discussed by the Safety Review Team (SRT).

A search of spontaneous cases in the OCEANS safety database was undertaken up to October 10 2013, yielding 210 cases of abuse assessed for evidence of an achieved "high" with bupropion and route of administration. The majority were spontaneous reports, predominantly from the US and Canada with a few from Germany. Two patterns were evident; individual cases of abuse (including a few published case reports) and reports from prisons. For the latter, the number of inmates involved is not known. In some cases, it was uncertain whether a "high" was obtained. However, the lack of confirmation of a "high" does not necessarily mean that the abuser did not achieve a "high" as reporters are more likely to describe adverse events (such as seizures). The nasal route was the most frequently reported route of administration for abuse and reported the highest rate of success in obtaining a "high". Some case narratives described a "high" similar to that of cocaine and a few stated that they had also abused other substances. Some cases described multiple routes of administration (e.g. snorting and injection).

Further, abuse of bupropion has been described in several published case reports. Reports of abuse, especially using nasal insufflations, were first observed in correctional settings where illicit drugs are less available and where bupropion may be widely ordered as a smoking deterrent for inmates. Buproprion abuse has mainly been reported among those with prior substance abuse problems, in cases both in and out of the prison system. [Kim, 2010; Baribeau, 2013; Hilliard, 2013; Reeves, 2013; Yoon, 2013]
SRT agreed that although the numbers of abuse reports was small relative to the total number of reports for bupropion in OCEANS, there was sufficient information in AERS to warrant investigation of the potential effect on public health.

To investigate the degree of misuse and abuse of bupropion (including non-oral routes of administration) in the United States, the Drug Abuse Warning Network will be used to examine the study period 2004-2011.

6.2. Rationale

Because there have been reports of increasing use of bupropirion in a manner which is not approved, this study will be conducted to investigate the estimated number of cases from the DAWN database demonstrating a non-oral route of administration of bupropion. The use of the DAWN dataset provides information on necessary variables not usually found in traditional databases suited for pharmacoepidemiology.

7. RESEARCH QUESTION AND OBJECTIVE(S)

There are two primary objectives to the study, which are as follows:

1. To examine the number of bupropion reports over time within the DAWN databse and to describe the number of all DAWN reports for prescription drugs.

This is analogous to the disproportionality analysis conducted within GCSP for the evaluation of safety signals.

2. To examine the number of reports for bupropion, stratfified by demographics, route of administration, and disposition of the patient.

Secondary objective:

1. If sample size permits, an evaluation of the disposition of the patients exposed to only bupropion at the time of ED visit will be conducted.

8. RESEARCH METHODS

8.1. Study Design

DAWN is a public health surveillance system that reports on drug-related visits to hospital EDs. DAWN is used to monitor trends in drug misuse and abuse, identify the emergence of new substances and drug combinations, assess health hazards associated with drug use and abuse, and estimate the impact of drug use, misuse, and abuse on the United States' health care system.

DAWN's target sample frame consists of all non-Federal, short-stay, general medical and surgical hospitals in the United States that have one or more EDs open 24 hours a day. DAWN employs a multistage sampling design for the selection of EDs for analysis. Stratified simple random sampling with oversampling in selected metropolitan areas is used to select the hospitals.

A DAWN case is any ED visit involving recent drug use. DAWN cases are identified through the review of ED medical records in participating hospitals. DAWN captures both ED visits that are directly caused by drugs and those in which drugs are a contributing factor but not the direct cause of the ED visit. These criteria encompass all types of drug-related events, including accidental ingestion and adverse reaction, as well as drug misuse or abuse. Within each hospital, 50 percent to 100 percent of the days of the month are systematically selected, and a census of ED visits is selected for review for these days.

DAWN collects data on all types of drugs—illegal drugs, prescription and over-the-counter medications, dietary supplements, and both pharmaceutical and nonpharmaceutical inhalants. DAWN notes whether alcohol is involved in addition to drug(s) for patients of all ages. Because alcohol is considered an illicit drug for minors, alcohol abuse without the involvement of other drugs is considered a drug-related ED visit for patients under the age of 21. DAWN does not report current medications (i.e., medications and pharmaceuticals taken regularly by the patient as prescribed or indicated) that are deemed by the ED medical staff to be unrelated to the ED visit.

DAWN classifies drugs using a modified version of the Multum Lexicon, © 2012, a drug vocabulary and classification tool originated by Multum Information Services, Inc.

DAWN has adapted the Lexicon to allow for the inclusion of illegal drugs, inhalants, and alternative medicines that are reported to DAWN.

8.2. Setting

The statistical and methodological design of the current DAWN system was introduced in data collection year 2004. A new stratified simple random sample of hospitals was drawn at that time from among the universe of eligible hospitals in the United States; oversampling was conducted in selected metropolitan areas (http://www.samhsa.gov/data/DAWN/apsx). For each participating sampled hospital and for each month of the year, days of the month are systematically selected and all ED visits for these days are reviewed for eligibility as DAWN cases. Data collection following the new sampling plan was fully implemented for the first time in the 2004 data collection year, and the original sample of hospitals has been followed longitudinally since then. That is, each year since 2004, new hospitals are given the opportunity to be sampled into the longitudinal panel of hospitals.

The DAWN sampling frame was built from among all hospitals meeting the DAWN criteria for eligible hospitals (i.e., non-Federal, short-stay, general medical and surgical hospitals in the United States that have one or more EDs open 24 hours a day, 7 days a week) that appeared on the 2001 American Hospital Association (AHA) Annual Survey Database (ASDB). A probability sample proportionate to the number of ED visits in each facility was drawn from among eligible hospitals.

Samples were drawn from the initial frame to provide the capability to make estimates for the United States as well as selected metropolitan areas. The metropolitan areas are referred to as oversampled areas (OS areas) or DAWN metropolitan areas. Two goals guided the selection of the DAWN metropolitan areas. The first was to preserve the ability to represent the 21 areas that had been part of DAWN since its inception. The second was to improve population and geographic coverage beyond these 21 legacy areas. Accordingly, the design ensured representation of the original 21 legacy areas plus the 5 most populous MSAs in each of the 9 census divisions. Oversamples were selected in a total of 48 MSAs; in 4 of those 48 MSAs, additional oversamples were drawn to allow reporting for subareas within those MSAs. Resources available to DAWN have allowed for data collection in only a portion of the OS areas.

The DAWN sample design was conceived to provide the statistical infrastructure to produce reliable and representative estimates for the United States and a portion of DAWN metropolitan areas (OS areas), depending on available resources and interest. To accomplish this objective, a subset of the hospitals within each OS area was identified a priori as having a dual purpose in estimation. Referred to as dual-purpose hospitals, these designated hospitals can contribute either to an estimate for the OS area in which they are located or to the estimate for the remainder area outside of OS areas. Dual-purpose hospitals carry two probabilities of selection (POS) and two stratum identifiers. One POS/stratum is associated with membership in an OS area oversample, and the other is associated with membership in the remainder area sample.

Each data year, the response rates and nonresponse patterns for each OS area are reviewed to determine data quality. Those OS areas with acceptable data quality are allowed to stand on their own as the basis for separate estimates; they are referred to as stand-alone OS areas. If it is determined on the basis of response rates and bias analyses that an OS area cannot stand alone, the design provides that the OS area is eliminated as a separate area but becomes part of the remainder area.

This study proposes to examine descriptive statistics for the 8 years of most recent DAWN data collection, 2004-2011.

8.3. Variables

Year of visit

Demographic: Age, Sex, Race

Case Type:

- Suicide Attempt
- Seeking detoxification
- Alcohol only (in case of patient under 21)
- Adverse Reaction
- Overmedication
- Malicious poisoning
- Accidental ingestion
- Other

Drug Mentions:

- Drug ID
- Route of Administration,
    - Oral
    - Injected
    - Inhaled, sniffed, snorted
    - Smoked
    - Other
    - Multiple routes of adminstration
- Toxicology Confirmed (Yes/No)

Patient Disposition:

- Discharged home
- Released to police/jail
- Referred to Detox/treatment
- ICU/Critical Care
- Surgery
- Chemical Dependency / Psychiatric unit
- Other inpatient unit
- Transferred
- Left Against Medical Advice (AMA)
- Died
- Other

8.4. Data sources

The data from this study are derived from public health surveillance system that reports on drug-related visits to hospital EDs. DAWN is used to monitor trends in drug misuse and abuse, identify the emergence of new substances and drug combinations, assess health hazards associated with drug use and abuse, and estimate the impact of drug use, misuse, and abuse on the United States' health care system.

DAWN's target sample frame consists of all non-Federal, short-stay, general medical and surgical hospitals in the United States that have one or more EDs open 24 hours a day. DAWN employs a multistage sampling design for the selection of EDs for analysis. Stratified simple random sampling with oversampling in selected metropolitan areas is used to select the hospitals.

8.5. Study size

There are no a priori specified hypotheses for this study which would drive sample size calculations. All eligible DAWN cases will be included in this analysis.

8.6. Data management

The DAWN data are de-identified and publicly available datasets. These datasets are located on the Internet for public use at http://www.icpsr.umich.edu/icpsrweb/SAMHDA/. Data use agreements are not required to use the publicly available datasets.

8.7. Data analysis

8.7.1. Essential analysis

Data on all reports of prescription drug misuse and abuse will be captured using the DAWN data sets from years 2004 to 2011, examined by year individually (Table 1). Data on all reports of bupropion misuse and abuse will be captured using the same data. These data will include reports of bupropion without mention of any other drug. However, such reports will also be analysed as a separate category. Percent change will be evaluated for each year, as compared to the previous year.

For each year in the study period, 2004-2011, a distribution of patient characteristics as well as case type and patient disposition will be captured in Tables 2-9. These tables will note the number of patients in the DAWN dataset (unweighted) as well as weighted N and weighted percentages of all the bupropion reports.

8.7.2. Exploratory analysis

If sample size permits, a univariate analysis of all reports of bupropion reports of non-oral route of administration and the patient disposition will be examined. These data will be specific to non-oral routes of administration and will be captured in Tables 10-17.

8.8. Limitations of the research methods

There are numerous limitations to the use of DAWN data. While it is the most comprehensive US-based dataset of drug abuse and misuse, there are inherent challenges in evaluating the true prevalence of drug misuse and abuse.

First, DAWN only captures patients presenting to the ED for a drug-related event. For example, a patient who enters the Emergency Department for a broken limb and reports using marijuana as a substance will not be entered into the DAWN database unless the physician reporting finds that the cause for the broken limb was the marijuana use.

Secondly, DAWN data will not capture all misuse or abuse that occurs outside the ED. Patients inhaling bupropion resulting in a "high" which does not lead to an ED admission will be missed. Thus, the DAWN data represents an underestimateof the overall prevalence of misuse and abuse of all drugs.

Third, an outcome or reason for ED admission cannot be tied to one single drug unless it is the only drug reported. A patient may enter the ED for a suicide attempt with reported bupropion misuse, but with an additional 7 reported substances. In this case it is not possible to tease out that the bupropion was the cause of the admission to the ED.

Finally, the data captured within the DAWN databases is specific to the case report only, and not the individual. It is possible that individuals may present more than once to a participating ED and thus be captured with each visit for a drug-related problem.

8.8.1. Study closure/uninterpretability of results

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

Informed consents are not collected in this nationally representative dataset. Ethics approval is not required.

9.2. Subject confidentiality

All data from DAWN are publicly available and de-identified.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

If, during the study, an adverse event (serious or non serious) is identified as explicitly attributed to any GSK product (including products not covered in the specific study objective), this will be reported. The study epidemiologist must forward the report to GSK central safety department within 24 hours of first becoming aware of the event as per SOP 52214 (Reporting and Disclosing Information from Observational Safety Studies and Analyses of Epidemiology Data).

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

GSK stakeholders will receive a report containing the information generated by this study, as well as contribute to the published literature. GSK stakeholders include the Global Safety Board, Safety Review Team, Global Clinical Safety & Pharmacovigilance and Global Regulatory Affairs. The results will be disseminated externally via regulatory submissions, and manuscripts/presentations.

11.2. Study reporting and publications

Upon protocol approval, protocol summary will be posted to both the EU PAS Register and the GSK Clinical Study Register.

Upon completion of the study, results summaries will be posted on the GSK Clinical Study Register, the EU PAS Register, and will be prepared in manuscript form for journal submission.

12. REFERENCES

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ANNEXURES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

No.	Document Reference No	Date	Title
1.	<No>	<Date>	<Text>
2.	<No>	<Date>	<Text>
N	<No>	<Date>	<text>

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain: 1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue) 1.1.2 The objectives of the study?	☐ ☐	☐ ☐	☐ ☐	
1.2 Does the formulation of the research question specify: 1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) 1.2.2 Which formal hypothesis(-es) is (are) to be tested? 1.2.3 if applicable, that there is no *a priori* hypothesis?	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	

Comments:

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	☐	☐	☐	
2.2 Is the planned study population defined in terms of: 2.2.1 Study time period? 2.2.2 Age and sex?	☐ ☐	☐ ☐	☐ ☐	

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.2.3 Country of origin?	☐	☐	☐	
2.2.4 Disease/indication?	☐	☐	☐	
2.2.5 Co-morbidity?	☐	☐	☐	
2.2.6 Seasonality?	☐	☐	☐	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☐	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☐	☐	
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☐	☐	☐	
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☐	
3.4 Is sample size considered?	☐	☐	☐	
3.5 Is statistical power calculated?	☐	☐	☐	

Comments:

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: 4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc) 4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc) 4.1.3 Covariates?	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	
4.2 Does the protocol describe the information available from the data source(s) on: 4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) 4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event) 4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐	
4.3 Is the coding system described for: 4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10) 4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events) 4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical	☐ ☐	☐ ☐	☐ ☐	

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
(ATC)Classification System)	☐	☐	☐	
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☐	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☐	
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	☐	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☐	

Comments:

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address: 7.1.1 Selection biases? 7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐ ☐	☐ ☐	☐ ☐	
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☐	
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☐	
7.4 Does the protocol address other limitations?	☐	☐	☐	

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☐	☐	☐	
8.2 Is the choice of statistical techniques described?	☐	☐	☐	
8.3 Are descriptive analyses included?	☐	☐	☐	
8.4 Are stratified analyses included?	☐	☐	☐	
8.5 Does the plan describe the methods for identifying: 8.5.1 Confounders? 8.5.2 Effect modifiers?	☐ ☐	☐ ☐	☐ ☐	
8.6 Does the plan describe how the analysis will address: 8.6.1 Confounding? 8.6.2 Effect modification?	☐ ☐	☐ ☐	☐ ☐	

Comments:

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☐	
9.2 Are methods of quality assurance described?	☐	☐	☐	
9.3 Does the protocol describe quality issues related to the data source(s)?	☐	☐	☐	

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☐	
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	☐	☐	☐	
9.5.2 Any progress report?	☐	☐	☐	
9.5.3 End of data collection?	☐	☐	☐	
9.5.4 Reporting? (i.e. interim reports, final study report)	☐	☐	☐	
9.6 Does the protocol include a section to document future amendments and deviations?	☐	☐	☐	
9.7 Are communication methods to disseminate results described?	☐	☐	☐	
9.8 Is there a system in place for independent review of study results?	☐	☐	☐	

Comments:

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☐	☐	☐	
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☐	
10.3 Have data protection requirements been described?	☐	☐	☐	

Comments:

Name of main author of study protocol: _____

Date: / /

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

Table Shells

Table 1 Distribution of Total Prescription Use/Misuse reports in US, 2004-2011, by year

	2004		2005		2006		2007		2008		2009		2010		2011	
	N (% of total)	% change	N (% of total)	% change from 2004	N (% of total)	% change from 2005	N (% of total)	% change from 2006	N (% of total)	% change from 2007	N (% of total)	% change from 2008	N (% of total)	% change from 2009	N (% of total)	% change from 2010
Total Reports (Pharmaceuticals)		NA														
Total Reports (any Buproprion)		NA														
Total Reports (Bupropion ONLY mentioned Drug)		NA														

% change indicated change from prior year.

Table 2 Distribution of Bupropion reports, DAWN data 2004 (repeat for each year 2005-2011)

	N (unweighted)	N Weighted	% (weighted)
Total Bupropion			-
Sex			
Male			
Female			
Age			
<18			
18-64			
55-64			
65+			
Route of Administration			
Oral			
Injected			
Inhaled/Sniffed/Snorted			

	N (unweighted)	N Weighted	% (weighted)
Smoked			
Other			
Multiple Routes			
Type of Visit			
Suicide Attempt			
Seeking Detox			
Alcohol only			
Adverse Reaction			
Overmedication			
Malicious Poisoning			
Accidental Ingestion			
Other			
Visit Disposition			

	N (unweighted)	N Weighted	% (weighted)
Discharged Home			
Released to Police/Jail			
Referred to Detox/Treatment			
ICU/Critical Care			
Surgery			
Chemical Detox			
Other inpatient unit			
Transferred			
Left AMA			
Died			
Other			

Table 3 Reports of Burpropion as only drug mentioned (repeat for each year 2005-2011)

	N (unweighted)	N Weighted	% (weighted)
Total Bupropion first drug mentioned			-
Sex			
Male			
Female			
Age			
<18			
18-64			
55-64			
65+			
Route of Administration			
Oral			
Injected			
Inhaled/Sniffed/Snorted			

	N (unweighted)	N Weighted	% (weighted)
Smoked			
Other			
Multiple Routes			
Type of Visit			
Suicide Attempt			
Seeking Detox			
Alcohol only			
Adverse Reaction			
Overmedication			
Malicious Poisoning			
Accidental Ingestion			
Other			
Visit Disposition			

	N (unweighted)	N Weighted	% (weighted)
Discharged Home			
Released to Police/Jail			
Referred to Detox/Treatment			
ICU/Critical Care			
Surgery			
Chemical Detox			
Other inpatient unit			
Transferred			
Left AMA			
Died			
Other			