Exponent®

Final Protocol

A Non-Interventional Study to Generate Real-World Evidence on the Cardiovascular Safety of CONTRAVE® in the United States (U.S.)

Prepared for

Michael Kyle, M.D.
Currax Pharmaceuticals LLC
+1 800 793 2145
mkyle@curraxpharma.com

Exponent contact

David Dore, Pharm.D., Ph.D.
Exponent Inc.
+1 508 654 5104
ddore@exponent.com

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1 RESPONSIBLE PARTIES

1.1 Sponsor and Primary Sponsor Contact

Currax Pharmaceuticals LLC
155 Franklin Rd, Suite 450
Brentwood, TN 37027
Contact: Michael Kyle, M.D.
+1 215 704 0475
mkyle@curraxpharma.com

1.2 Principal Investigator and Author of Record

David Dore, Pharm.D., Ph.D.
Principal Scientist
Exponent Inc.
1075 Worcester Street, Natick, MA 01760 U.S.A.
+1 508 654 5104
ddore@exponent.com

2 DRUG DESCRIPTION

The product of interest is a fixed-dose combination of naltrexone hydrochloride (HCl), 8mg, and bupropion HCl, 90mg, for oral use via extended-release oral tablet. The product is marketed under the trade name CONTRAVE® in the United States (U.S.). It is a combination of an opioid antagonist (naltrexone) and an aminoketone antidepressant (bupropion). Each constituent active ingredient is available separately in various doses and formulations.

Following conventions within previous documents, hereafter we refer to the product CONTRAVE® as the branded product, under regulation. Use of CONTRAVE® *or* concomitant initiation of its constituent active ingredients, naltrexone and bupropion, will be referred to as NB within this protocol.

CONTRAVE® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).[1]

CONTRAVE® is recommended to be initiated according to a dose-escalation schedule beginning with one tablet each morning in week one and increasing to up to two tablets twice daily beginning in week four.

The labeled contraindications include known allergy to any ingredient within CONTRAVE®; uncontrolled hypertension; seizure disorders; anorexia nervosa or bulimia; undergoing abrupt discontinuation of alcohol; use of benzodiazepines, barbiturates, or antiepileptic drugs; chronic opioid use; and taking currently, or within the past 14 days, a monoamine oxidase inhibitor.

As specified in the product labeling under Warnings and Precautions and Limitations of Use, the effect of CONTRAVE® on cardiovascular morbidity and mortality has not been established. Additionally, the safety and effectiveness of CONTRAVE® in combination with other products intended for weight loss, including prescription drugs, over-the-counter drugs, and herbal preparations, have not been established. In this protocol, we propose to evaluate the potential effects of NB on cardiovascular endpoints.

3 ABSTRACT

Title:	A Non-Interventional Study to Generate Real-World Evidence on the Cardiovascular Safety of CONTRAVE® in the United States (U.S.)
Background and Rationale:	The fixed-dose combination of naltrexone 8mg and bupropion 90mg extended-release oral tablet is marketed under the trade name CONTRAVE® in the U.S. In this protocol, we propose to generate real-world evidence (RWE) from electronic health records (EHR) and linked claims data to assess the cardiovascular safety of CONTRAVE® and all NB in usual clinical practice.
Research Question and Objectives:	The main objective of this study is to compare the incidence of the primary endpoint (major adverse cardiovascular events [MACE]) between initiators of NB and initiators of an active comparator, lorcaserin (1.0). The study will also compare the incidence of the secondary endpoint (each *component* of MACE) between initiators of NB and initiators of lorcaserin, overall and across subgroups of interest (1.1) This study includes three additional objectives to support the assessment of the robustness of the results for the primary and secondary endpoints: • To assess the comparability of the results from the same EHR data to the results of the 2018 randomized clinical trial assessing cardiovascular endpoints among lorcaserin users, in a manner consistent with the Randomized Controlled Trials Duplicated Using Prospective Longitudinal Insurance Claims: Applying Techniques of Epidemiology Initiative (RCT DUPLICATE) (2.0); • To quantify differences in cardiovascular safety endpoints between the 2018 trial and the results of this EHR study (2.1); • To conduct other sensitivity analyses, including a self-controlled, case-crossover analysis to quantify the potential effect of NB on MACE (2.2).
Study Design:	Retrospective, new-user cohort study.
Population:	The primary study population includes initiators of NB or the active comparator, lorcaserin.

	Inclusion and exclusion criteria for the main objective will ensure that only new users are included, and that the NB and comparison groups are comparable on risk factors for MACE after application of propensity score (PS) matching weights. Inclusion and exclusion criteria for the additional objectives will align with those used in the 2018 trial assessing cardiovascular endpoints among lorcaserin users, insofar as the data support a comparable replication.
Variables:	The key variables are initiation of NB, initiation of lorcaserin (active comparator), time on treatment, and the endpoint of MACE. The individual components of MACE will also be quantified. Covariates will be derived from clinical measurements, past medical history, diagnoses, observations, and prescription records. Multiple imputation will be applied to address missing data, coupled with PS analyses to address confounding.
Data Sources:	EHR and linked claims data from Arcadia Data Research. The data currently cover approximately 75 million people in the U.S.
Study Size:	There are approximately 37,000 apparent NB initiators in the Arcadia data. There are approximately 16,000 apparent lorcaserin initiators.
Data Analysis:	Descriptive statistics of the study cohorts, multiple imputation of missing covariates, estimation of crude incidence rates of MACE among initiators of NB, and adjusted incidence rates of MACE after applying PS matching weights will be calculated (1.0 and 1.1). Analogs to intention-to-treat and per-protocol cohort analyses will be conducted. The analysis will also follow the principles of the RCT DUPLICATE Initiative (2.0 and 2.1) to assess the concordance between findings in an EHR study to those in the lorcaserin cardiovascular safety endpoints trial. In addition, we will conduct a case-crossover study to assess the effects of NB on MACE (2.2) and other sensitivity analyses.
Milestones:	Start of Data Collection — September 2014 End of Data Collection — February 2020

4 RATIONALE AND BACKGROUND

The U.S. Food and Drug Administration (FDA) approved CONTRAVE® on September 10, 2014, for chronic weight management in obese adults (body mass index [BMI] ≥30 kg/m^2) and in those who are overweight (BMI ≥27 kg/m^2) with at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia). CONTRAVE® is used as an adjunct to a reduced-calorie diet and increased physical activity. The labeling indication includes two Limitations of Use, one of which states that the effect of CONTRAVE® on cardiovascular morbidity and mortality has not been established. Since 2014, real-world data (RWD) on NB have accumulated through use in clinical practice and afford an opportunity to generate RWE on the drug's safety profile. This protocol proposes the generation of RWE from EHRs and linked claims data to assess the cardiovascular safety of NB in usual clinical practice.

We also include several additional objectives; prime among them is assessing the comparability of findings using RWD to those generated from a clinical trial. RWD studies are often more cost-effective and feasible compared to their RCT counterparts. When sufficiently calibrated, RWD studies can reach similar conclusions to RCTs and can contribute meaningfully to evidence generation for therapeutics in real-world clinical practice[2,3]. The RCT DUPLICATE Initiative supports this goal and was created to quantify differences between RCT findings and corresponding RWD replications, to understand the types of research questions suitable for RWD, and to understand the methods that should be used for such studies. Comparisons to trial results can help to assess and quantify the presence of (potential) biases in RWD studies.

This protocol was developed in accordance with regulatory guidance, draft and international society guidelines, and frameworks for observational database studies involving RWE[4-6].

5 RESEARCH QUESTIONS AND OBJECTIVES

The study will assess whether patients who initiate treatment with NB are at an elevated risk of MACE compared with patients who initiated treatment with lorcaserin, an active comparator chosen to reduce potential confounding[7,8]. Lorcaserin was approved in the U.S. under the brand names BELVIQ® and BELVIQ XR® for the same indication as NB, and withdrawn from the market due to cancer safety concerns in 2020[9-11]. Lorcaserin is not believed to have adverse effects on cardiovascular outcomes. The CAMELLIA-TIMI 61 trial was a comparison of lorcaserin relative to placebo in overweight and obese patients with cardiovascular disease and cardiovascular disease risk factors. The trial found no difference in the rate of cardiovascular events[12].

The study's main objective is to compare the incidence of the primary endpoint (MACE) between initiators of NB and initiators of lorcaserin (1.0). The study will also compare the incidence of the secondary endpoint, consisting of each *component* of MACE, between initiators of NB and initiators of lorcaserin, across the following subgroups (1.1):

- Patients with obesity (i.e., most recent BMI measurement ≥30 kg/m2);
- Patients with a diagnosis of hypertension, regardless of BMI;
- Patients with a diagnosis of type 2 diabetes mellitus, regardless of BMI;
- Patients with a diagnosis of dyslipidemia, regardless of BMI.

The study's additional objectives aimed at testing the robustness of the methods are:

- To assess the comparability of findings from an EHR study to those of a 2018 clinical trial, aligning with the RCT DUPLICATE Initiative (2.0);
- To quantify differences in cardiovascular safety endpoints between the clinical trial and the results of this EHR study (2.1);
- To conduct other sensitivity analyses, including a self-controlled, case-crossover analysis to quantify the potential effect of NB on MACE (2.2).

6 RESEARCH METHODS

6.1 Study Design

A retrospective cohort study design will be used for the main objective and endpoints. Initiators of NB will be identified between September 2014 and February 2020. Contemporaneously, we will identify all lorcaserin users between 2012 and 2020. A self-controlled, case-crossover design will be used for the sensitivity analysis (2.2).

6.2 Settings

The cohorts for all study objectives will be drawn from a large EHR data source, representing a geographically diverse patient population. The data will include diagnoses, procedures, medications (prescribed and administered), clinical measures (biometric and laboratory values), and observations derived from clinical notes. A subset of the population will have linked, adjudicated claims data available to support sensitivity analyses.

EHR data, generated from routine clinical care offer timely clinical information not typically available in claims databases, including information on patient attributes, observations from physicians' notes, patient symptoms and history, diagnostic information, and planned and actual treatments, and prescription medicines not covered by health plans (e.g., CONTRAVE®). Notably, EHR data include measures of BMI for descriptive analysis and evaluation as a potential confounder and effect modifier. These EHR data will be linked to proprietary information from First Databank to identify medications of interest accurately, including NB.

6.3 Inclusion Criteria

For the main objective (1.0, 1.1), patients are eligible if they meet the following inclusion criteria:

- Have at least one prescription for NB between September 2014 and February 2020, including concurrent prescriptions (within 15 days) for naltrexone and bupropion; or have at least one prescription for lorcaserin;
- Have at least 180 days of data available prior to cohort entry with no evidence of prescriptions or dispensings of NB or lorcaserin;
- Have at least one BMI value available in the 180 days prior to cohort entry, inclusive of the index date;
- Have documentation of at least one outpatient medical visit 180 or more days prior to cohort entry, and at least one healthcare interaction in the 180 days prior to cohort entry;

- Are at least 18 years of age on the cohort entry date.

Of note, having at least one BMI value is the only inclusion criterion that is potentially missing within the EHR. Documentation of at least one outpatient medical visit more than 180 days prior to cohort entry, and at least one healthcare interaction in the 180 days prior to cohort entry is required. This criteria will facilitate the inclusion of individuals who appear to have sufficient engagement with an Arcadia-contributing health system and would have enough clinical data to meet the study objectives.

For the comparability study (2.0 and 2.1), inclusion criteria will be based on the CAMELLIA-TIMI 61 trial, insofar as the information is available in the data. Examples include:

- BMI ≥27 kg/m^2;
- Age ≥40 years with history of documented myocardial infarction (MI) or ischemic stroke >1 month prior to baseline, peripheral artery disease, revascularization or significant unrevascularized coronary arterial stenosis;
- Women age ≥55 years or men age ≥50 years who have type 2 diabetes mellitus without established cardiovascular disease but at least one cardiovascular risk factor (hypertension, dyslipidemia, calculated creatinine clearance ≥30 to ≤60 mL/min, or urinary albumin-to-creatinine ratio ≥30 µg/mg)[13].

The full list of inclusion criteria are included in the CAMELLIA-TIMI 61 publication and protocol[12].

Where variables are not available in the EHR or claims data, we will search for suitable proxies based on the literature and the recommendations of a U.S.-licensed physician consultant.

For the case-crossover study (2.2), patients are eligible if they meet the following inclusion criteria:

- Experience a MACE event ("index event") after September 2014;
- Have at least one prescription or dispensing of NB prior to the index event;
- Are at least 18 years of age at the time of the first prescription/dispensing of interest.

6.4 Exclusion Criteria

For the main objective, patients are not eligible if they have a diagnosis of any of the following conditions in the 180 days before the cohort entry date:

- Epilepsy;
- Bulimia;
- Anorexia nervosa;
- Surgical procedure for weight loss.

Patients also must not have been prescribed opioids or monoamine oxidase inhibitors in the 180 days before entry into the cohort.

Patients with prescriptions for both NB and lorcaserin will be randomly assigned to a baseline treatment group to preserve sample size and mitigate selection bias.

Patients are not eligible for inclusion in the comparability study if they have any of the following, as feasibly measured in the Arcadia data, including:

- Congestive cardiac failure;
- Known left ventricular ejection fraction <20%;
- Moderate or higher pulmonary hypertension ;
- Known severe valvular disease;
- Moderate renal impairment, severe renal impairment, or end-stage renal disease;
- Severe hepatic impairment;
- Use of other products intended for weight loss;
- Use of, within 1 month prior to baseline, more than one other serotonergic drug including, but not limited to:
  - Selective serotonin reuptake inhibitors;
  - Serotonin norepinephrine reuptake inhibitors;
  - Tricyclic antidepressants;
  - Bupropion;
  - Triptans;
  - St. John's Wort and tryptophan;
  - Monoamine oxidase inhibitors, linezolid, dextromethorphan, lithium;
  - Tramadol, antipsychotics or other dopamine antagonists;
- Use of drugs known to increase the risk for cardiac valvulopathy within 6 months prior to baseline including, but not limited to:
  - Cyproheptadine;
  - Amoxapine;
  - TCAs;
  - Mirtazapine;
  - Pergolide;
  - Ergotamine;

  - Methysergide;
  - Cabergoline;
- History or evidence of clinically significant disease (e.g., malignancy, cardiac, respiratory, gastrointestinal, renal or psychiatric disease);
- Use of lorcaserin HCl within 6 months prior to screening;
- Hypersensitivity to lorcaserin HCl or any of the excipients.

The full list of exclusion criteria are included in the CAMELLIA-TIMI 61 publication and protocol[12].

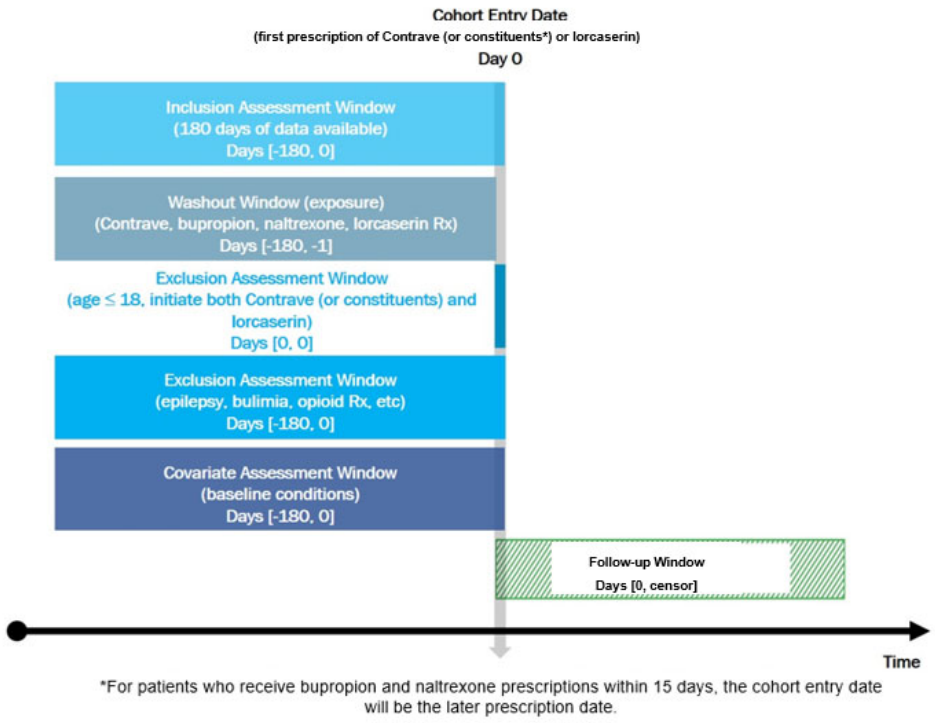
Similar to the exclusion criteria for the primary objective, patients with any of the diagnoses or prescriptions for opioids and/or monoamine oxidase inhibitors in the 180 days prior to the index event date will be excluded from the case-crossover analysis.

6.5 Variables

6.5.1 Exposure

Initiation of NB and lorcaserin will be identified using Hierarchical Ingredient Code Lists (HICLs) from First Databank. If necessary, individual searches of National Drug Codes (NDCs) and free-text strings will also be used. See **Figure 1** for visual depiction of the study design.

Figure 1. NB safety study design

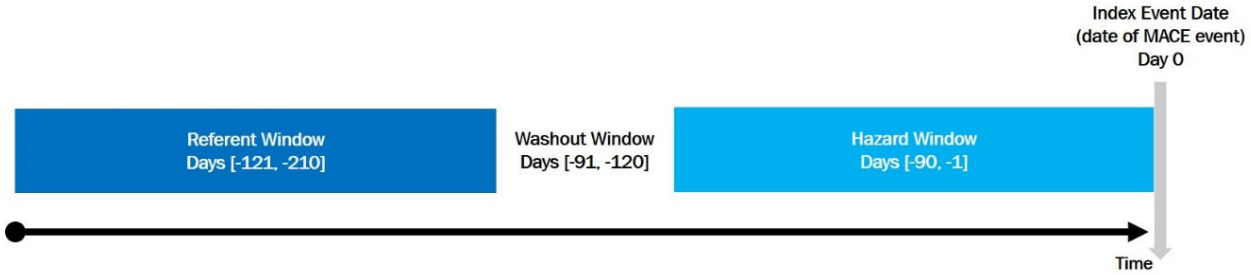


For the cohort, among the subset of patients with EHR data whose records can be linked to health insurance claims, we will assess the concordance between receiving a prescription for NB and lorcaserin (in the EHR) and filling the prescription (in the claims).

The time of entry into the NB cohort will be the date of first prescription for those taking CONTRAVE®, the date of the second overlapping prescription of naltrexone or bupropion in the case of concomitant use of naltrexone and bupropion, or the date of first prescription for lorcaserin from date of approval in the U.S. to withdrawal from the market, as applicable.

In the case-crossover study, a 90-day hazard window will immediately precede the index event date within which the occurrence of a prescription or dispensing will define exposure status. Similarly, a 90-day referent window will precede the hazard window, with exposure status designated comparably. A 30-day washout window between the hazard and referent windows will be used to mitigate any carryover effects from the prior exposure. Please see **Figure 2** for a visual depiction of the case-crossover study design.

Figure 2. Case-crossover study design



6.5.2 Outcomes and follow-up

The primary study endpoint is MACE, defined as the composite of:

- Medically attended non-fatal acute myocardial infarction;
- Medically attended non-fatal stroke;
- Cardiovascular-related death.

The secondary endpoints are:

- Individual components of MACE, analyzed separately, as (1) medically attended non-fatal acute myocardial infarction; (2) medically attended non-fatal stroke; and (3) cardiovascular-related death.

In accordance with the CAMELLIA-TIMI 61 trial, the comprability study will examine safety endpoints for the secondary objectives (2.0 and 2.1).

The safety endpoint was defined as a composite of:

- Cardiovascular death;
- Myocardial infarction;
- Stroke[12].

For all study objectives, information on myocardial infarction and stroke will be obtained from the EHR data, while information on death will be obtained from Datavant. Datavant compiles mortality data from government sources, obituaries, newspapers, and claims data for more than 90% of the U.S. population. Cause of death will be ascertained from the subset of individuals whose records can be linked to death certificates; otherwise, diagnoses adjacent to death will be identified, as feasible, using information from the EHR (e.g., cardiovascular-related hospitalizations or emergency department visits immediately preceding date of death).

A U.S.-licensed physician consultant, blinded to exposure, will review the detailed chronological listing of individual-level EHR data (and claims, where relevant) of a randomly selected subset of apparent MACE cases to determine whether MACE occurred. The adjudication process will compare the operational definition of MACE in the EHR to the physician's professional judgement and the occurrence of MACE in the EHR and claims data. If the initial EHR-based definition of MACE does not meet a pre-specified threshold for concordance, then adjustments to the initial list of diagnoses and procedure codes will be made to improve the accuracy of the operational definition of MACE[14,15].

Follow-up time will be calculated separately for each study endpoint. Patients will be followed starting the day after initial exposure until the first of the following censoring events: (1) the study endpoint of interest, (2) death (for those who do not have the endpoint of interest), or (3) end of available data for those who do not have the event of interest (i.e., censoring due to end of available EHR data). Person-time will be calculated by summing the days from cohort entry (day 0) to the date of the first relevant censoring event.

To test the robustness of assumptions about the date of censoring, analyses with differing censoring definitions will be performed, and estimates compared:

- To assess whether the censoring date needs to be adjusted, the physician consultant will review a random sample of patient health profiles to determine whether there is a clear indicator of censoring. Insofar as there appears to be a clear indicator of censoring, the physician will record this date (blinded to exposure), and this information will be used to

adjust the censoring date. Indeed, this information may be treated as an annotation for a machine learning model.

- To account for a patient still being on the insurance plan but not accessing the healthcare system, adjust the end of follow-up to be 6 months, 1 and 2 years following their last healthcare encounter in the EHR.
- To assess the reliability of our method for computing time until censoring in the EHR, compare follow-up times in the EHR to those observed in the claims enrollment files using a subset of those with EHR and claims data.
- To test robustness of the method for computing follow-up time in the EHR, compute the distribution of follow-up times based on enrollment spans within the subset of individuals with claims and EHR data and apply the median follow-up time within populations with particular health profiles.
- To implement a more specific definition of follow-up time, assume that a last healthcare encounter with a primary care provider, endocrinologist, or geriatric care provider in combination with no death information is the end of enrollment.

6.5.3 Covariates

A range of demographics will be assessed for each patient at cohort entry, including the following:

- Age;
- Sex;
- Race/ethnicity.

A set of comorbidities will be assessed in the 180 days before cohort entry, including the following:

- Acute myocardial infarction;
- Stroke;
- Dyslipidemia;
- Type 2 diabetes mellitus;
- Transient ischemic attack;
- Hypertension;
- Heart failure;
- Unstable angina;
- Peripheral vascular disease;
- Coronary heart disease;
- Cerebrovascular disease;
- Chronic kidney disease;

- Sleep apnea;
- Mood disorders.

A set of concomitant medications will be assessed in the 180 days before cohort entry, including the following:

- Medications that affect cardiovascular outcomes, including:
    - Antihypertensives;
    - Statins;
    - Anticoagulants;
    - Antiplatelets;
    - Antihyperglycemics.

- Other medications listed in the CONTRAVE® Prescribing Information Drug Interactions, including:
    - Selective serotonin reuptake inhibitors;
    - Tricyclic antidepressants;
    - Antipsychotics;
    - Beta-blockers;
    - Type 1C antiarrhythmics (e.g., propafenone and flecainide);
    - Digoxin;
    - Antiplatelets.

A set of relevant laboratory test results and biometric values will be assessed during the 180 days before cohort entry, including the following:

- BMI;
- Blood glucose or HbA1c;
- Liver function;
- Dyslipidemias;
- Resting heart rate;
- Respiratory rate;
- Systolic blood pressure;
- Diastolic blood pressure;
- Glomerular filtration rate/serum creatinine.

Where multiple values are available, the most recent will be selected. Where no value is present, multiple imputation procedures will be used to generate a value under the assumption that the values are missing at random.

7 DATA SOURCES

7.1 Arcadia Data Research

The study will use EHR data and linked claims data from Arcadia, which has assembled one of the largest EHR datasets available to life science organizations, currently covering approximately 75 million individuals in the U.S. Arcadia partners with health systems and payers to create a centralized, physically integrated EHR system that has nationwide coverage and integrates clinical data from multiple electronic medical records within and across health systems via their Master Patient Index, a proprietary person-matching technology that identifies distinct patients across disparate data sources[16]. The typical research extract includes patient demographics, encounters, appointments, provider data, charges, assessments, immunizations, health maintenance and medical history, orders/results, vitals, insurance, prescriptions and active medications, problem lists, and allergy information.

Arcadia's EHR data are sourced from large integrated delivery networks, academic medical centers, ambulatory, primary care, core hospitals, and other providers. Arcadia's de-identified dataset for research includes a mix of populations representing individuals with commercial insurance, along with Medicare and Medicaid coverage. Adjudicated claims data from multiple payers are available for approximately 46% of the EHR patients.

7.2 Datavant Death Data

We will link data from Arcadia to death data from Datavant, a private U.S. data curator, specializing in organizing health data[17]. Datavant's mortality database contains information on deceased individuals in the U.S. and Canada[18]. Datavant's Death Index contains information on individual deaths including year and month of death, gender, and cause of death, where available. Information is obtained from the Social Security Administration's Death Master File in addition to private obituaries, newspapers and claims data, and is updated on a weekly basis[18,19]. In 2018, information was present for just over 2.4 million deaths[18].

In order to de-identify records, names, addresses, and social security numbers are removed in addition to modifications such as changing a person's date of birth to year of birth alone[19]. Datavant's proprietary technology adds encrypted tokens to each record, constructed from the underlying personally identifiable information. Since these tokens correspond to unique individuals, they can be used to link death information to other health-related datasets.

8 STUDY SIZE AND STATISTICAL POWER

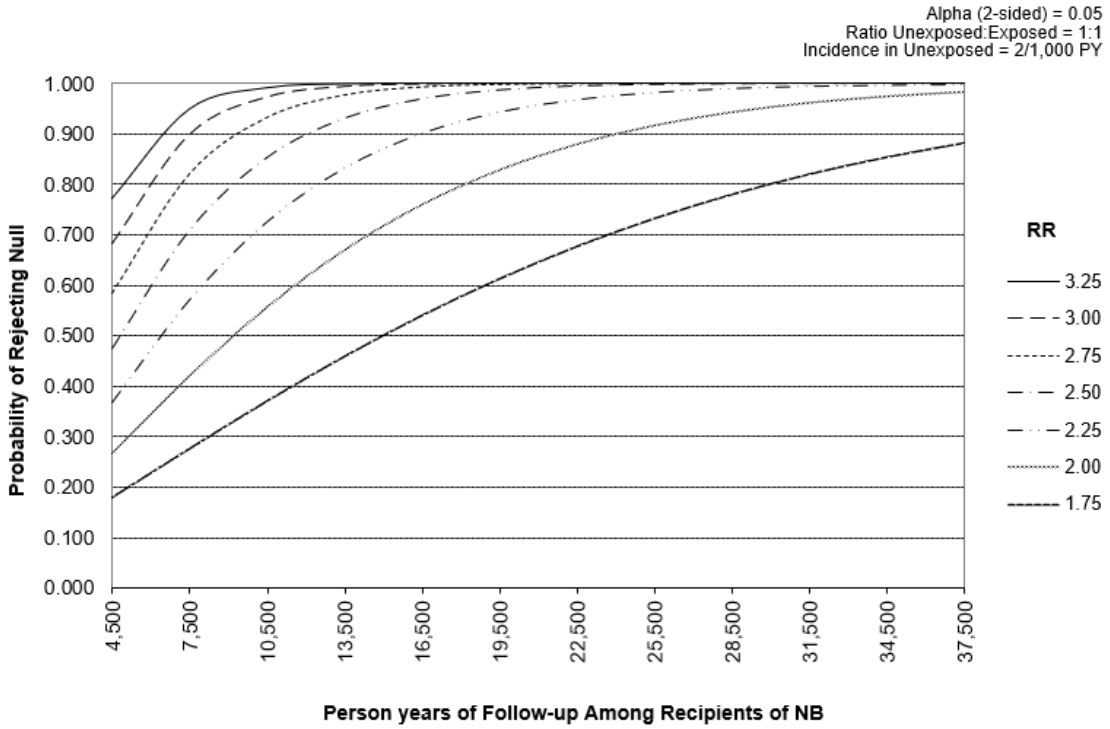
8.1 Study Size

According to the most recent available data from Arcadia (delivered to Exponent November 2022), ~37,000 patients had an apparent initiation of NB. Of those patients ~64% had linked, adjudicated claims data at some point in time. Seventy percent of apparent initiators were women.

8.2 Ranges of Statistical Power for MACE

In a similar population of overweight/obese individuals, Ritchey et al.[20] found that the incidence rate of MACE was estimated at 2/1,000 person-years among individuals unexposed to weight loss drugs (95% confidence interval [CI], 1.85–2.17). Guided by this estimated incidence rate of MACE, **Figure 3** describes a range of plausible estimates for the statistical power of the NB safety study.

Figure 3. Range of power estimates for the endpoint of MACE in the NB safety study



This Figure was generated using a general cohort power calculation methodology.
Abbreviation: NB, Naltrexone and Buproprion; PY, person-years; RR, relative risk

Assuming an incidence rate of MACE of 2 per 1,000 years of follow-up within this study, and that there are ~37,000 initiators of NB, it appears that we have greater than 80% power to detect a relative risk of 2.0.

9 DATA MANAGEMENT

9.1 Descriptive Statistics

Descriptive statistics will be used to summarize each covariate by treatment group for all study objectives. For dichotomous variables, we will report the number and proportion of patients with each covariate. For categorical variables, we will report the number and proportion of patients in each level of the covariate. For continuous variables, the mean and standard deviation will be estimated. Standardized differences in means and proportions will be used to assess covariate balance between weighted treatment groups.

9.2 Missing Data

Some biometric variables within the EHR (e.g., laboratory values, such as HbA1c) are expected to be missing in a non-random way. We will employ multiple imputation methods to address missing covariate data at baseline by creating standard intervals (e.g., within periods of one, three or six months) for ascertainment of important missing values. If multiple results are available in an interval, we will select the valid observation that is most proximal to the cohort entry date.

Consistent with our previous research on missing data within EHRs[21,22], we will then use multiple imputation methods to impute missing values within intervals with no observed values for a given patient. To account for the uncertainty of imputed values, we will produce 10 complete datasets to quantify within- and between-dataset variance and to correct standard errors. That is, the full analysis will be conducted within each of the 10 complete datasets, the results will be averaged across the datasets, and the measures of statistical uncertainty (e.g., CIs) corrected for the imputation. Because of the number of possible covariates requiring imputation, we will use a fully conditional specification of the multiple imputation procedure (i.e., chained equations), which does not require the stringent assumption that some models make about the joint distribution of missing covariates[23].

The multiple imputation procedure reduces the potential for missing data bias at the population level and relaxes the assumptions necessary to interpret results as unbiased estimates. Dr. Dore designed and successfully conducted a cohort study with a large EHR using these techniques, and the results of that study were similar to trial results of the same comparisons[21].

9.3 Crude Incidence Rate Difference (IRD) and Incidence Rate Ratio (IRR) Estimates

The incidence rate for each group is the cumulative number of observed endpoint events, divided by the total person-years of follow-up. The crude IRD is the absolute difference in the observed incidence rate between initiators of NB and initiators of lorcaserin, with no adjustment for differences in patient characteristics between groups. The crude IRR is the relative difference (i.e., ratio) in the observed incidence rate of initiators of NB, divided by the observed incidence rate for initiators of lorcaserin, with no adjustment for differences in patient characteristics between groups.

9.4 PS Matching Weights

PS matching weights will be used to control for confounding between treatment groups[24,25]. A logistic regression model will be used to estimate the predicted probability of treatment with NB versus treatment with lorcaserin, conditional on pre-specified covariates. Each patient's PS, or predicted probability from the model, will be the probability that the patient received NB. The complement of each patient's PS (i.e., 1-PS) will be the probability that the patient received lorcaserin. Each patient will be assigned a matching weight, which is a function of their PS and the treatment received. The numerator of the matching weight is the smaller of the PS or the complement of the PS (1-PS). The denominator is the PS if the patient received NB, and it is 1-PS if the patient received lorcaserin. For example, a patient with a PS value of 0.6 (1-PS = 0.4) who received NB would have a matching weight of 0.4/0.6 or 0.667. These weights will be used in regression models to account for confounding.

Similar methods will be used to generate propensity score weights within the CAMELLIA-TIMI 61 comparability cohort. Covariates will include demographics, calendar time of treatment initiation, comorbidities, medications, cardiovascular procedures, and indicators of health care utilization as proxy for overall disease state, care intensity, and surveillance.

Matching weights are the weighting analog of 1:1 PS matching, but include the entire eligible patient population, are more statistically efficient than matching, and produce better balance on covariates. Thus, matching weights standardize the distribution of patient characteristics to the area of common support (or empirical equipoise[26]) in which patients could have reasonably received either treatment.

9.5 Estimation of Adjusted IRD and IRR Estimates

This study will include analogs of intention-to-treat (ITT) and per-protocol analyses, in accordance with clinical trial conventions. Both analyses estimate the effect of NB on the incidence of MACE relative to comparators, but differ in the handling of person-time, as described below. We adopt the term ITT and refer to the per-protocol analogue as the *as-treated* analysis.

9.5.1 Intention-to-Treat Analysis

The ITT defines each day of follow-up for everyone according to their exposure status at the time of cohort entry (e.g., initiation of NB). Classification of person-time in the ITT analysis is subject to exposure misclassification as individuals discontinue treatment or switch to the other study drug before their end of follow-up. In contrast, the ITT estimate preserves the balance in

baseline covariates that will be achieved through PS matching weights because individuals remain in the cohort to which they were assigned at baseline, when the PS weights are applied. The results from this approach are best interpreted as providing an estimate of the effect of starting treatment – or intending to start treatment – on the rate of the outcomes.

9.5.2 As-Treated Analysis

The ITT analysis will be juxtaposed with analyses of person-time classified by actual exposure to NB and lorcaserin, grouped into categories of current, recent, and past use. These person-time classifications estimate the effect of being on (or off) the treatment on the rate of the outcomes. Such estimates are often desirable for drug safety questions because they avoid misclassification of exposure that arises in ITT analysis; however, the balance introduced at baseline by PS matching weights may deteriorate as patients switch non-randomly among different study drugs. Therefore, the ITT and *as-treated* analyses are best interpreted together.

To obtain the hazard ratios necessary to compare trial results to those obtained through use of RWD, we will use an ITT analysis for the primary analyses, and as-treated for sensitivity analyses, as was done in the CAMELLIA-TIMI 61 trial.

9.5.3 Statistical Model for Cohort Analysis

For all primary study objectives, weighted Poisson models will be used to estimate IRDs and IRRs (and 95% CIs), adjusted for all covariates included in the PS model. Robust variance estimators will be used to account for the weighting. Analyses will be conducted amongst the overall NB cohort and also stratified by initiators of CONTRAVE® and those with overlapping, concomitant use of Naltrexone and Bupropion.

For the secondary objective of assessing the comparability of findings in a RWD cohort with the lorcaserin clinical trial, we will conduct a time-to event analysis in the propensity-score matched cohort. We will produce hazard ratios (HR) and 95% confidence intervals using a weighted Cox proportional-hazards model with the stratification factor as a covariate.

Additionally, informed by previous work in the RCT DUPLICATE Initiative, we will examine the following metrics in concert to assess the comparability in findings between the CAMELLIA-TIMI 61 trial and findings in the data:

- Regulatory agreement, which is the ability of the study using RWD to replicate the direction and magnitude of the RCT;

- Estimate agreement, defined as a HR from the replication study that was within the 95% CI for the RCT estimate;
- Standardized difference between the RCT and replication effect estimate, with a p-value < 0.05 considered statistically significant.

Conditional logistic regression models will be used to compare the odds of exposure to NB in the hazard window to the odds of exposure in the referent window (i.e., odds ratio) for the case cross-over design.

9.6 Quality Control

The study will be carried out according to Exponent's Quality Management System (QMS), with specific procedures being consistent with the International Society for Pharmacoepidemiology's Guidelines for Good Pharmacoepidemiology Practices (http://www.pharmacoepi.org), as well as the FDA Best Practice Guidance document (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/)[4-6,27]. In particular, the QMS at Exponent ensures that processes and deliverables are documented, reviewed, and validated in sufficient detail to allow for subsequent re-examination or replication. Exponent's quality management system is independently assessed against the most recognized and comprehensive international standard for quality management systems, ISO 9001. Exponent complies with the ISO 9001:2015 standard; the ISO 17025:2017 standard; U.S. Code of Federal Regulations, Title 10, Part 50, Appendix B; U.S. Code of Federal Regulations, Title 10, Part 21; and the respective advertising policy for each registration, accreditation, and approval.

The core project team will consist of at least one Principal Scientist who will provide scientific oversight of the study, a senior epidemiologist who will manage day-to-day aspects of the scientific conduct of the study, research analyst(s), and a project manager. Project management is integrated into the project team and supports the development of the project plan, monitoring timelines and budgets, securing appropriate study resources, and facilitating completion of contracted deliverables. In addition, Exponent staff members will support the project team by providing review and quality assurance of documents and programs associated with the conduct of the study, including assurance of appropriate data confidentiality, storage, and management.

10 LIMITATIONS OF THE DATA AND RESEARCH METHODS

10.1 Electronic Health Data

All EHR databases and healthcare registries have certain inherent limitations because the data are collected for clinical patient management, administration, and other non-research purposes. EHR data represent the intent of the prescriber through the written prescription for a medication; they do not indicate that a medication was filled, consumed, or taken as prescribed.

The EHR data will not include healthcare encounters or prescriptions from providers that do not contribute to the EHR aggregating entity (Arcadia). This can result in under-capture of some medication exposure. In addition, patients prescribed medications may not have them dispensed and may not consume them as prescribed even when they are dispensed. This can overestimate some patients' actual medication exposure.

10.2 Unmeasured Patient Risk Factors

In this study, robust PS adjustment relies on accurate measurement of risk factors for MACE. As such, the lack of important risk factors can introduce unmeasured confounding, where these risk factors remain imbalanced between groups after PS adjustment. The use of an active comparator will mitigate some unmeasured confounding, because it shares the same indication as NB[28]. Self-controlled designs are not subject to measured or unmeasured confounding by factors that do not vary over the observation window. Therefore, the case-crossover study will help inform the extent to which residual confounding may affect the cohort analysis.

11 PROTECTION OF HUMAN SUBJECTS

Confidentiality of patient records will be maintained at all times. All analyses will be performed in accordance with applicable laws and regulations. All study reports will only contain aggregated results and will not identify individual patients or physicians. At no time during the study will Currax, Exponent, or any consultants on the study receive patient-identifying information.

12 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

For this study using previously collected and deidentified electronic healthcare data, the research team does not anticipate any new adverse events to be identified. If, however, new adverse events are found during the course of the study, they will be vetted through the

pharmacovigilance processes at Currax Pharmaceuticals LLC and reported to regulatory authorities, as appropriate.

13 PLANS FOR DISSEMINATION AND COMMUNICATING STUDY RESULTS

A report of the findings of this study will be presented to FDA upon finalization of study output. Additionally, Currax Pharmaceuticals LLC intends for the research team to publish the results in a peer reviewed journal expeditiously and in keeping with ISPE GPP (2015) and authorship guidelines presented by the International Committee of Medical Journal Editors (ICMJE) recommendations (2019).

14 REFERENCES

1. Contrave Prescribing Information. (https://contrave.com/contrave-pi/).
2. Franklin JM, Patorno E, Desai RJ, et al. Emulating randomized clinical trials with nonrandomized real-world evidence studies: first results from the RCT DUPLICATE initiative. Circulation 2021;143(10):1002-1013.
3. Merola D, Young J, Schrag D, Lin KJ, Robert N, Schneeweiss S. Oncology Drug Effectiveness from Electronic Health Record Data Calibrated Against RCT Evidence: The PARSIFAL Trial Emulation. Clinical Epidemiology 2022;14:1135-1144.
4. Administration FaD. Framework for FDA's Real-World Evidence Program. (https://www.fda.gov/media/120060/download).
5. Administration FaD. Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory DecisionMaking for Drug and Biological Products Guidance for Industry. (https://www.fda.gov/media/152503/download).
6. Administration FaD. Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products Guidance for Industry. (https://www.fda.gov/media/124795/download).
7. Schneeweiss S, Patrick AR, Stürmer T, et al. Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. Medical care 2007;45(10 SUPL):S131.
8. Suissa K, Schneeweiss S, Kim DW, Patorno E. Prescribing trends and clinical characteristics of patients starting antiobesity drugs in the United States. Diabetes, Obesity and Metabolism 2021.
9. BELVIQ Prescribing Information. Revised 4/2018. Available from: https://www.belviq.com/pdfs/Belviq_Prescribing_information-pdf.pdf. Accessed May 30, 2021.
10. BELVIQ Prescribing Information. (https://www.belviq.com/pdfs/Belviq_Prescribing_information-pdf.pdf).
11. FDA requests the withdrawal of the weight-loss drug Belviq, Belviq XR (lorcaserin) from the market: Potential risk of cancer outweighs the benefits. https://www.fda.gov/media/135189/download: U.S. Food and Drug Administration; 2020.
12. Bohula EA, Wiviott SD, McGuire DK, et al. Cardiovascular safety of lorcaserin in overweight or obese patients. New England Journal of Medicine 2018;379(12):1107-1117.
13. Valente MA, Hillege HL, Navis G, et al. The Chronic Kidney Disease Epidemiology Collaboration equation outperforms the Modification of Diet in Renal Disease equation for estimating glomerular filtration rate in chronic systolic heart failure. European journal of heart failure 2014;16(1):86-94.
14. Cutrona SL, Toh S, Iyer A, et al. Validation of acute myocardial infarction in the Food and Drug Administration's Mini-Sentinel program. Pharmacoepidemiol Drug Saf 2013;22(1):40-54. (In eng). DOI: 10.1002/pds.3310.
15. Davis LA, Mann A, Cannon GW, Mikuls TR, Reimold AM, Caplan L. Validation of diagnostic and procedural codes for identification of acute cardiovascular events in US veterans with rheumatoid arthritis. EGEMS 2013;1(3).

16. Arcadia. Aggregate Pop. Health Data. 2021 (https://arcadia.io/products/aggregate-your-data/).
17. Datavant. Health and Data Analytics. (https://datavant.com/solutions/health-data-analytics/).
18. Du M, Hou J, Hsu B, et al. Incorporating Datavant's Death Index in Mortality Analysis. (https://www.soa.org/globalassets/assets/files/resources/research-report/2021/population-mortality-comparisions.pdf#:~:text=Datavant%2C%20Inc.%2C%20a%20private%20U.S.%20company%20specializing%20in,databases%2C%20can%20be%20aggregated%20and%20modeled%20for%20analysis.).
19. Datavant. Mortality Data in Healthcare Analytics Sourcing Robust Data in a HIPAA-Compliant Manner. (https://datavant.com/wp-content/uploads/dlm_uploads/2018/09/White-Paper_-Mortality-Data-in-Healthcare.pdf).
20. Ritchey ME, Harding A, Hunter S, et al. Cardiovascular safety during and after use of phentermine and topiramate. The Journal of Clinical Endocrinology & Metabolism 2019;104(2):513-522.
21. Loughlin AM, Qiao Q, Nunes AP, et al. Effectiveness and tolerability of therapy with exenatide once weekly vs basal insulin among injectable-drug-naïve elderly or renal impaired patients with type 2 diabetes in the United States. Diabetes, Obesity and Metabolism 2018;20(4):898-909. DOI: 10.1111/dom.13175.
22. Nunes AP, Loughlin AM, Qiao Q, et al. Tolerability and effectiveness of exenatide once weekly relative to basal insulin among type 2 diabetes patients of different races in routine care. Diabetes Therapy 2017;8(6):1349-1364.
23. Lee KJ, Carlin JB. Multiple imputation for missing data: fully conditional specification versus multivariate normal imputation. American journal of epidemiology 2010;171(5):624-632.
24. Harder VS, Stuart EA, Anthony JC. Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. Psychological methods 2010;15(3):234.
25. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T. Variable selection for propensity score models. American journal of epidemiology 2006;163(12):1149-1156.
26. Lee BK, Lessler J, Stuart EA. Weight trimming and propensity score weighting. PloS one 2011;6(3):e18174.
27. (ISPE) ISfP. Guidelines for Good Pharmacoepidemiology Practices (GPP). (https://www.pharmacoepi.org/resources/policies/guidelines-08027/).
28. Seeger JD, Nunes A, Loughlin AM. Using RWE research to extend clinical trials in diabetes: an example with implications for the future. Diabetes, Obesity and Metabolism 2020;22:35-44.