EXHIBIT 1

Zofran Study - Brief Study Protocol

Last Updated: 02/03/16

Objective:

To evaluate the safety of currently utilized pharmaceutical therapies for the treatment of nausea and vomiting in pregnancy (NVP)

Exposure Definition:

Exposure to Diclegis, Zofran, Metoclopramide, Promethazine, and Methylprednisolone in the first trimester of pregnancy. First trimester exposure will be defined as follows:

- The database will contain the date at which the drug was dispensed.
- We will consider a mother/baby pair exposed during the first trimester if a drug was dispensed during the first trimester.
- Dates to define the first trimester will be derived from date of delivery. Although a typical pregnancy lasts 266 days following conception, there is some natural variability in its duration. This in turn translates to uncertainty about the date of conception on the basis of the delivery date. We will assign dates for the first trimester as follows:

Delivery Type	Conception Date	First Trimester Definition
Full term - Singleton	259-287 days (37-41 weeks) before delivery	Earliest possible date of conception through 91 days following the latest possible date of conception (287-147 before delivery)
Full term - Multiples	238-273 days (34-39 weeks) before delivery	273-147 days before delivery
Pre-Term	252 days (<37 weeks) before delivery, or earlier	252-133 days before delivery
Example(s) *Full-term singleton* *Date of delivery:* *01/01/12* *Pre-term singleton* *Date of delivery:* *01/01/12*	*03/20/11 - 04/17/11* *04/24/11 - 05/22/11*	*03/20/11 - 07/17/11* *04/24/11 – 08/21/2011*

- Where ICD-9-CM diagnosis codes indicating the specific weeks of gestation at birth are used, we will apply these to calculate the estimated conception date.

765.20 — Unspecified weeks of gestation;
765.21 — Less than 24 completed weeks of gestation;
765.22 — 24 completed weeks of gestation;
765.23 — 25 to 26 completed weeks of gestation;
765.24 — 27 to 28 completed weeks of gestation;
765.25 — 29 to 30 completed weeks of gestation;
765.26 — 31 to 32 completed weeks of gestation;
765.27 — 33 to 34 completed weeks of gestation;
765.28 — 35 to 36 completed weeks of gestation; or
765.29 — 37 or more completed weeks of gestation.

Information on Drugs of Interest:

- Diclegis was pulled from the market in 1983 following lawsuits claiming it caused birth defects. The manufacturer (Merrell Dow) maintained the drug (then called Bendectin) was safe, but discontinued it in the face of prohibitive insurance and legal costs. Diclegis was approved by the FDA in 2013 for the treatment of NVP; currently it is the the only FDA-approved treatment for nausea and vomiting due to pregnancy.
- Ondansetron (Zofran) is used off-label for treatment for nausea and vomiting due to pregnancy. According to a recent web-based international survey of therapy use for NVP, ondansetron was the most frequently used conventional medication in the United States (Heitmann 2015); ondansetron use was approximately 10% in the survey sample.
- Metoclopramide (Reglan) is also used off-label for the treatment of NVP; in the United States metoclopramide is used in only the most severe cases. The safety of this medication during pregnancy has been examined however results are conflicting (Matok 2009).
- Promethazine (Phenergan, Phenadoz, Promethegan) is an antihistamine, which can be used to treat allergies an motion sickness. It can help control nausea, vomiting, and pain, and can also be used as a sedative or sleep aid (King 2009). Although it is unknown whether and how promethazine can harm an unborn fetus, promethazine is commonly prescribed to alleviate NVP.
- Methylprednisolone (Medrol, Solu-Medrol, A-Methapred) is a steroid used to treat inflammation, severe allergies, and chronic illnesses such as arthritis. Methylprednisolone has been used in patients with hyperemesis gravidarum, a severe form of NVP that leads to serious complications for both mother and fetus. Although concerns exist about association between oral clefts and methylprednisolone use in the first trimester, there is conflicting data on whether or at what point methylprednisolone can be harmful to a developing fetus (Niebyl, 2010).

Outcome Definition:

- Outcomes will include [See Appendix A for full list]:
  - Neural tube defects (ICD9 740.x-741.x, excluding congenital codes)
  - Orofacial clefts (ICD9 749.x, excluding congenital codes)
  - Circulatory system defects (ICD9 745.x-747.x, excluding congenital codes)
  - Renal collecting system anomalies (ICD9 753.x, excluding congenital codes)
  - Miscarriage and low birthweight / preterm delivery (ICD9 634 and 765, respectively)
  - Craniosynostosis (ICD9 756)
  - Musculoskeletal defects specific to feet (ICD9 754.x, excluding congenital codes).

- Outcomes will be identified using relevant diagnosis codes (ICD-9-CM)
- We will require that diagnoses and procedures be associated with claims for physician services or hospitalizations and found within 30 days of the delivery date on the mother's claims or within 365 days of the birth date on the infant's claims. Justification concerning similar studies of NVP medications and fetal outcomes is as follows:
    - Dinur and colleagues investigated fetal safety of macrolides by linking three computerized databases that drew direct information from original sources involving both mother and baby. In this study, information regarding malformations diagnosed in newborns or infants until the age of 12 months was collected from ICD9 database (Dinur 2013).
    - Mines and colleagues designed a linked database study, examining the association of topiramate usage in pregnancy and oral cleft birth prevalence, with diagnoses associated with medical claims found within the same parameters as our proposed study; "within 30 days of the delivery date on the mother's claims or within 365 days of the birth date on the infant's claims" (Mines 2014).
    - In a prospective observational study of the safety of ondansetron for NVP and associated major fetal malfunctions, Einarson and colleagues contacted women between 4-6 months after delivery to obtain outcome data related to the newborn (Einarson 2004).
- Potential cases identified with concurrent diagnoses of syndromic, genetic, or chromosomal defects will be excluded.

Inclusion Criteria:

- Continuous enrollment in the health plan ≥ 3 months prior to conception
- At least 365 days of post-delivery enrollment
- Maternal age 15-49 years old on the delivery date

Exclusion Criteria:

- Mother–infant pairs with a history of infection with any of the TORCH agents ("TORCH" is an acronym meaning (T)oxoplasmosis, (O)ther Agents, (R)ubella (also known as German Measles), (C)ytomegalovirus, and (H)erpes Simplex. Infection with any of these agents may cause a constellation of similar symptoms in affected newborns.)
- Women with exposure to thalidomide or isotretinoin, both potent teratogens, during the 6 months preceding the presumed conception date or at any point during the pregnancy

Covariates:

- Concomitant drug use:
    - SSRIs
    - Macrolide antibiotics
    - Prescription folic acid use
- Preexisting conditions that may be reasons for drug use:
    - Epilepsy (TPM)
    - A diagnosis of cancer within 6 months of pregnancy
    - Prior child with birth defect

- Socio-demographic variables:
  - Race/ethnicity
  - Maternal age
  - Maternal weight
  - Parity
  - Gender of the child
  - Geography
- Other maternal risk factors:
  - Hypertension
  - Diabetes
  - Prior preterm delivery
  - Multi-fetal pregnancy
- Calendar year of delivery
- Duration of claims history

Unless specified otherwise, covariates will be assessed using all available data prior to the start of pregnancy.

Statistical Analysis:

- The primary study design will be nested case-control study
- To address confounding by indication, each drug will be evaluated against a series of comparator groups (i.e. other prescription drugs for treatment of NVP)
- The primary reference group will be no use of prescription drugs for NVP
- Logistic regression models will be used to calculate odds ratios and 95% confidence limits

Power Calculations:

Using effect size estimates from the literature (OR=1.4 for cardiovascular defects, OR=1.8 for septum defects, and 1.9 for cleft palate), we calculated a range of sample sizes needed to achieve 80% power with alpha set to 0.05 to detect a difference between the groups. In these calculations, we assume that the sampling ratio ($N_{exposed}$ / $N_{unexposed}$) ranged from 0.05 to 0.10, which is aligned with the exposure rates from published studies. Depending on the outcome and the sampling ratio, we estimate that we would need between 1,657 and 6,655 exposed pairs and 16,996 to 128,708 unexposed pairs to detect a difference in risk should one exist.

Outcome Examples (Justification)	Odds Ratio*	Sampling Ratio	Exposed (N)	Unexposed (N)
Cardiovascular defect (Danielsson 2014)	1.422	0.05	N = 6,435	N = 128,708
		0.10	N = 6,655	N = 66,548
Septum defect (Danielsson 2014)	1.805	0.05	N = 3,172	N = 63,444
		0.10	N = 3,258	N = 32,582
Cleft palate (Anderka 2012)	1.909	0.05	N = 1,657	N = 33,138
		0.10	N = 1,700	N = 16,996

*per literature justification

Based on preliminary sample size estimates from Truven's database (from 2000 – 2012), we expect to have information on 207,272 mother/baby pairs that were exposed to zofran or its generic form, ondansetron at some point during pregnancy. This number will drop once we apply our filters limiting the population to first trimester exposure, maternal age, continuous enrollment, history of infections, and exposure to teratogens. On the other hand, it will increase to reflect the additional exposures of interest. However, given the magnitude of the sample size from which we are starting, we will be sufficiently powered to conduct subgroup analyses, looking at the relationship between the drugs and specific birth defects individually, as well as other sub-analyses, while maintaining our control for the appropriate confounders.

Limitations:

- Inability to control for OTC use of folic acid
- Inability to control for OTC use of antiemetics
- Inability to quantify NVP medication usage after the prescription is dispensed
- Only an estimated calculation of the first trimester

Appendix A

ICD-9 Codes	Descriptions
754.6 754.7	Certain musculoskeletal deformities (valgus deformities of feet, other deformities of feet/club foot, respectively)
756.0	Craniosynostosis
634.xx	Miscarriage
765.0 – 765.2x V21.30 – V21.35	Low birth weight/preterm delivery
753.3 753.4 753.5	Anomalies of urinary system (anomalies of the kidney, ureter, and bladder, respectively)
745.4 745.5 745.6	Cardiovascular defects (ventricular septal defect; atrial septal defect, ostium secundum type atrial septal defect; atrioventricular septal defect, respectively)
749.0-749.2 748.3	Craniofacial defects (orofacial cleft; cleft lip only; cleft lip with or without palate (CL/P); cleft palate only (CPO); laryngeal cleft, respectively)
740.0 740.1 740.2 741.0-741.9	Malformations of nervous system and/or neural tube defects (anencephalus; craniorachischisis; iniencephaly; spina bifida with and without mention of hydrocephalus, respectively)