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May 22, 2020

By E-mail and FDA Docket

Stacy Cline Amin, Esquire
Chief Counsel
Office of the Chief Counsel
U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Carol J. Bennett
Deputy Director
Office of Regulatory Policy
Center for Drug Evaluation and Research
U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Re: FDA Docket FDA-2019-P-5151

Dear Ms. Amin and Ms. Bennett:

I write regarding the citizen petition submitted by GlaxoSmithKline LLC ("GSK") on November 1, 2019 (docketed at FDA-2019-P-5151) regarding four categories of information concerning the use of a prescription drug Zofran (ondansetron) in pregnancy. GSK's citizen petition noted that FDA may be reviewing, together with Zofran's current NDA holder, Novartis, Zofran's safety profile and labeling as a result of newly available epidemiological studies and an assessment of Zofran's labeling by the Pharmacovigilance Risk Assessment Committee (PRAC).

Following the submission of GSK's citizen petition, FDA Chief Counsel Stacy Amin invited GSK and lawyers from the Plaintiffs' Steering Committee in *In re Zofran (Ondansetron) Products Liability Litigation*, No. 15-mdl-2657 (D. Mass.) to meet with FDA. In materials provided to FDA in connection with its meeting, the Plaintiffs' Steering Committee further referenced the PRAC assessment. *See* Docket Entry 73, Attachment 2. The PRAC assessment was also the subject of follow-up correspondence to Ms. Amin by GSK (April 15, 2020 letter from Amy Saharia, docketed at Docket Entry 76) and the Plaintiffs' Steering Committee (April 15, 2020 letter from Robert Jenner, undocketed).

For the reasons previously set forth by GSK, the PRAC assessment and the newly available epidemiological studies are not the subject of GSK's citizen petition. Nevertheless, in light of the foregoing, GSK deems it appropriate to inform FDA that GSK has recently corresponded with PRAC concerning its assessment. Specifically, on May 5, 2020, Dr. Sabine Luik, GSK's Chief Medical Officer, wrote to Dr. Sabine Straus and Dr. Martin Huber, Chair and Vice-Chair of PRAC, respectively, concerning the PRAC assessment and its discussion of Zambelli-Weiner A et al. *First Trimester Ondansetron Exposure and Risk of Structural Birth Defects*. Reprod Toxicol. 2019 Jan; 83: 14–20. I have attached Dr. Luik's letter to PRAC and the exhibits thereto to this letter.

Please do not hesitate to let me know if you have any questions.

Sincerely,

Amy Mason Saharia

Encl.

cc Plaintiffs' Steering Committee
FDA Docket FDA-2019-P-5151

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May 5, 2020

Dr. Sabine Straus, Chair of PRAC
nlhphar@cbg-meb.nl

Dr. Martin Huber, Vice-Chair of PRAC
martin.huber@bfarm.de

Dear Dr. Straus and Dr. Huber,

I write on behalf of GlaxoSmithKline (GSK) in relation to the "Updated Signal assessment report on birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications with ondansetron" prepared by the Pharmaceutical Risk Assessment Committee (PRAC) in 2019.[1] The report discusses a study authored by Dr. Zambelli-Weiner. Zambelli-Weiner A et al. *First Trimester Ondansetron Exposure and Risk of Structural Birth Defects*. Reprod Toxicol. 2019 Jan; 83: 14–20 (the "2019 Study").

As the original marketing authorization holder for Zofran (ondansetron) in the European Union, and elsewhere, GSK is involved in product liability litigation in the United States in relation to Zofran (the "U.S. litigation"). Through that litigation and the related discovery process, GSK has become aware of additional documents that contain information related to the Study. The documents in question include information that, as we understand it, PRAC requested from the lead author.

More specifically, as part of the product liability litigation in the U.S., GSK requested and obtained documents relevant for an evaluation of the reliability of the study and an understanding of Dr. Zambelli-Weiner's role as a paid consultant for lawyers representing claimants/plaintiffs against GSK in the U.S. litigation. Dr. Zambelli-Weiner was performing this role of paid consultant since 2014, including while she conducted the 2019 Study.[2]

GSK learned from these documents, in particular, that Dr. Zambelli-Weiner suggested the conduct of the 2019 Study to plaintiffs' lawyers. GSK also learned that the plaintiffs' lawyers funded the conduct of this study in the amount of $210,000.[3]

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[1] Updated Signal assessment report, available at https://www.ema.europa.eu/en/documents/prac-recommendation/updated-signal-assessment-report-birth-defects-following-utero-exposure-during-first-trimester_en.pdf ("PRAC Report").

[2] *See* 7/25/19 Order, attached as Tab 1; and 4/1/20 Order at 1, attached as Tab 2

[3] *See* 7/25/19 Order, attached as Tab 1; and 4/1/20 Order at 1, 7, Tab 2. As part of her initial consulting agreement with plaintiffs' lawyers in 2014, Dr. Zambelli-Weiner evaluated the state of the science relating to Zofran and

Based on the publication of the PRAC Report, GSK understands that the PRAC considered the 2019 Study during its evaluation of ondansetron's product labeling and posed certain questions to the author of that study, including whether the author considered a sensitivity analysis comparing the risk of birth defects with Zofran to that with other antiemetics. This is reflected in Section 3.1.1.1 of the PRAC Report at page 25 ("Did the authors consider a sensitivity analysis using women diagnosed with NVP/HG and treated with other antiemetic in pregnancy as a comparator?").

GSK considers that the documents that were very recently made public by the court overseeing the U.S. litigation are relevant to the PRAC's questions and analysis of the findings of the 2019 Study. In particular, the documents contain information that GSK believes is relevant to a full understanding of the background to the 2019 Study. GSK also believes that this information should be made available to the PRAC, as well as to the Co-Ordination Group for Mutual Recognition and Decentralised Procedures - Human (CMD(h)) as it was the recipient of the PRAC Report and the PRAC recommendations for consideration nationally by the EU Member States.

GSK wishes, therefore, to share the following documents for the PRAC and the CMD(h)'s consideration, as appropriate:

- Dr. Zambelli-Weiner's "Zofran Study – Brief Study Protocol," which describes the author's intent to conduct a sensitivity analysis "[t]o address confounding by indication, each drug will be evaluated against a series of comparator groups (i.e. other prescription drugs for treatment of NVP)." *See* Zofran Study – Brief Study Protocol at 4, attached as Tab 4.
    - **NOTE:** This sensitivity analysis is not referenced in the author's responses to PRAC's questions or in the publication of the 2019 Study.
- Unpublished analyses comparing Zofran to other prescription drugs for the treatment of NVP (anti-emetics). When compared to other prescription anti-emetics, there was either no association or a statistically significant decreased risk of cardiac and cardiac septal defects with Zofran use.
    - **NOTE:** These analyses were not referenced in the author's responses to PRAC's questions; in the published study; or in an on-line supplement to the published article.[4]
- An unpublished draft of Zambelli-Weiner 2019, prepared for submission to the New England Journal of Medicine. The unpublished draft describes the "medical administration" analysis as a "sub-analysis" and not a "primary analysis," as described in the final, published study.[5]
- An affidavit from Dr. Zambelli-Weiner in response to GSK's request for information regarding the underlying statistical coding and output for the study, in which she explains that: "When the Stata output was generated for the study as published in Reproductive Toxicology, to the best of my recollection the

proposed a nested case-control study as an "[a]dditional [a]venue [] for [i]nquiry" for plaintiffs' lawyers. *See* Causation Briefing Document, attached as Tab 3.

[4] *See* Unpublished Analyses, AZW-472 to AZW-488, attached as Tab 5.

[5] *See* New England Journal of Medicine Draft, attached as Tab 6.

results were copied and pasted into manuscript tables in real time. To my knowledge the Stata output was not printed out or saved electronically in any additional format."[6]

If you have questions about this information or the attached documents, please let me know.

Sincerely,

Sabine Luik, MD, MBA
Chief Medical Officer, Senior VP Global Medical, Regulatory and Quality
GlaxoSmithKline LLC

CC:
Ms. Laura Oliveira Santamaria
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[6] *See* Zambelli-Weiner Aff. (Nov. 6, 2019), attached as Tab 7.

Tab 1

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

IN RE: ZOFRAN (ONDANSETRON) PRODUCTS LIABILITY LITIGATION	)	**MDL No. 1:15-md-2657-FDS**
This Document Relates To:	)	
All Actions	)	

MEMORANDUM AND ORDER ON *IN CAMERA* PRODUCTION OF DOCUMENTS CONCERNING DR. APRIL ZAMBELLI-WEINER

SAYLOR, J.

This is a multi-district litigation ("MDL") proceeding arising out of product-liability claims that the use of the drug Zofran (ondansetron) by pregnant women caused certain types of birth defects in their children.

Defendant GlaxoSmithKline LLC ("GSK") has moved to compel the production of certain documents by plaintiffs and a third-party witness, April Zambelli-Weiner, Ph.D. Plaintiffs and Dr. Zambelli-Weiner have withheld the documents from production, contending that they are protected from discovery as attorney work product under Fed. R. Civ. P. 26(b)(3) and as consulting expert information under Fed. R. Civ. P. 26(b)(4)(D).[1]

Dr. Zambelli-Weiner is the co-author of an epidemiological study on which plaintiffs rely as evidence that Zofran causes birth defects. At the time she conducted the study, she was a paid consultant to plaintiffs' counsel. The study itself was funded by plaintiffs' counsel in the amount of $210,000. Dr. Zambelli-Weiner also participated, with plaintiffs' counsel, on a panel at a conference in Las Vegas concerning this litigation.

[1] Plaintiffs have also on occasion characterized the documents at issue as "privileged," but there is no evidence of an attorney-client relationship between plaintiffs' counsel and Dr. Zambelli-Weiner.

When counsel for GSK sought to depose her in this case, she sought a protective order, and submitted an affidavit that included a number of falsehoods. She claimed in that affidavit, among other things, that plaintiffs' counsel had paid her for other work, not for the study at issue. Her counsel, upon discovering the falsehoods, filed a corrective notice with the Court and withdrew his appearance.

The issue before the court is whether certain documents concerning the relationship between Dr. Zambelli-Weiner and plaintiffs' counsel, which have been provided to the Court for *in camera* review, should be produced to GSK. For the reasons set forth below, the Court concludes that the documents are not protected from discovery and should be produced.

I. Background

April Zambelli-Weiner, Ph.D., is a researcher and the founder, president, and principal epidemiologist of Translational Technologies International Health Research & Economics ("TTi"). (Docket No. 1271-1, *Curriculum Vitae*).

Dr. Zambelli-Weiner is the co-author of a study published in the journal of *Reproductive Toxicology*, titled "First Trimester Ondansetron Exposure and Risk of Structural Birth Defects." (Docket No. 1271-2).[2] That study, which has become a central piece of plaintiffs' experts' causation opinions in this litigation, found a statistically significant association between early pregnancy ondansetron (Zofran) exposure and specific structural birth defects. (*Id.*).

On August 10, 2018, in anticipation of Dr. Zambelli-Weiner's forthcoming study, GSK served a set of request for production of documents and interrogatories on plaintiffs. Plaintiffs were asked to produce, among other things, all communications between plaintiffs' attorneys and

[2] *See* Zambelli-Weiner A, et al., *First Trimester Ondansetron Exposure and Risk of Structural Birth Defects*, 83 Reproductive Toxicology (2019), 14-20.

Dr. Zambelli-Weiner or her company (TTi) concerning the then-unpublished study. (Docket No. 1406-1).

On September 10, 2018, plaintiffs' counsel objected to those requests, contending that the request called for information not discoverable under Fed. R. Civ. P. 26(b)(3) and 26(b)(4)(D), and provided no responsive information. (Docket No. 1406-2).

Meanwhile, on October 29, 2018, the journal *Reproductive Toxicology* published an abstract of the study, titled "First Trimester Ondansetron Exposure and Risk of Structural Birth Defects." (Docket No. 1271-2).

GSK then issued subpoenas seeking to depose Dr. Zambelli-Weiner and a co-author, Dr. Russell Kirby. On November 26, 2018, plaintiffs moved on her behalf for a protective order seeking to prevent the depositions. (Docket No. 1224). In their motion, plaintiffs characterized Dr. Zambelli-Weiner as a research scientist. They did not reveal that she was a paid consulting expert for plaintiffs, and did not cite or rely on the protections of Rule 26(b)(3) or 26(b)(4)(D).

The Court denied the motion for a protective order on December 7, 2018. The Court stated that it would permit a deposition focused principally on the financial aspects of her relationship with plaintiffs' counsel—that is, what money was paid and how; what communications with counsel, direct or indirect, were made; and how those payments and communications may have affected the study. (Docket No. 1243).

GSK then served a subpoena *duces tecum* on Dr. Zambelli-Weiner. That prompted her to move for a protective order on January 9, 2019. (Docket No. 1271). In support of that motion, she submitted an affidavit to the Court setting forth the factual basis of her claims. (Docket No. 1272).

On January 18, 2019, the Court denied the motion for a protective order. (Docket No.

1292).

That same day, counsel for Dr. Zambelli-Weiner filed an emergency motion to withdraw his appearance, notifying the Court that he had learned that "factual representations" made in her affidavit were "inaccurate." (Docket No. 1293). Counsel also filed a "Notice Advising the Court of Factual Inaccuracies" in the affidavit and motion for protective order. (Docket No. 1294). That notice included the following statements:

> 9. At the time the Motion for Protective Order and Affidavit were filed, all counsel for Dr. Zambelli-Weiner believed that the factual assertions contained in those documents were accurate. Thereafter, Attorney Marder received information indicating that certain of the factual assertions in Dr. Zambelli-Weiner's Motion for Protective Order and Affidavit were inaccurate.
>
> 10. As required by Massachusetts Rule of Professional Conduct 3.3 and Maryland Rule of Professional Conduct 19-303.3, Attorney Marder remonstrated with Dr. Zambelli-Weiner about the inaccuracies in the Motion for Protective Order and her Affidavit.
>
> 11. Undersigned Counsel can no longer represent to this Court that all of the factual assertions in Dr. Zambelli-Weiner's Motion for Protective Order and Affidavit are accurate.

(*Id.*).

As events later proved, the affidavit contained at least three false statements. First, Dr. Zambelli-Weiner swore that she had "not been retained as an expert witness by any party in this case." (Docket No. 1272). In fact, she had been a paid consulting expert to plaintiffs since at least December 9, 2014. Second, she swore that she had "no direct factual information about the litigation." (*Id.*). That, too, was false. Her work as a consulting expert clearly was focused on this litigation; moreover, she had participated in a presentation on the litigation with plaintiffs' counsel at a conference in Las Vegas called "Mass Torts Made Perfect" in October 2015. Third, she swore that none of the funds paid by the plaintiff law firms "were paid to directly fund the study," but were instead "paid to my company for unrelated work." (*Id.*). In fact, her company

was paid more than $200,000 for her work on the study.

In January 2019, *Reproductive Toxicology* published the full article reporting Dr. Zambelli-Weiner's study.

On January 29, 2019, through new counsel, Dr. Zambelli-Weiner served a supplemental affidavit on GSK. That affidavit acknowledged for the first time that TTi had entered into two "consulting arrangements" with Grant & Eisenhofer P.A., one of the law firms represented on plaintiffs' steering committee. (Docket No. 1406-5). According to the affidavit, the two "arrangements" covered two specific time periods: December 10, 2014, to "approximately" March 2015, and March 29, 2017, to "approximately" November 2017. (*Id.*).

On January 30, 3019, GSK served a second set of interrogatories and fifth set of requests for production on plaintiffs concerning Dr. Zambelli-Weiner. (Docket No. 1406-6).

On February 1 and 22, 2019, Dr. Zambelli-Weiner was deposed by GSK. Among other things, she testified that she had received $13,500 between December 2014 and March 2015 in her first consulting arrangement with Grant & Eisenhofer. She further testified that she had received approximately $200,000 for her second consulting arrangement with the firm.

On March 1, 2019, plaintiffs responded to GSK's second set of interrogatories and fifth set of requests for production concerning Dr. Zambelli-Weiner. In that response, plaintiffs stated, among other things, that "Plaintiffs' Leadership Attorneys paid $210,000 as financial support relating to a study that was ultimately completed and published by Zambelli-Weiner A, et al., ..." (Docket No. 1406-7).

On March 8, 2019, GSK moved to compel the production of full responses by plaintiffs and Dr. Zambelli-Weiner to its discovery requests. (Docket Nos. 1388, 1405).

On March 19, 2019, plaintiffs and Dr. Zambelli-Weiner filed a cross-motion for a

protective order, again contending that the documents are protected from discovery under Fed. R. Civ. P. 26(b)(3) and 26(b)(4)(D). (Docket No. 1411).

At the hearing on the motion to compel, the Court ordered Dr. Zambelli-Weiner and plaintiffs to produce the withheld documents for *in camera* review. The parties subsequently delivered their document production to the Court.

After reviewing the documents *in camera*, and for the reasons set forth below, the Court will direct that the documents are not protected as attorney work product or consulting expert information and should be produced to GSK.

II. Legal Standard

A. Rule 26(b)(3)

Fed. R. Civ. P. 26(b)(3) essentially codifies the work-product doctrine. It provides as follows:

> (3) ***Trial Preparation: Materials***.
>
> > (A) *Documents and Tangible Things*. Ordinarily, a party may not discover documents and tangible things that are prepared in anticipation of litigation or for trial by or for another party or its representative (including the other party's . . . consultant . . .). But, subject to Rule 26(b)(4), those materials may be discovered if:
> >
> > > (i) they are otherwise discoverable under Rule 26(b)(1); and
> > >
> > > (ii) the party shows that it has substantial need for the materials to prepare its case and cannot, without undue hardship, obtain their substantial equivalent by other means.
> >
> > (B) *Protection Against Disclosure*. If the court orders discovery of those materials, it must protect against disclosure of the mental impressions, conclusions, opinions, or legal theories of a party's attorney or other representative concerning the litigation.

Fed. R. Civ. P. 26(b)(3).

Rule 26(b)(3) is limited to "things that are prepared . . . by or for another party or its

representative." Fed. R. Civ. P. 26(b)(3)(A); *see also F.T.C. v. Grolier Inc.*, 462 U.S. 19, 25 (1983) (stating that "the literal language of the Rule protects materials prepared for any litigation or trial as long as they were prepared by or for a party to the subsequent litigation"). The reviewing court must consider two questions: First, were the documents prepared in anticipation of litigation? Second, has the party seeking discovery made a showing of substantial need and an inability without undue hardship, to obtain their substantial equivalent by other means? *See Hoffman v. Owens-Illinois Glass Co.*, 107 F.R.D. 793, 794-95 (D. Mass. 1985).

B. Rule 26(b)(4)(D)

Fed. R. Civ. P. 26(b)(4)(D) addresses discovery directed to consulting experts. It provides in relevant part as follows:

> (4) ***Trial Preparation: Experts.***
>
> . . .
>
> (D) *Expert Employed Only for Trial Preparation*. Ordinarily, a party may not, by interrogatories or deposition, discover facts known or opinions held by an expert who has been retained or specially employed by another party in anticipation of litigation or to prepare for trial and who is not expected to be called as a witness at trial. But a party may do so only:
>
> (i) as provided in Rule 35(b); or
>
> (ii) on showing exceptional circumstances under which it is impracticable for the party to obtain facts or opinions on the same subject by other means.

Fed. R. Civ. P. 26(b)(4)(D).

III. Analysis

A. Records Concerning the Las Vegas Conference

Some of the documents that plaintiffs have submitted for *in camera* review do not fall under the protections of Rule 26 at all. Specifically, the documents include what appear to be

slides from a presentation delivered by plaintiffs' counsel and Dr. Zambelli-Weiner at "Mass Torts Made Perfect," a conference for plaintiff attorneys held in Las Vegas in October 2015. The documents in question thus were not intended to remain confidential, and appear to have been disclosed to dozens, perhaps hundreds, of other persons.

Work-product protection can be waived by third-party disclosure. *Bryan Corp. v. Chemwerth, Inc.*, 296 F.R.D. 31, 38 (D. Mass. 2013). That waiver is not automatic, however, and occurs "only when documents are used in a manner contrary to the doctrine's purpose, when disclosure substantially increases the opportunity for potential adversaries to obtain the information." *Murphy v. Harmatz*, 2016 WL 7104831, at *6 (D. Mass. Dec. 5, 2016) (quoting *Bryan Corp.*, 296 F.R.D. at 40); *see also United States v. Massachusetts Inst. of Tech.*, 129 F.3d 681, 687 (1st Cir. 1997). "[T]he critical inquiry 'is whether disclosure of documents protected by the work product doctrine . . . [substantially] increases the opportunities for potential adversaries to obtain the information.'" *Bryan Corp.*, 296 F.R.D. at 40 (quoting *In re Raytheon Sec. Litig.*, 218 F.R.D. 354, 360 (D. Mass. 2003)).

Presenting materials at a public, or quasi-public, conference is surely antithetical to the basic premise of confidentiality. It also, no doubt, substantially increases the opportunities for potential adversaries, such as GSK, to obtain the information. The slides in question, therefore, are not protected confidential information under Rule 26(b)(3).

The documents also involve communications between plaintiffs' counsel and Dr. Zambelli-Weiner in October 2015, when she (according to plaintiffs) was no longer a consulting expert. Thus, the protections of Rule 26(b)(4)(D) likewise do not apply.

Accordingly, to the extent that the documents at issue consist of materials concerning Dr. Zambelli-Weiner's participation in the "Mass Torts Made Perfect" conference in Las Vegas in

October 2015, they are not shielded from discovery and should be produced.

B. Records Concerning Facts Known or Opinions Held as a Consulting Expert

Dr. Zambelli-Weiner is a consulting, not a testifying, expert. Under normal circumstances, "facts known" or "opinions held" by her would not be discoverable through a deposition or interrogatories. Fed. R. Civ. P. 26(b)(4)(D).

As a threshold matter, the issue before the Court involves the production of documents, not interrogatories or a deposition. It therefore appears (at least on its face) that the protection of Rule 26(b)(4)(D) as to discovery of "facts known or opinions held by" a consulting expert do not apply.

Furthermore, to the extent that the documents also involve communications between plaintiffs' counsel and Dr. Zambelli-Weiner when she was not a consulting expert—for example, documents created between March 2015 and March 29, 2017—Rule 26(b)(4)(D) does not apply.

In any event, (1) this matter clearly presents an "exceptional circumstance" within the meaning of Rule 26(b)(4)(D)(ii); (2) GSK has established a "substantial need" for the materials within the meaning of Rule 26(b)(3)(A)(ii); and (3) the protection of those rules has been waived by litigation misconduct.

As noted, the epidemiological study at issue is one of the central pieces of evidence supporting plaintiffs' proof of general causation; arguably, it is the most critical single piece. Plaintiffs' counsel paid for the study, and appear to have consulted with Dr. Zambelli-Weiner during the course of the study.

It is troublesome, to say the least, for a party to engage a consulting, non-testifying expert; pay for that individual to conduct and publish a study, or otherwise affect or influence the study; engage a testifying expert who relies upon the study; and then cloak the details of the

arrangement with the consulting expert in the confidentiality protections of Rule 26(b) in order to conceal it from a party opponent and the Court. The Court can see no valid reason to permit such an arrangement to avoid the light of discovery and the adversarial process. Under the circumstances, GSK has made a showing of substantial need and an inability to obtain these documents by other means without undue hardship.

Furthermore, in this case, the consulting expert made false statements to the Court as to the nature of her relationship with plaintiffs' counsel. The Court would not have been made aware of those falsehoods but for the fact that her attorney became aware of the issue and sought to withdraw. Certainly plaintiffs' counsel did nothing at the time to correct the false impressions created by the affidavit. At a minimum, the submission of those falsehoods effectively waived whatever protections might otherwise apply. The need to discover the truth and correct the record surely outweighs any countervailing policy in favor of secrecy, particularly where plaintiffs' testifying experts have relied heavily on Dr. Zambelli-Weiner's study as a basis for their causation opinions. In order to effectively cross-examine plaintiffs' experts about those opinions at trial, GSK is entitled to review the documents. At a minimum, the documents shed additional light on the nature of the relationship between Dr. Zambelli-Weiner and plaintiffs' counsel, and go directly to the credibility of Dr. Zambelli-Weiner and the reliability of her study results.

To the extent that the documents contain plaintiffs' counsel's "mental impressions, conclusions, opinions, or legal theories"—which is doubtful at best, based on the Court's review of the materials—that protection is likewise waived. Again, plaintiffs' counsel have provided more than $200,000 to fund Dr. Zambelli-Weiner's research on Zofran; plaintiffs' experts rely on that study in support of their causation opinions; and Dr. Zambelli-Weiner has not been

forthcoming with the Court about that funding and her relationship to this litigation. Again, in order to be able to effectively cross-examine plaintiffs' experts about their causation opinions, GSK is entitled to a complete understanding as to the relationship between plaintiffs' counsel and Dr. Zambelli-Weiner.

In short, the documents that have been produced *in camera* are not protected from discovery, either as attorney work product or consulting expert information. The Court makes no finding as to the admissibility of the documents at trial.

IV. Conclusion

For the foregoing reasons, Dr. Zambelli-Weiner and plaintiffs are ordered to produce the responsive set of documents, previously produced to the Court for *in camera* review, to counsel for GSK within 7 days of this order, or by August 1, 2019.

So Ordered.

/s/ F. Dennis Saylor IV
F. Dennis Saylor IV
United States District Judge

Dated: July 25, 2019

Tab 2

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

IN RE: ZOFRAN (ONDANSETRON) PRODUCTS LIABILITY LITIGATION	)	**MDL No. 1:15-md-2657-FDS**
This Document Relates To:	)	
All Actions	)	

ORDER ON DEFENDANT'S MOTION TO DE-DESIGNATE CERTAIN DOCUMENTS AS CONFIDENTIAL UNDER THE PROTECTIVE ORDER

SAYLOR, C.J.

This is a multi-district litigation ("MDL") proceeding arising out of product-liability claims that the use of the drug Zofran (ondansetron) by pregnant women caused birth defects in their children.

Defendant GlaxoSmithKline LLC ("GSK") has moved to "de-designate"—that is, no longer treat as confidential under the relevant protective order—four documents that were produced by a third-party witness, April Zambelli-Weiner, Ph.D. She is the co-author of an epidemiological study that plaintiffs cite as evidence that Zofran causes birth defects. At the time she conducted the study, she was a paid consultant to plaintiffs' counsel. The study itself was funded by plaintiffs' counsel in the amount of $210,000. Dr. Zambelli-Weiner also participated, along with plaintiffs' counsel, on a panel at a conference in Las Vegas concerning this litigation.

The Court previously ordered Dr. Zambelli-Weiner to produce several documents concerning that study and her relationship with plaintiffs' counsel. *See In re Zofran (Ondansetron) Prod. Liab. Litig.*, 392 F. Supp. 3d 179 (D. Mass. 2019). The history of her

involvement in this litigation is set forth in greater detail in that order. *See id.* at 182-84.

The present issue is whether four of the documents produced by Dr. Zambelli-Weiner pursuant to subpoena should continue to be designated as confidential. GSK contends that the documents were improperly designated, and, alternatively, that their "de-designation" is necessary to reveal information about the study that would be material to the public, including medical researchers and regulatory agencies.

On May 18, 2016, the Court issued MDL Order No. 13, which governs the discovery of confidential and privileged materials in this litigation. (*See* MDL Order No. 13 (Dkt. No. 242)). Under the terms of that order, a party may designate any documents or material as "confidential" if it reasonably and in good faith believes that it is confidential information. (*Id.* at 1-2). That order set forth several examples of confidential information entitled to protection. (*Id.*). It also provided that "[i]f, at any time, a Party in good faith objects to a Confidentiality Designation" and the parties dispute that designation, "the disputing Party may apply by motion to the Court for a ruling as to whether the designated Discovery Material may properly be treated as confidential." (*Id.* at 8). In that event, "[t]he designating party shall have the burden of proof . . . to establish the propriety of its Confidentiality Designation." (*Id.*). Materials that are properly designated as confidential may nevertheless be disclosed by order of the Court. (*Id.* at 9-10).

GSK has objected to the confidentiality designation of four documents: (1) a Zofran study protocol prepared by Dr. Zambelli-Weiner; (2) unpublished analyses that compared the birth defects risks associated with Zofran to those with other anti-emetic medications; (3) a draft of Dr. Zambelli-Weiner's study prepared for submission to the New England Journal of Medicine; and (4) a "Causation Briefing Document" prepared for plaintiffs' counsel by Dr.

Zambelli-Weiner. (*See* GSK's Mem. (Dkt. No. 1819), Exs. 1-4).

At the outset, none of the documents at issue are of the type ordinarily considered confidential. They do not, for example, contain sensitive personal, financial, or medical information. Dr. Zambelli-Weiner contends in general terms that they all include confidential business and proprietary information, but she does so in a merely conclusory fashion. *Cf. Anderson v. Cryovac, Inc.*, 805 F.2d 1, 7 (1st Cir. 1986). Moreover, it is unclear how or why that is true. She is not, for example, engaged in the business of conducting research to develop a pharmaceutical drug or other proprietary medical product or device. Indeed, her research appears to be unrelated to any proprietary or business enterprise of any kind, except to the extent she is acting in her capacity as a paid consultant for plaintiffs' counsel. As the Court noted in its earlier order, her misrepresentations to the Court concerning the nature of that relationship at the very least diminish whatever discovery protections might otherwise apply. *See In re Zofran*, 392 F. Supp. 3d at 186. Furthermore, she has not identified how the disclosure of the disputed documents to the public could prejudice her proprietary or business interests in any way.

Dr. Zambelli-Weiner further complains that GSK seeks to disclose the documents not to protect public health and safety, as it contends, but to promote its own litigation strategy and self-interest. That may well be true. But the motive of the party seeking disclosure is not the critical inquiry; private litigants are almost always acting in their own self-interest. Rather, the issues are whether the documents at issue were properly designated as confidential in the first instance, and if they were, whether de-designating them is nevertheless justified under the circumstances.

The first document is the Zofran study protocol, which sets forth the research plan for how Dr. Zambelli-Weiner and her co-authors intended to conduct their study. She first contends

that the protocol has never been published before. But that is not a basis to keep it confidential; indeed, based on multiple sources—including the journal that later published the study and the International Society of Pharmacoepidemiology ("ISPE"), of which she is a member—it appears that researchers in her field are routinely encouraged to publish such protocols. (*See* GSK's Mem., Ex. 14 at 13-14, Ex. 15 at 130:20-23, Ex. 16 at 5).[1][2]

Dr. Zambelli-Weiner further contends that the study protocol also includes proprietary plans for other, future research. However, the document that she refers to in support of that argument is an entirely different document—one that she claims is a later version of the protocol, but which is dated more than a year later and bears little resemblance to the document at issue. (*Compare* GSK's Mem., Ex. 1 *with* Zambelli-Weiner Surreply (Dkt. No. 1848), Ex. E). It is therefore unclear whether her plans for future research topics are set out in the document. If they are, it would appear to be reasonable to redact any such material prior to public disclosure. Otherwise, she has not demonstrated why the document should remain confidential.

The second document consists of the unpublished analyses comparing Zofran's birth-defect risks to those of other anti-emetic medications. It is doubtful that the document was properly deemed confidential in the first instance. It is true that it includes a header that deems it "Confidential & Proprietary" and that it was saved in a folder entitled "Internal deliverables." (*See* GSK's Mem., Ex. 2). But under ISPE guidelines, researchers have an ethical obligation to

[1] This type of study protocol, which is addressed to epidemiological research and appears unrelated to product development, is distinguishable from the "[p]roprietary design, development, research, and testing regarding products" that was defined as Confidential Information under MDL Order No. 13. (*Id.* at 2).

[2] According to GSK, the reason that study protocols are typically made public is so that other researchers can verify whether a study's authors have adhered to the protocol or adequately justified any departures from it. (See GSK Mem., Ex. 17 at 5-6). *See* Charles J. Walsh & Marc S. Klein, *From Dog Food to Prescription Drug Advertising: Litigating False Scientific Establishment Claims Under the Lanham Act*, 22 SETON HALL. L. REV. 389, 431 (1992) (explaining that adherence to a chosen study protocol "is essential to avoid 'data dredging'—looking through results without a predetermined plan until one finds data to support a claim").

report "findings that could have a significant impact on public health." (GSK's Mem., Ex. 16 at 8). And Dr. Zambelli-Weiner herself has stated that information comparing the risk of birth defects from ingesting Zofran to that of other antiemetic medications, such as that contained in this document, is the type of important public-health information that ordinarily should be shared. (GSK's Mem., Ex. 15 at 200:22-201:8).

In any event, even if the analyses were properly deemed confidential in the first instance, their disclosure is warranted here. The published version of Dr. Zambelli-Weiner's study emphasized that "alternative therapies" to Zofran exist and that medical practitioners should rely on "the best data to inform policy and practice." (GSK's Mem., Ex. 18 at 19). The unpublished analyses that compare the risk of ingesting Zofran to the risk of ingesting other anti-emetic medications thus seem to be potentially material omissions from her published study. Indeed, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency specifically asked Dr. Zambelli-Weiner whether she had performed such analyses. (GSK's Mem., Ex. 6). In her response to PRAC, she did not reveal that these unpublished analyses existed. (*See id.*). Two months later, PRAC recommended a change to Zofran's label, relying in part on her study. (*See* GSK's Mem., Ex. 5 at 98). Similarly, plaintiffs have indicated that they intend to submit that study to the FDA as it considers GSK's citizen petition. (*See* Pls. Mem. (Dkt. No. 1745) at 10). As both PRAC's inquiry and Dr. Zambelli-Weiner's own testimony indicate, these regulatory authorities would likely want to know of any data that may show Zofran is safer (or more dangerous) than other anti-emetics. Thus, it appears that there would be considerable public benefit in disclosing the analyses. *See Anderson*, 805 F.2d at 8 (calling public-health concerns a "compelling justification" for disclosing confidential information).[3]

[3] Again, Dr. Zambelli-Weiner argues that GSK has ulterior motives to de-designate this document because altering regulators' decisions may affect its business and even its liability in this matter. Even assuming the truth of

And again, Dr. Zambelli-Weiner has offered no compelling countervailing interest in keeping the analyses confidential.

The third document is the draft of Dr. Zambelli-Weiner's study that was prepared for submission to the New England Journal of Medicine. Dr. Zambelli-Weiner contends that this is an internal draft shared between her and her co-authors. (*See* GSK's Mem., Ex. 4). While that appears to be true, she does not explain how any differences between this draft and the study as it was later published could constitute proprietary business information, or describe any actual prejudice that might result from its disclosure. Thus, she has failed to demonstrate why the document should continue to bear the "confidential" designation.

The fourth document is a research brief prepared for plaintiffs' counsel by Dr. Zambelli-Weiner. It appears that Dr. Zambelli-Weiner prepared the brief pursuant to a consulting arrangement with the law firm of Grant & Eisenhofer, P.A., which is counsel to plaintiffs in this matter. (*See* Zambelli-Weiner Aff. (Dkt. No. 1406-5) ¶¶ 1-2; GSK's Mem., Ex. 3). The brief summarizes the state of the evidence as to whether Zofran may cause birth defects. It appears that it was created to assist plaintiffs' counsel in devising its litigation strategy and does not appear intended for publication. (*See* GSK's Mem., Ex. 3). Thus, it is plausibly proprietary and non-public business information, and the Court will assume it was properly designated in the first instance.

However, that does not mean it should remain confidential. As with the unpublished analyses, the document is almost certainly relevant to scientists and regulatory authorities evaluating the design and implementation of Dr. Zambelli-Weiner's study. Those authorities

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that statement, there are still persuasive public-interest reasons to disclose the document—namely, permitting those regulators to perform their duties more effectively by providing a more complete picture of the relevant research.

would likely consider it material that four years before the study's publication, and as part of a paid consulting arrangement with plaintiffs' counsel, she proposed conducting a similar study as an "[a]dditional [a]venue[] for [i]nquiry." (GSK's Mem., Ex. 3 at 11). Dr. Zambelli-Weiner contends that her financial relationship with plaintiffs' counsel was sufficiently disclosed in the conflict of interest statement in her published study. But that statement was only one sentence long, and indicated only that her organization had received funds from plaintiffs' counsel. It did not state or suggest that Dr. Zambelli-Weiner had consulted with counsel as to the nature of the study itself, or provide any detail about the extent of that relationship. (*See* GSK's Mem., Ex. 18 at 19). This document sheds additional light on that relationship and therefore its disclosure will also be permitted.

For the foregoing reasons, Defendant's Motion to De-Designate Certain Documents as Confidential Under the Protective Order is GRANTED. The four documents described in this Memorandum and Order shall not be considered "confidential" pursuant to MDL Order No. 13, issued May 18, 2016, except with respect to any possible redactions that Dr. Zambelli-Weiner may make that are consistent with this Memorandum and Order.

So Ordered.

/s/ F. Dennis Saylor IV
F. Dennis Saylor IV
Chief Judge, United States District Court

Dated: April 1, 2020

Tab 3

DATE: **February 4th, 2015**
TO: **Thomas V. Ayala**
Senior Counsel
Grant & Eisenhofer P.A.
FROM: **April Zambelli-Weiner, Ph.D. - TTI**
RE: **Zofran**

Causation Briefing Document: Zofran (Ondansetron) and Cardiac Birth Defects

Introduction

All epidemiologic studies can be characterized by strengths and weaknesses that influence the results and interpretation of results to varying degrees. A number of methodological issues inherent in epidemiologic research may preclude the identification of positive associations, attenuate the risk estimates or reduce the precision of risk estimates. Examples include insufficient statistical power (too few study subjects), inadequate length of follow-up, bias and uncontrolled confounding, among others.

Three (3) epidemiological studies examined the association between prenatal exposure to Zofran and risk of cardiac malformations (Pasternak et al. 2013; Andersen et al. 2013; Danielsson et al. 2014). These studies have some limitations that would serve to bias the results to the null, including: exposure misclassification and limited follow-up. Despite these limitations tending to bias the results towards the null, all three studies show elevated risk ratios for cardiac malformations, including risk ratios greater than 2.0 for specific septal defects. An overview of each study is presented below followed by a separate evaluation section.

Overview of Epidemiology Studies

Pasternak et al. 2013

This historical registry-based Danish cohort study examined the use of Ondansetron during pregnancy and risk of adverse fetal outcomes defined as: spontaneous abortion, stillbirth, any major birth defect, preterm delivery, low birth weight, and small size for gestational age. Over 608,385 pregnancies in Denmark from the Medical Birth Registry and National Patient Register that resulted in a single live birth, still birth, or ended with any abortive outcome between January 1, 2004 through March 31, 2011 were considered in the study. Women who were exposed to Ondansetron and those who were not exposed were included in matched analyses of spontaneous abortion (1,849 exposed women vs 7,396 unexposed women), still birth (1,915 vs 7,660), any birth defect (1,233 vs 4,932), preterm delivery (1,792 vs 7,168) and birth of infants at low birth weight and small for gestational age (1,784 vs 7,136). The unexposed group was defined as women who did not fill a prescription for Ondansetron during the exposure time window. The exposure time window was defined as the first trimester (through 12 gestational weeks) for any major birth defect. Prescription data was obtained from the National Prescription Registry. The timing of exposure was defined by the date the prescription was filled. Estimates were adjusted for hospitalization, nausea and vomiting during pregnancy and the use of other antiemetics.

Risk estimates for cardiac birth defects were not presented in the study; however, counts were provided in the supplemental material. Risk estimates were calculated and were elevated for septal defects, excluding ASD, but none of the results were statistically significant due to small sample sizes. Specifically, mothers taking Ondansetron during the first trimester, compared to women who did not take Ondansetron, were: 22% more likely to have offspring with any septal defect; 41% more likely to

have offspring with a VSD and greater than 4-times more likely to have offspring with an AVSD (however the latter was based on only 2 cases).

Andersen et al. 2013

In this Danish nationwide registry-based cohort study, the relationship between Ondansetron use during the first trimester and subgroups of congenital malformations was examined. The results of this study have not yet been published as a manuscript; they are presented in abstract form from the 29th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, August 28, 2013, Montréal, Canada. All women giving birth in Denmark between 1997 and 2010 were included in the study. These women were identified using the same Medical Birth Registry examined in Pasternak et al. 2013, and all offspring with a record of congenital malformation were identified using the National Hospital Register. All of the major malformations and subgroupings used in this study followed the EUROCAT classification system. Exposure was defined as filling a prescription during the first trimester and prescription data were obtained from the National Prescription Registry. A total of 903,207 births were identified in the study period and 1368 women filled a prescription for Ondansetron in the first trimester, of which 4.7% had an offspring with a congenital malformation compared to 3.5% in the unexposed group. The adjusted odds ratio (OR) of having an offspring with any cardiac defect was 1.6 (95% CI, 1.1-3.1). The risks for specific septal defects were much higher: ASD, OR=2.1 (95% CI, 1.3- 3.6); VSD, OR=2.3 (95% CI, 1.2-4.2); and AVSD, 4.8 (95% CI, 1.5-15.1). These results indicate that mothers who took Ondansetron in the first trimester have a 2- to 4-fold greater risk of having a child with a septal defect compared to mothers who did not take Ondansetron in the first trimester.

Danielsson et al. 2014

This Swedish registry-based case-control study investigated the teratogenic risks associated with Ondansetron use during pregnancy and risk of cardiac congenital malformations, specifically. The Swedish Medical Birth Registry combined with the Swedish Register of Prescribed Drugs were used to identify 1,349 infants born to women who had taken Ondansetron in early pregnancy, from 1998-2012. Exposure was defined as Ondansetron use in "early pregnancy," a term that is not explicitly defined in the manuscript. One might infer from the introduction that "early pregnancy" means first trimester exposure but it is unclear from the published manuscript. Exposure was assessed in two ways: by direct interview at the prenatal visit around weeks 10-12 and through the Swedish prescription register. The total number of births in the study was 1,501,434 infants, and 43,658 had malformations classified as major (2.9%). Among the major malformations, 14,872 had cardiovascular defects (34%) and 10,491 had a cardiac septum defect (24%).

The results from the study indicated statistically significantly elevated risk for cardiovascular defects and septal defects, specifically, for women taking Ondansetron versus those who did not. The risk estimate for any cardiovascular defect was 1.62 (1.04–2.14), indicating that mothers who took Ondansetron during early pregnancy had a 62% increased risk of having offspring with a cardiovascular defect compared to those who did not take Ondansetron during early pregnancy. Further, mothers who took Ondansetron had a greater than 2-fold increased risk in having an offspring with a septal defect, specifically, compared to mothers who did not take Ondansetron (RR=2.05; 95% CI, 1.19–3.28). Sensitivity analyses were conducted to control for confounding by indication. Specifically, risk estimates were calculated for women filling prescriptions for meclizine and showed no association for any malformation group, indicating that confounding by indication is not a problem in this study population.

Evaluation of Epidemiological Studies

Exposure misclassification can happen in various ways in epidemiological studies of drug exposures and birth defects (and cardiac malformations specifically), depending upon how exposure is defined. First, because the outcome of interest is a congenital malformation, the only relevant maternal exposures are those that occur during organogenesis, and development of the heart specifically. Even first-trimester exposure to Ondansetron that occurs after this window of development would be non-relevant and violate the temporality criterion of a causation analysis. Classifying individuals as exposed when they were not in fact exposed within the relevant developmental window would serve to underestimate the true effect of Ondansetron on cardiac birth defects. Organ formation begins 3 weeks after fertilization in a normal human pregnancy. The heart is the first organ to form during embryogenesis, and it begins its formation generally by about day 16 or 17 of gestation. The heart is also the first organ that becomes functional in the vertebrate embryo and it begins to pump fluid through blood vessels by day 20.

As seen in the chart below, the heart is not finished developing until approximately week 9. From an epidemiological study perspective defining exposure as during the entire first trimester creates the possibility that some women may have taken the drug only during the non-developmental period (9-12 weeks).

Developmental Timeline of Human Heart Embryology[1]	
Day	**Developmental Process**
0	Fertilization.
1-4	Cleavage and movement down the oviduct to the uterus.
5-12	Implantation of the embryo into the uterus.
13-14	Primitive streak formation (midstreak level contains precardiac cells).
15-17	Formation of the three primary germ layers (gastrulation): ectoderm, mesoderm, and endoderm. Midlevel primitive streak cells that migrate to an anterior and lateral position form the bilateral *primary heart field*.
17-18	Lateral plate mesoderm splits into the somatopleuric mesoderm and splanchnopleuric mesoderm. Splanchnopleuric mesoderm contains the myocardial and endocardial cardiogenic precursors in the region of the primary heart field.
18-26	Neurulation (formation of the neural tube)
20	Cephalocaudal and lateral folding brings the bilateral endocardial tubes into the ventral midline of the embryo.
21-22	Heart tube fusion.
22	Heart tube begins to beat.
22-28	(3–4 wk) Heart looping and the accretion of cells from the *primary* and *secondary heart fields.*
22-28	(3–4 wk) *Proepicardial cells* invest the outer layer of the heart tube and eventually form the epicardium and coronary vasculature.
22-28	(3–4 wk) Neural crest migration starts.
32-37	(5–6 wk) *Cardiac neural crest* migrates through the aortic arches and enters the outflow tract of the heart.
57+	(9 wk) Outflow tract and ventricular septation complete.

[1] Adapted from Handbook of Cardiac Anatomv, Physiologv, and Devices. laizzo, P.A (Ed.) 2005, Hardcover

For studies that rely upon prescription data, there is always the risk of exposure misclassification related to non-compliance or non-utilization. Specifically, some individuals will fill a prescription but not actually take the medication, or will not take it according to the prescription. In these instances, individuals will be classified as exposed who are in fact non-exposed (or exposed to a lesser degree). This can also serve to bias the risk estimates towards the null. Estimates of medication non-adherence rates typically range from 30% to 60%, depending upon the condition, the treatment, the patient, and the setting (Meichenbaum, 1987). As an example, one study (Keene, 2005) found that approximately 54% of patients initiating SSRI therapy were non-compliant over 6 months. A separate study (Chan, 2012) showed that 42% of cancer patients were non-compliant with the dose protocol for an antiemetic drug. The Andersen, Pasternak and Danielsson studies all relied upon prescription registry data for exposure information and, therefore, the possibility for exposure misclassification exists. The effect of exposure misclassification in these studies would be to bias the results towards the null, as some individuals being classified as exposed would actually be unexposed and this underestimates the risk.

Another methodological limitation related to exposure is the use of drug-exposed individuals in the control group. In a cohort study, the unexposed group should have the same baseline risk of the outcome as the exposed group, other than the effect of the exposure itself. If exposure to other drugs during pregnancy is associated with an increased risk of birth defects, the risk ratios in the study may be under-reported, creating the false impression that the risk of the outcome in the Ondansetron group as compared to the unexposed group is lower than the true risk ratio. In fact, we know this to be the case, as the utilization of SSRI antidepressants in pregnancy is relatively common and certain SSRIs, such as Paxil, have been shown to be associated with increased risk of cardiac malformations. It is unclear from the three published studies what other drugs women in both the exposed and unexposed groups may have been taking.

Length of follow-up is a characteristic of epidemiological study design that must be considered, both in the planning of a study and in the evaluation of existing studies. Length of follow-up should be chosen based on the objectives of the study (e.g. efficacy, patient safety) and taking into consideration the mechanisms by which the exposure may exert its effects. In the study by Pasternak et al., follow-up was only done one year after birth, which means that some congenital cardiac malformations, such as VSD and ASD, may not have been detected[2]. A short follow-up period such as this will underestimate the prevalence of congenital cardiac defects, as some defects are not detected until later in life. The consequence of having too short a duration of follow-up is reduced power to detect a true association.

Despite these limitations which would serve to bias the results towards the null or reduce the power of the study (and precision of the risk estimates), all three studies show elevated risk ratios for cardiac malformations, including risk ratios greater than 2.0 for specific septal defects. Due to the small

[2] "Thirteen heart defects have so far come to light among the 14 572 children born between 1996 and 2003 when they were more than 12 months old. VSDs accounted for a third of these late diagnoses." C Patton, E Hey. How effectively can clinical examination pick up congenital heart disease at birth? Arch Dis Child Fetal Neonatal Ed 2006;91:4 F263-F267

"Furthermore, because an ASD is usually asymptomatic and has murmurs that are often soft, these defects frequently do not lead to early diagnosis or referral. This is why many of these subjects present in adult life (2-3), so the incidence in childhood usually underestimates the true incidence of the lesion." Hoffman J, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol.*2002;39(12):1890-1900. doi:10.1016/S0735-1097(02)01886-7.

number of epidemiological studies specifically addressing Ondansetron and cardiac birth defects (and the small sample sizes underlying those studies), a weight-of-evidence approach is necessary. Consideration of mechanistic data and data in humans for similar prenatal drug exposures will be important.

Causation Assessment Using Bradford Hill Paradigm

1. **Strength of the Association (Risk Ratios and 95% Confidence Limits)**
   - **a.** Pasternak et al. 2013 [Denmark, 2004-2011]
     - VSD/ASD/AVSD combined, RR=1.22 (0.62-2.39)
     - VSD, RR=1.41 (0.56-3.57)
     - ASD, RR=0.88 (0.30-2.62)
     - AVSD, RR=4.0 (0.25-63.91, based on 2 cases)
     - Risk estimates calculated from supplemental material
   - **b.** Andersen et al. 2013 [Denmark, 1997-2010]
     - Heart defects, OR=1.6 (1.1-3.1)
     - ASD, OR=2.1 (1.3-3.6)
     - VSD, OR=2.3 (1.2-4.2)
     - AVSD, OR=4.8 (1.5-15.1)
   - **c.** Danielsson et al. 2014 [Sweden, 1998-2012]
     - Cardiovascular defect, OR=1.62 (1.04-2.14)
     - Septum defect, OR=2.05 (1.19-3.28)
   - **d.** Results are particularly compelling for septal defects and AVSD, in particular, where both studies examining that outcome showed risks for mothers taking Ondansetron to be >4-fold greater than those who did not take it.

2. **Consistency of the Association**
   - **a.** There have only been a small number of studies, but these have demonstrated consistently elevated risk ratios.

3. **Specificity**
   - **a.** Not necessary to establish causation – and one of the weakest of Hill's guidelines
   - **b.** Teratogens are capable of causing multiple birth defects, and birth defects often do not occur in isolation.
   - **c.** The grouping of birth defects in epidemiological studies is possible because specificity is not a necessary criterion to establish causation.

4. **Temporality**
   - **a.** Established generally for exposure in the first trimester, but this is not the most accurate or restrictive period that could be applied.
   - **b.** The relevant exposure window will depend on the outcome of interest and the timing of formation/differentiation for that organ system.

c. Organs are typically at their most susceptible stage early in their differentiation, so it is possible that prolonged exposure to a teratogen may affect numerous organs, each at its own critical stage of differentiation or development.

d. Exposure to teratogenic agents during the embryonic period has the greatest likelihood of causing a structural anomaly, although the pattern of defects produced depends upon which systems are differentiating at the time of exposure.

5. Dose Response

a. Most studies define exposure as yes/no, sometimes during a specified timeframe (e.g. first trimester exposure), therefore dose information is largely unavailable.

b. Filling one prescription is typically how exposure is defined in the epidemiological studies; no data on actual use/ingestion is available.

c. There appears to be a small range of doses (4•8 mg orally every 8 hours as needed) for which physicians are prescribing Ondansetron in pregnancy (Badell, 2006).

6. Biological Plausibility

Three possible mechanisms of cardiac malformation have been identified that support a causal relationship between maternal first-trimester Ondansetron exposure and cardiac birth defects in offspring.[3]

a. Perturbations of non-neural serotonin regulated migration of cardiac neural crest cells

- The cardiac neural crest develops into melanocytes, cartilage, connective tissue and neurons of some pharyngeal arches. This gives rise to regions of the heart such as the musculo-connective tissue of the large arteries, and part of the septum, which divides the pulmonary circulation.
- Serotonin promotes neural crest cell migration and inhibition of serotonin transport causes craniofacial malformations. Neural crest progeny are critical elements in the formation of the peripheral nervous system, the cardiac outflow tract and craniofacial features. The wide distribution of neural crest cells in the organism and their high rate of proliferation make neural crest progeny (including cardiac tissue) vulnerable to environmental insults and genetic mutations. (Sieber-Blum, 2002)
- Serotonin can also regulate cell proliferation, cell movements and cell differentiation. Serotonin is required for embryonic heart development. Genetic ablation of the 5-HT2B receptor (serotonin receptor 2B) leads to partial embryonic and postnatal lethality with abnormal heart development. (Etienne et al., 2003)

b. Blocked serotonin receptors

- 5-HT increases the proliferation of fetal heart cells. Abnormal 5-HT level or misuse of 5-HT uptake blocker may alter heart development. (Sari, 2003)
- Overexpression of 5-HT2BR leads to hypertrophic cardiomyopathy and is associated with altered mitochondrial function in mice. (Nebigil, 2003)

[3]Results are from a preliminary literature search and not meant to be exhaustive of all available literature on potential mechanisms of action (MOA) or these MOAs, in particular.

- 5HT3 receptors mediate Bezold-Zarish reflex, which is an autonomic reflex consisting of bradycardia, hypotension and apenia. Suppression of this reflex by Zofran leads to tachyarrhythmias. (Chandrakala, 2008)
- 5HT3 receptor blockade could possibly lead to unopposed action of 5HT2 and 5HT4 receptors , resulting in tachyarrhythmias and hypertension. (Chandrakala, 2008)

c. QT prolongation

- It is established that ondansetron causes QT prolongation. (Hafermann, 2011)
- Antepartum use of selective serotonin-reuptake inhibitor antidepressants is associated with QT interval prolongation in exposed neonates. (Dubnov-Raz, 2008)
- There is an increased prevalence of septal heart defects among children whose mothers were prescribed QT prolongating drugs (SSRIs) in early pregnancy. (Pedersen, 2009)

7. Coherence

a. Associations have been observed between first trimester exposure to other drugs that cause QT-interval prolongation

- SSRIs (Paxil, Celexa) are known to both elongate the QT interval and cause congential malformations in the fetus. This includes heart defects. (Wogelius, 2006 and Pedersen, 2009)
- Anti-obesity drugs (sibutramine) have been shown to elongate QT interval and have also been linked to increased risk for cardiac defects. (Kallen, 2013)

b. Associations have been observed between insults to the neural crest and cardiac defects.

- Studies have shown that neural crest progeny are critical elements in the formation of the peripheral nervous system, the cardiac outflow tract and craniofacial features. (Sieber Blum, 2002 and Keyte, 2012)
- Serotonin is known to play a role in neural crest migration. (Sieber Blum, 2002)

8. Experimental Evidence

a. This tenet is also known as challenge – dechallenge - rechallenge. It is not applicable here because the impact of intervention, or removal of the exposure has not been tested. The patient insert (PI) states: "Reproduction studies have been performed in pregnant rats and rabbits at daily oral doses up to 15 and 30 mg/kg/day, respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to Ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed."

b. There are many reasons why animal studies may not be predictive of risk in humans, including but not limited to differences in drug metabolism and genetics. (Bracken 2009)

c. The reported lack of fetal harm in exposed rats and rabbits is not necessarily inconsistent with the presence of an increased risk of harm in human fetuses. In fact, the absence of an effect in animals should not be interpreted as evidence for no effect in humans. There are many examples of exposure scenarios where animal and human data were strikingly dissimilar. Thalidomide is a well-known example of a case where a drug was teratogenic in humans (causing congenital defects) but fairly extensive animal data failed to produce the same effect. (Shanks et al. 2009)

9. **Analogy**
    - **a.** As stated above, associations have been observed between first trimester exposures to other drugs that cause QT-interval prolongation.
    - **b.** As stated above, associations have been observed between insults to the neural crest and cardiac defects.

10. **Alternative Explanations**
    - **a.** Genetics
    - **b.** Confounding by Indication
        - Confounding by indication can be described briefly a type of bias wherein a condition or symptom that causes a medication to be prescribed is actually associated with increased risk of the outcome and can, therefore, contribute to the observation of an association between the drug and the outcome that may not actually exist.
        - In this case, the question is whether nausea and vomiting in pregnancy is associated with risk of congenital cardiac defects in offspring.
        - The existing data does not show increased risk of cardiac birth defects in offspring of women taking other antiemetics, demonstrating that confounding by indication is not a likely explanation for the observed increase in risk associated with use of Ondansetron.
        - There is some theory and evidence to support the idea that nausea and vomiting in pregnancy may be protective against adverse pregnancy outcomes:
            1. Nausea and vomiting as a protective mechanism from environmental toxins
                a. There is some evidence to suggest that nausea in pregnancy (NP) is triggered by animal products which may contain parasites and harmful bacteria.
                b. If morning sickness is a defense mechanism against the ingestion of toxins, the prescribing of anti-nausea medication to pregnant women may have the undesired side effect of causing birth defects by encouraging, or enabling, harmful dietary choices.
            2. Nausea and vomiting as a surrogate for healthy hormonal balance
                a. A study by Boneva and colleagues (1999) demonstrated a protective effect of NP and NP-medications (Bendectin and other unidentified medications) on risk of congenital cardiac defects in offspring.
                b. The authors hypothesize that the protective effect may best be explained by the following: "nausea during early gestation is a marker of normal production of pregnancy hormones and pregnancy-specific growth factors, either of which may play a role in heart development" (page 724).
                c. The authors further offer that the reported protective effect of nausea medications on risk of congenital cardiac defects may, in fact, be a result of confounding by indication because severe nausea itself resulted in women being less likely to have a child with a congenital heart defect than women with no nausea.

- The potentially protective effect of NP on risk of cardiac birth defects may have no effect on the risk estimates or may serve to underestimate the true risk of Ondansetron.
- Specifically, if we assume that NP is protective to the same degree in women taking Ondansetron and those taking other medications, then the observed risk estimate will not be biased when comparing women with NP who took Ondansetron to those taking other NP medications.
- However, there are two situations in which the observed risk estimate for Ondansetron use and congenital cardiac defects may be biased toward the null (i.e. underestimated) if we assume that NP is protective[4]:
    1. If we compare pregnant women who are taking a drug for NP versus all other pregnant women (not necessarily with NP), then the competing protective mechanism of NP on Ondansetron users may underestimate the true risk of Ondansetron use among all pregnant women;
    2. If women with more severe nausea are more likely to take a prescription medication like Ondansetron (and if more severe nausea is associated with increased protection as in Boneva et al. 1999) then the observed risk for cardiac birth defects among Ondansetron users compared to all other pregnant women may underestimate the true risk of the drug alone among all pregnant women.

Other Considerations

- The ideal epidemiological study of birth defects would be able to examine the association between exposure to a potential teratogen and risk of specific congenital malformations. However, this is rarely possible given a number of limitations inherent in studying birth defects and in studying certain potential teratogens. The more rare the disease and the smaller the exposed population, the less likely that a particular study will find a statistically significant t elevation, even under circumstances in which a true causal connection exists.

- The relatively small sample sizes of either exposed children and/or children affected with specific types of birth defects results in very limited power to detect statistical differences in risk between exposed and unexposed, particularly for specific malformations. This makes the detection of even a substantial drug-induced increase in the rate of any individual defect difficult.

- An additional consideration for epidemiologic research is the high rate of fetal loss related to birth defects. Thus, if only live births are considered, the impact of teratogenic factors may be greatly underestimated or overlooked in a study.

[4] These assume that nausea during pregnancy, and severity thereof, were not controlled for in the study design or analysis

Additional Avenues for Inquiry

- Further assess the strength of the evidence for confounding by indication
- Systematic, comprehensive literature review to further develop mechanism of action
- Analysis of FDA AERS database for safety signal
- Nested case-control study of administrative claims database to contribute US-based data with the power to examine specific cardiac birth defects

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Tab 4

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)

Tab 5

Descriptives

Antiemetic	n	% (of those with exposure)
Ondansetron	131775	13.90%
Promethazine	72160	7.60%
Diclegis	1834	0.20%
Methylprednisolone	22777	2.40%
Metoclopramide	25578	2.70%
Any Antiemetics	199355	21.00%
Unexposed	949790	82.65%
Total population	1149145	

Concomitant Antiemetic Usage during First Trimester

Main antiemetic	n	Concomitant Ondansetron use	Concomitant Diclegis use (restricted to 2013-14)	Concomitant Metoclopramide use	Concomitant Promethazine use	Concomitant Methylprednisone use
Ondansetron	131,775	NA	2.3	9.5	24.2	3.7
Diclegis	1,834	48.8	NA	7	16.5	4.4
Metoclopramide	25,578	49.2	3.3	NA	30.1	4.1
Promethazine wide	72,160	44.3	1.7	10.7	NA	4
Methylprednisone wide	22,777	21.2	3.3	4.6	12.8	NA

Women with medical administration of zofran only, n=27,335

Frequency of Birth Defects

Birth Defect		n	%	CDC estimate 2004-2006
Cardiac malformation		**39,071**	**3%**	
Septal defects		38,112	**3%**	
Cardiac malformation subgroups	Great vessel transposition	-	0%	
	Tetralogy of fallot	1,149	0.10%	0.4%
	Ventricular septal defect	11,491	1.00%	
	Ostium secundum defect	32,176	2.80%	
	Atrioventricular septal	1,084	0.09%	0.2%
	Atroventricular septal with procedures	-	0%	
	Other congenital heart	10,997	0.96%	
	Hypoplastic heart	460	0%	0.2%
Other congenital circulatory		8,044	1%	
Orofacial cleft (749.xx)		**1,839**	**0.16%**	**0.6-.11%**
Orofacial cleft subgroups	Cleft palate (749.0)	-	0%	
	Cleft lip (749.1)	-	0%	
	CL/P (749.20-749.25)	919	0%	
Other anomalies (larynx/trachea/bronchus)		9,193	1%	
Spina bifida		-	0%	
Limb reduction		689	0.06%	0.2-0.4%
Craniosynostosis		14,939	1%	
Diaphragmatic hernia		575	0.05%	0.2%
Renal anomalies		**10,342**	**1%**	

Renal anomalies subgroup	Renal agnesis	689	0%	
Any birth defect (structural and non-structural defects)		221,930	19%	
Total sample size		1,149,145		

Distribution of First Use of Antiemetic by Week of Pregnancy

Quartile percent	Any antiemetic %	Ondansetron %	Promethazine %	Diclegis %	Methylprednisolone %	Metoclopramide %
1st Quartile (25%)	8	9	9	10	2	9
3rd Quartile (75%)	12	13	13	14	6	14

Danielsson et al 2014 - Ondansetron

Table 1
Distribution by pregnancy week (counted from last menstrual period) of the date of filling the first prescription for ondansetron.

Week	Number	
<5	7	
5	10	
6	34	
7	109	
8	142	
9	187	68%
10	145	
11	169	
12	136	

Risk Estimates:

Exposure Groups

- 1. Exposed=Zofran (not exclusive), non-exposed=no antiemetic exposure
- **2. Exposed=Zofran (exclusive), non-exposed=no antiemetic exposure**
- 3. Exposed=Zofran (not exclusive), non-exposed=exposure to other antiemetics
- 4. Exposed=Zofran (exclusive), non-exposed=exposure to other antiemetics

We know there is exposure misclassification, exploring how best to address

Medical claims only = No exposure misclassification

Ondansetron – Crude ORs, Exposure = Any First Trimester

Birth Defect	Type of prescriptions	Exposure 1 OR (95% CI)	**Exposure 2 OR (95% CI)**	Exposure 3 OR (95% CI)	Exposure 4 OR (95% CI)
Cardiac defects	Medical and rx claims	1.116 (1.081-1.151)	1.090 (1.050-1.132)	0.984 (0.823-1.176)	0.916 (0.753-1.114)
	Rx claims only	1.072 (1.035-1.109)	1.051 (1.010-1.095)	0.938 (0.891-0.988)	0.915 (0.868-0.964)
	Medical claims only	1.098 (1.062-1.135)	1.484 (1.321-1.667)	1.035 (0.884-1.212)	1.030 (0.879-1.207)
Septal defects	Medical and rx claims	1.117 (1.083-1.153)	1.092 (1.051-1.134)	0.996 (0.833-1.191)	0.925 (0.760-1.127)
	Rx claims only	1.073 (1.036-1.110)	1.053 (1.011-1.096)	0.939 (0.891-0.989)	0.915 (0.869-0.965)
	Medical claims only	1.099 (1.064-1.136)	1.491 (1.327-1.676)	1.031 (0.881-1.208)	1.026 (0.876-1.202)
Orofacial clefts	Medical and rx claims	1.173 (1.023-1.345)	1.143 (0.970-1.347)	0.718 (0.305-1.691)	0.498 (0.171-1.451)
	Rx claims only	1.174 (1.014-1.361)	1.153 (0.970-1.372)	1.046 (0.836-1.309)	1.013 (0.807-1.271)
	Medical claims only	1.178 (1.022-1.359)	1.318 (0.763-2.277)	0.805 (0.397-1.631)	0.814 (0.402-1.650)

- What is the OR for cardiac and orofacial if you restrict the analysis to women who had at least one medical claim (so not only medical claims and not both medical and rx, but at least one medical claim for ondansetron)? **OR (cardiac) = 1.348 (1.22 – 1.49)**
- Need to address potential confounding by indication for medical claims results (use metoclopramide medical claims as a comparator)

Effect of Confounding

*Not final set of confounders[1] – preliminary only

Exposure Groups

- 1. Exposed=Zofran (not exclusive), non-exposed=no antiemetic exposure
- 2. Exposed=Zofran (exclusive), non-exposed=no antiemetic exposure
- 3. Exposed=Zofran (not exclusive), non-exposed=exposure to other antiemetics
- 4. Exposed=Zofran (exclusive), non-exposed=exposure to other antiemetics

Medical claims only = No exposure misclassification

Ondansetron – Adjusted ORs

Birth Defect	Type of prescriptions	Exposure 1 OR (95% CI)	Exposure 2 OR (95% CI)	Exposure 3 OR (95% CI)	Exposure 4 OR (95% CI)
Cardiac defects	Medical and rx claims	1.045 (1.012-1.078)	1.010 (0.973-1.050)	0.949 (0.790-1.139)	0.890 (0.728-1.086)
	Rx claims only	1.006 (0.972-1.042)	0.978 (0.939-1.019)	0.846 (0.802-0.893)	0.827 (0.783-0.873)
	Medical claims only	1.326 (1.193-1.474)	1.337 (1.189-1.503)	0.991 (0.842-1.166)	0.985 (0.836-1.160)
Septal defects	Medical and rx claims	1.044 (1.011-1.078)	1.001 (0.972-1.050)	0.959 (0.798-1.151)	0.898 (0.734-1.097)
	Rx claims only	1.006 (0.972-1.042)	0.977 (0.938-1.018)	0.846 (0.801-0.892)	0.827 (0.783-0.873)
	Medical claims only	1.328 (1.194-1.477)	1.341 (1.192-1.508)	0.986 (0.838-1.162)	0.981 (0.832-1.156)
Orofacial clefts	Medical and rx claims	1.154 (1.004-1.325)	1.116 (0.944-1.318)	0.878 (0.364-2.117)	0.585 (0.196-1.742)
	Rx claims only	1.155 (0.995-1.341)	1.128 (0.946-1.344)	1.039 (0.822-1.313)	1.007 (0.794-1.277)
	Medical claims only	1.190 (0.715-1.983)	1.270 (0.734-2.195)	0.688 (0.334-1.415)	0.696 (0.338-1.431)

List of Confounders

- Age of mother
- Birth date
- Gender of infant
- History of high risk pregnancy
- Family history of birth defects
- Folic acid use
- Obesity
- Epilepsy
- Cancer
- Diabetes
- Hypertension

NVP Diagnosis as a Marker of Probability of Exposure

- Misclassification of exposure decreases as severity of indication increases; in the Rx claims data we achieve a comparable risk estimate among those with Severe HG as to those with medical claims only
- The trend persists when the comparator group is "other antiemetic exposed", demonstrating either (1) increasing severity of HG is a marker of increasing probability of exposure, or (2) an interactive effect between severity of NVP and ondansetron.

Adjusted ORs among those with no nausea diagnosis, Exposure 2

Birth Defect	Type of prescriptions	No Dx	NVP Dx	HG Dx	Severe HG
Cardiac defects	Rx claims only	0.981 (0.941-1.022)	0.413 (0.163-1.051)	0.807 (0.258-2.526)	1.320 (0.191-9.144)
	Medical claims only	1.350 (1.200-1.520)	0.959 (0.226-4.059)	0.775 (0.149-4.035)	1

To Control for Confounding by Indication: Use Exposure 4 (zofran ONLY versus other)

Birth Defect	Type of prescriptions	No Dx	NVP Dx	HG Dx	Severe HG
Cardiac defects	Rx claims only	0.825 (0.781-0.871)	0.825 (0.240-2.837)	1.178 (0.363-3.819)	72.823 (0.027-196472.3)

Crude and Adjusted ORs – Individuals with repeated co-exposure to ondansetron and promethazine

- Exposure is defined as someone who has been prescribed both ondansetron and promethazine on the same day >1 time (n=237)
- Exposure misclassification is decreased due to repeated co-exposure of this unique treatment regimen; when compared to "any" ondansetron, suggests either (1) the degree and presence of exposure misclassification in the "any exposure" variable or (2) the effect of promethazine.
    - The effect is not an independent effect of promethazine because the risk is increased from promethazine alone.

***Run this compared to individuals with at least 2 consecutive ondansetron prescriptions (instead of just "any" exposed) and also run against ondansetron only exposed if max dose >=the mean

Birth Defect	Comparator Group	Crude OR	Adjusted OR
Cardiac defects	Unexposed	1.461 (0.772-2.766)	1.355 (0.715-2.570)
	Ondansetron only	1.341 (0.708-2.540)	1.340 (0.705-2.544)
	Promethazine only	1.624 (0.856-3.083)	1.330 (0.698-2.533)
Septal defects	Unexposed	1.478 (0.781-2.797)	1.368 (0.722-2.595)
	Ondansetron only	1.354 (0.715-2.565)	1.353 (0.713-2.570)
	Promethazine only	1.647 (0.868-3.126)	1.345 (0.707-2.566)
Orofacial defects	Unexposed	3.025 (0.423-21.610)	2.949 (0.412-21.080)
	Ondansetron only	2.646 (0.368-19.014)	2.617 (0.364-18.825)
	Promethazine only	2.461 (0.340-17.813)	2.510 (0.343-18.348)

Promethazine ONLY exposed Cardiac OR (prom vs. no exposure)$_{crude}$ = 0.90 (0.85-0.96) OR (prom vs. no exposure)$_{adj}$ = 0.97 (0.91-1.0)	Orofacial Clefts OR (prom vs. no exposure)$_{crude}$ = 1.23 (0.97-1.56) OR (prom vs. no exposure)$_{adj}$ = 1.25 (1.0-1.59)

Adjusted ORs among by # Rx or other measure of higher probability of exposure - TBD

Zofran vs Other Antiemetics

Birth Defect	Type of prescriptions	#Rx			
Cardiac defects	Medical and rx claims				
	Rx claims only				
Septal defects	Medical and rx claims				
	Rx claims only				
Orofacial clefts	Medical and rx claims				
	Rx claims only				

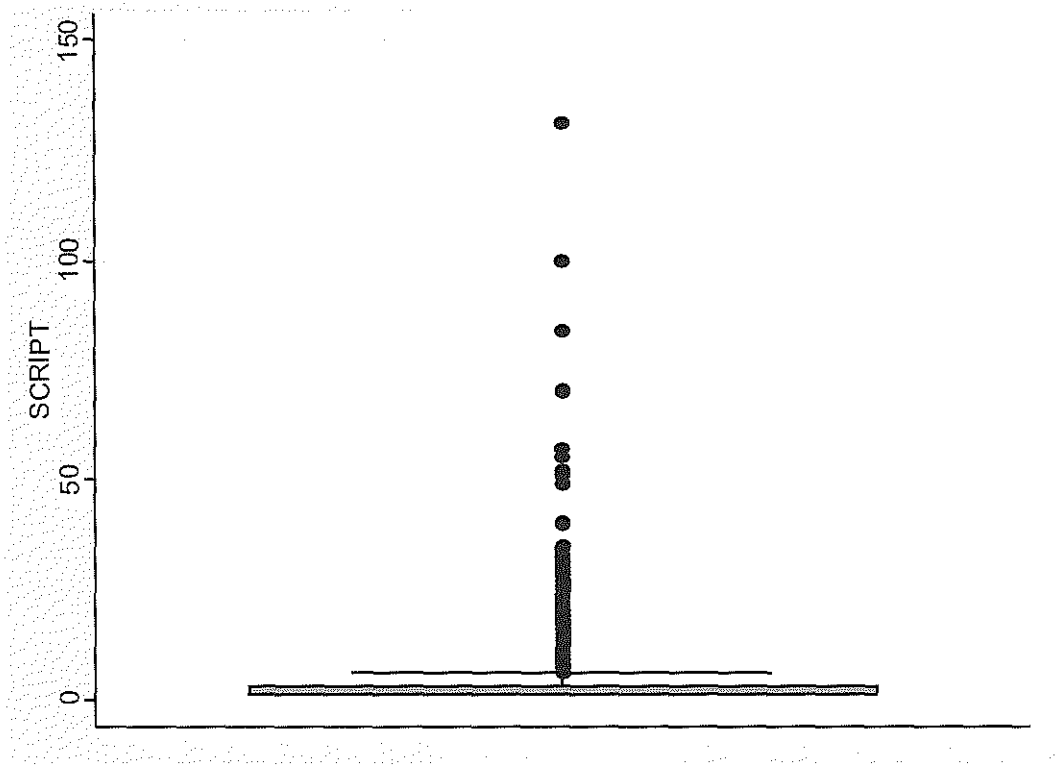
Descriptives – Exposure Metrics

Number of prescriptions

Antiemetic	5th percentile	10th percentile	25th percentile	50th percentile	75th precentile	90th percentile	95th percentile	maximum
Ondansetron	1	1	1	1	2	4	6	77
All antiemetics	1	1	1	1	3	4	6	131

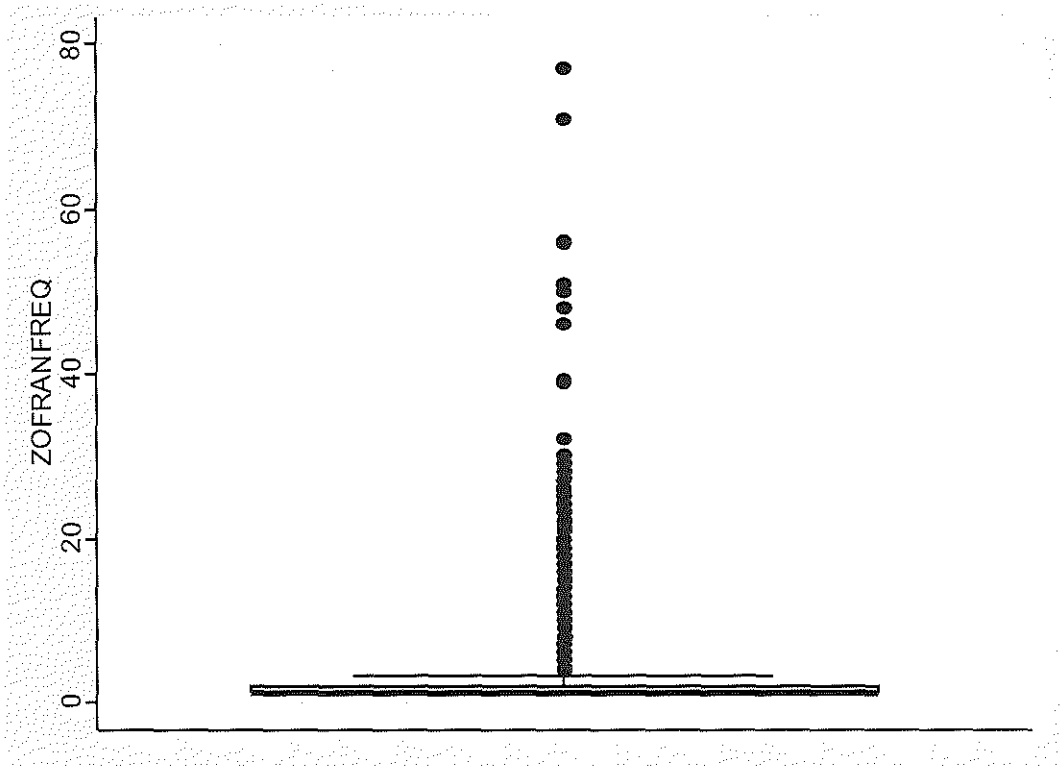
Zofran vs Other Antiemetics

Number of all antiemetic prescriptions



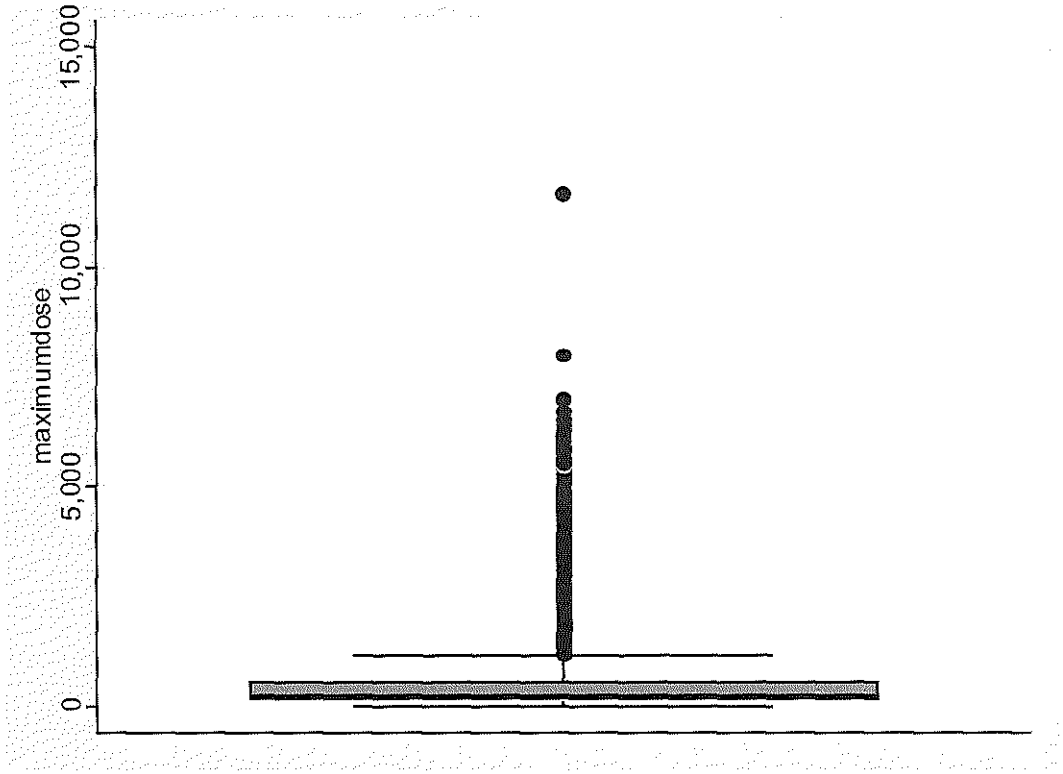
Antiemetic	5th percentile	10th percentile	25th percentile	50th percentile	75th percentile	90th percentile	95th percentile	maximum
All antiemetics	1	3	5	10	23	41	60	

Number of Ondansetron prescriptions



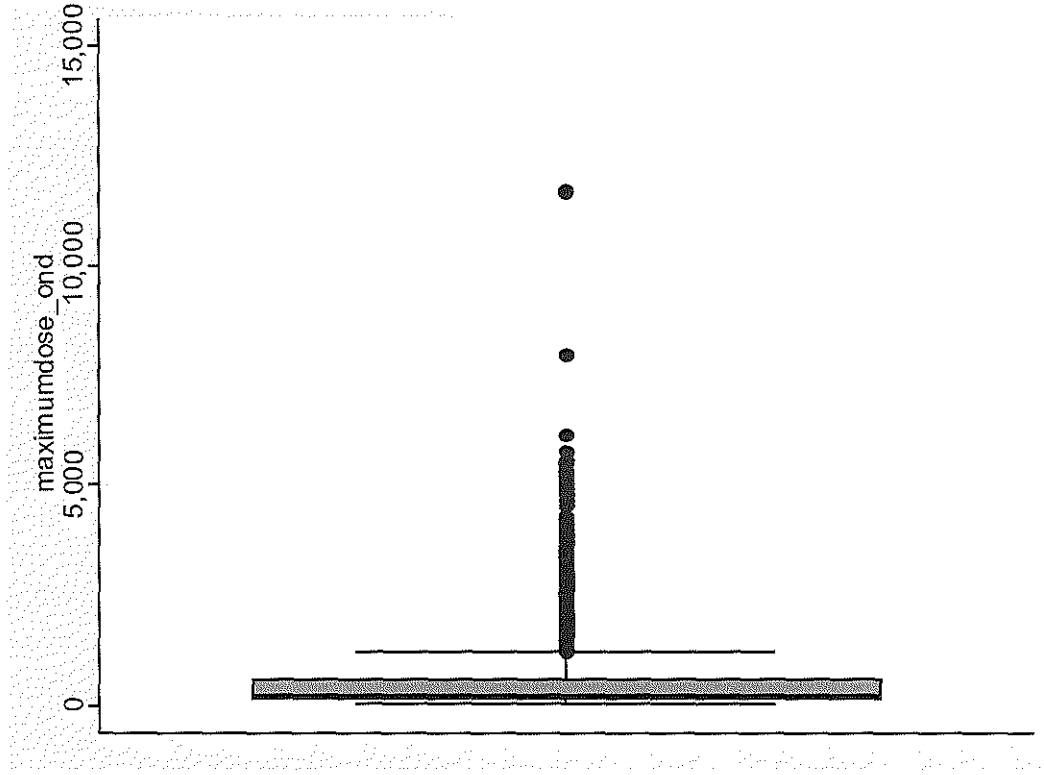
Antiemetic	5th percentile	10th percentile	25th percentile	50th percentile	75th precentil	90th percentile	95th percentile
All antiemetics	1	1	1	1	3	4	6

Maximum first trimester dose for all antiemetics



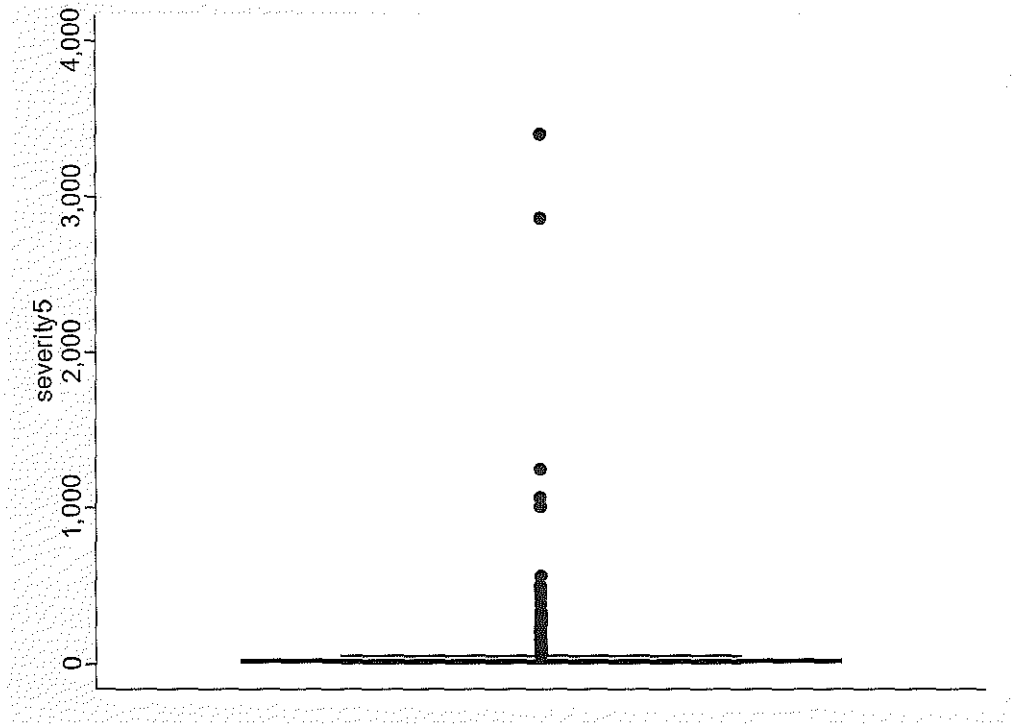
Antiemetic	5th percentile	10th percentile	25th percentile	50th percentile	75th precentil	90th percentile	95th percentile
All antiemetics	30	64	125	250	525	100	1400

Maximum first trimester dose of Ondansetron



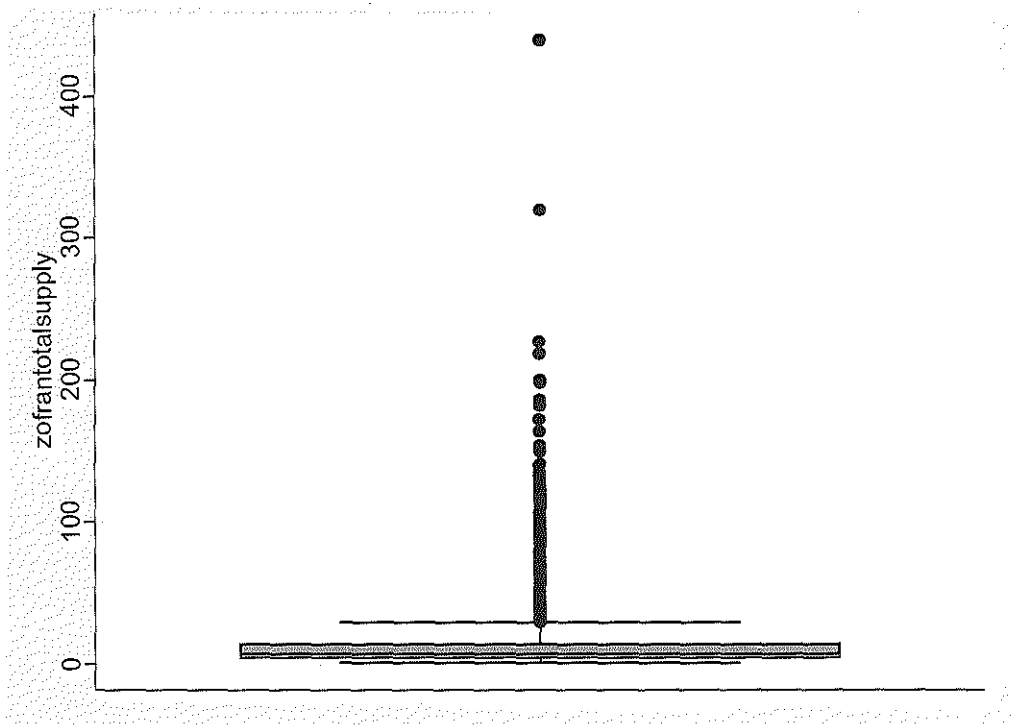
Antiemetic	5th percentile	10th percentile	25th percentile	50th percentile	75th precentil	90th percentile	95th percentile
Ondansetron	75	100	150	250	575	950	1350

Days supply, All Antiemetics



Antiemetic	5th percentile	10th percentile	25th percentile	50th percentile	75th precentil	90th percentile	95th percentile
All antiemetics	1	3	5	10	23	41	68

Days supply, Zofran



Antiemetic	5th percentile	10th percentile	25th percentile	50th percentile	75th precentil	90th percentile	95th percentile
Zofran	1	1	4	7	14	30	30

[1]

Tab 6

TTi Health Research & Economics

April Zambelli-Weiner <aweiner@transtechint.com>

Draft of Zofran paper

8 messages

Christina Via <cvia@transtechint.com> Sat, Dec 16, 2017 at 1:32 PM
To: "Kirby, Russell" <rkirby@health.usf.edu>
Cc: "Dr. April Zambelli-Weiner" <aweiner@transtechint.com>

Hi Russ,

Attached is the first draft of our Zofran paper, as well as the next version of the tables. Please note that the orofacial cleft data still needs to be added. I just received that data from Truven, and should be able to get you the updated tables by early next week. If you could give us feedback in the next two weeks (preferably by Friday, 12/29), that would go a long in helping us keep our goal submission date of early January. If you have any questions, feel free to call my office at 800-580-2990 ext 106, or my cell at 203-988-3104.

Thanks and Happy Holidays!
Christina

--

Christina Via, Epidemiologist

cvia@transtechint.com 800.580.2990
ext.106

www.transtechint.com

Check out our brief video!

2 attachments

NEJM Draft_12.15.17_v4_clean.docx
52K

Ondansetron NEJM tables_12.14.17_v2.xlsx
28K

Christina Via <cvia@transtechint.com> Mon, Dec 18, 2017 at 3:02 PM
To: "Kirby, Russell" <rkirby@health.usf.edu>
Cc: "Dr. April Zambelli-Weiner" <aweiner@transtechint.com>

Hi Russ,

Attached are updated tables with orofacial cleft data added.

Thanks!
Christina
[Quoted text hidden]

Ondansetron NEJM tables_12.18.17_as sent.xlsx
25K

Christina Via <cvia@transtechint.com> Sun, Dec 31, 2017 at 6:52 PM
To: "Dr. April Zambelli-Weiner" <aweiner@transtechint.com>

Hi April,

Just wanted to give you an update on the antiemetic paper. Russ says he should be able to get it back to me by Tuesday. As soon as I get it, I will merge with any additional edits I've made and get it to you as soon as possible. I apologize for the delay!

Thanks and Happy New Year!
Christina

---------- Forwarded message ----------
From: **Kirby, Russell** <rkirby@health.usf.edu>
Date: Sun, Dec 31, 2017 at 6:01 PM
Subject: Re: Draft of Zofran paper
To: Christina Via <cvia@transtechint.com>

Will try to get this back to you Tuesday.

Sent from my iPhone

On Dec 31, 2017, at 5:54 PM, Christina Via <cvia@transtechint.com> wrote:

> Hi Russ,
>
> I hope your holidays are going well! I just wanted to follow up to see if you had a chance to review the Zofran draft manuscript. If you have any questions, please let me know!
>
> Thanks!

NEJM Requirements: 2700 words total, 250 word abstract, 5 figures/tables, 40 references

TITLE: EARLY PREGNANCY EXPOSURE TO ONDANSETRON AND RISK OF STRUCTURAL BIRTH DEFECTS

AUTHORS: Zambelli-Weiner, April; Via, Christina; Yuen, Matt; Weiner, Daniel; Kirby, Russell

ABSTRACT:

Background

Methods

Results

Conclusions

INTRODUCTION

Nausea and vomiting in pregnancy (NVP) is a frequent complaint of women during early pregnancy. According to recent studies, 70-90%[1,2] of women report having experienced NVP, with .5-1.5%[3,4] being diagnosed with the more severe hyperemesis gravidarum (HG). There are numerous approaches to managing NVP and HG, including natural remedies such as ginger,[5–7] over-the-counter drugs including antihistamines,[6,8,9] and prescription pharmaceutical treatments.[6,10] The use of prescription medications for NVP has been increasing in recent years,[11,12] with a total of five drugs listed in the 2004 clinical guidelines from the American College of Gynecology(ACOG): ondansetron, Diclegis (Doxylamine Succinate and Pyridoxine Hydrochloride), metoclopramide, promethazine, and methylprednisolone. Of those five, Diclegis is the only one specifically approved for use in pregnancy.[10] According to a recent paper by Taylor and colleagues, ondansetron represents the most frequently prescribed medication for the treatment of NVP and HG, despite the fact that the 2004 ACOG guidelines algorithm lists it the last line of therapy and the 2015 ACOG guidelines continue to note that, "there are insufficient data on fetal safety with ondansetron use and further studies are warranted".[10,13]

Prior studies on the fetal safety of ondansetron have produced varied results, likely a reflection of the heterogeneity in study populations, methods, and sample size. In general, studies that failed to detect a connection between ondansetron and birth defects examined smaller populations,[2,14,15] while studies showing an association between ondansetron and birth defects relied on large registries.[16–18] Mixed results can also result from differing methods used including: ondansetron exposure definition (recall[14] vs. claims or records),[16,18] or lumping and splitting of outcomes ("major defects"[19,20] vs. multiple birth defect categories).[16–18]

To address these significant limitations and gaps in the literature on the risk of congenital anomalies in the US population, we conducted a population-level study using US administrative claims data to study the association between ondansetron use during early pregnancy and risk of

structural congenital malformations, while considering the impact of important potential modifying factors such as disease severity, timing, and concomitant drug exposure.

METHODS

Database

We conducted a retrospective cohort study using a large US-based administrative health care database, the Truven Health MarketScan Commercial Database. This database captures the full episode of care for each patient during their plan enrollment, including both inpatient and outpatient medical care, prescription drug use and other medical resource utilization. Diagnosis and procedure codes are identified by the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) and Current Procedural Terminology codes. Drug exposures were identified through the specific compilation of lists derived from The National Drug Code Directory.

Institutional Review Board approval was not required, as this study used existing, fully de-identified data and as such is exempt from 45 CFR 46 requirements.

Study Population

The source population included mother-child pairs resulting from all live births between 2000 to 2014 who had one year of follow-up for the infant(s). Mothers were eligible if they were continuously enrolled in the health plan for 16 months prior to delivery and were between the ages of 15 and 49 years old on the date of delivery. Mother-child pairs were excluded if there was an increased baseline risk of congenital malformations due to family history or exposure to known teratogens, defined as: a maternal diagnosis in the 16-month pre-birth period of chromosomal anomalies (ICD-9 758.xx), toxoplasmosis, other, rubella, cytomegalovirus, and herpes (TORCH) infectionsk or if the mother filled a prescription for thalidomide or isotretinoin in the pre-birth period. Those exposed to Diclegis, promethazine, metoclopramide, or methylprednisolone during pregnancy were also excluded.

Exposure Measurement

The number of ondansetron prescriptions or medical administrations occurring during the first trimester was identified using NDC codes and trade names. The period of first trimester exposure was defined as the period from the beginning of the estimated date of conception to the end of the first trimester (91 days following the estimated conception date), specifically 287 to 147 days prior to delivery, based on an estimated conception period of 287-252 days prior to delivery for a singleton birth and 273-238 days prior to delivery for a multiple birth based on a previously published algorithm for a study using the Truven Marketscan data.[21]

In our primary analyses we considered ondansetron exposure as a dichotomous (ever/never) first-trimester (or early pregnancy) exposure. Because antiemetics can be prescribed prophylactively to be used on a "as needed" basis, there is a significant risk of exposure misclassification. It may be difficult to ascertain whether someone who had a

prescription filled actually took the medication. To decrease misclassification bias, we performed a subanalysis examining those with medical administrations of ondansetron only, guaranteeing those in the exposed cohort were truly exposed.

Birth Outcomes

Outcomes were identified using ICD-9-CM diagnosis codes. Cases were identified as having one or more claims with a relevant diagnosis code within 365 days of the date of birth.

Covariates

Potential confounders were identified through a review of the literature and the team's understanding of both the clinical care of pregnant women and the epidemiology of birth defects. Potential confounders that were identified and available in our database included:maternal age at birth, infant year of birth, infant gender, US region of birth, medical history(obesity, diabetes mellitus, epilepsy, hypertension, cancer, prior preterm delivery, family history of birth defects), medications taken in early pregnancy (initiation of acid-reducing therapies, psychotropics, prescription folic acid, macrolide antibioitcs, corticosteroids, anticonvulsants), low birth weight, multiple gestation, high risk pregnancy diagnosis, and diagnosis of NVP or HG. True confounders, by definition, must be associated with both the exposure and the outcome under investigation, but cannot be in the causal pathway or an intermediate (i.e., influenced by exposure). Potential confounders were evaluated by adding the variable to the base exposure-outcome model and evaluating the change in the risk estimate. If the risk estimate changed by $\geq$10% this indicated the presence of confounding and that variable was included in the multivariate models. Further, to control simultaneously for all potential confounders data, a propensity score was developed.

Maternal medical history, comorbidities and other medications were measured from medical and prescription claims occurring during the pre-birth period. Comorbid conditions were flagged as being present if a patient had $\geq$ 1 medical claim with an ICD-9 diagnosis code for the condition of interest in any diagnosis position. Additional medication use was identified if a patient had $\geq$ 1 claim in the early pregnancy period, as previously described.

Statistical Analysis

The statistical analyses were performed with using Stata software, Stata/MP 13.1 (College Station, TX; StataCorp LP). Characteristics of mother child pairs exposed to ondansetron in early pregnancy were compared to mother-child pairs who were unexposed to any antiemetics in early pregnancy using chi-square test or Fisher's exact test for categorical variables and Student's t-test for continuous variables. Logistic regression models were used to test for a statistical association between early pregnancy ondansetron use and risk of specific birth defects in offspring. Prevalence odds ratios and 95% confidence intervals were calculated.

Further analyses evaluated disease severity and ascertainment bias. We controlled for confounding by indication (disease severity) by comparing the exposed cohort to only those with both no antiemetic exposure during pregnancy and a diagnosis of NVP/HG. We controlled for ascertainment bias by stratifying the analysis by year, with yearly cut-off points relating to increased awareness/publicity of possible risks associated with taking ondansetron in early pregnancy. This includes the first study published showing ondansetron crosses the placenta in 2006[22] and the FDA warning regarding risks of adverse events when using ondansetron in late 2011.[23]

RESULTS

Study Population

After exclusions, a total of 991,060 mother-infant pairs were identified. Early exposure to ondansetron occurred in 88,695 mother-infant pairs (8.95%), and early exposure to medical administration of ondansetron occurred in 6,442 mother-infant pairs (0.71%). The median number of prescriptions overall was 1 per mother-baby pair (interquartile range, 1-2 prescriptions).

Table 1 shows the characteristics of women included in the analysis by disease status. There were 927,215 infants with no birth defects, 73,593 infants with structural birth defects, 38,538 infants with cardiovascular birth defects, and xxx infants with orofacial cleft defects. Because of the large sample sizes, most variables differed significantly between birth defect cohorts. However, when potential confounders were evaluated by adding the variable to the base exposure-outcome model, none of them reached the 10% change threshold. We therefore only adjusted for infant year of birth, infant gender, and mother's age at infant birth in the main analyses.

Primary Analysis

Table 2 shows the analyses of birth defects associated with exposure to ondansetron in early pregnancy, with and without adjustment for mother's age at birth, infant gender, and infant year of birth. Pregnant women who were exposed to ondansetron were at increased risk of cardiac defects (unadjusted OR: 1.11 (1.04-1.16); adjusted OR: 1.04 (1.00-1.08) and orofacial cleft defects (unadjusted OR: x.xx (x.xx-x.xx); adjusted OR: x.xx (x.xx-x.xx)). This association was strengthened when analysis is restricted to eliminate exposure misclassification bias (OR: 1.52 (1.35-1.70) for cardiac defects and x.xx (x.xx-x.xx) for orofacial cleft defects).

Sensitivity Analyses

Table 3 shows results from the two sensitivity analyses. After only includine those with the disease (NVP/HG) in those control group, an association between ondansetron use in early pregnancy and subsequent specific structural birth still existed: (cardiac defects: unadjusted OR: 1.51 (1.24-1.85); adjusted OR: 1.56 (1.21-2.03). Therefore it is unlikely that counfounding by indication is biasing our results. Similarly, stratifying the results by year does not eliminate the

associated between ondansetron use and birth defects, making ascertainment bias unlikely (cardiac defects: 2000-2006 – OR: 1.54 (0.79-3.01); 2007-2011 – OR: 1.30 (1.10-1.54); 2012-2014: 1.60 (1.35-1.89)).

DISCUSSION

Our retrospective observational study is the first to demonstrate a statistically significant association between early pregnancy (i.e., first trimester) exposure to ondansetron and a range of specific structural defects birth defects in offspring in a large, nationally representative US population. Previous studies have demonstrated an increased risk of cardiovascular defects[16,24] and septal defects,[16,24] with particularly elevated risks for specific septal defects.[16] Data has been more limited in the US with studies showing increased risk of cleft palate[25] and clubfoot.[25]

Our results in a US population are markedly similar to the results published by previous studies examining the relationship between early pregnancy ondansetron exposure and risk of birth defects in offspring. Specifically, Daniellson and colleagues report elevated risks for cardiovascular defects and septal defects ($OR_{cardiovacsular}$=1.62, 95% CI: 1.04-2.14; OR_{septal}=2.05, 95% CI: 1.19-3.28)[24] comparable to those reported in our study (OR=1.52, 95% CI: 1.35-1.701.35-1.70); OR=1.53, 95% CI: 1.36-1.71), respectively). In the study by Pasternak and colleagues unadjusted relative risks for septal defects are calculated to be 1.22 (95% CI 0.62-2.39) in Pasternak et al[19] and are 1.53, 95% CI: 1.36-1.71in our study. Pasternak and colleagues show risk to be highest for atrioventricular septal defects (OR=4.8, 95% CI: 0.25-63.91) and similarly highest in our study (OR=2.68, 95% CI: 1.61-4.47). Similar trends are observed in an abstract by Andersen and colleagues.[16]

In contrast, other studies failed to detect a connection between ondansetron and specific birth defects. However, this may be due to biases and study design limitations. Some studies may have lumped all examined birth defects into a binary categorical variable rather than investigating specific birth defects individually, due to smaller sample sizes and power issues.[19,20] Given a larger sample size and adequate power, the most accurate estimate of any individual birth defect would investigating each birth defect rather than an aggregate lumping of birth defects. For example, multiple studies where significant correlation was detected for ondansetron and some individual birth defects also found no correlation in lumped major birth defects in the same study.[16,18,24] Additionally, other studies relied on subject recruited cohorts or a single hospital system which introduce selecton bias and generalizability issues.[14,15]

The goal in epidemiology is always to minimize the risk of bias (that is, maximize internal validity) in a study, and there are various biases to be concerned with. Our study sought to address some of the concerns around bias present in previous studies such as recall bias in case control studies and exposure misclassification and limitations suchas low exposure prevalence and small sample sizes that reduce study power and may have precluded important subgroup analyses. Utilizing an administrative claims database removes the risk of recall bias that may be present in case-control studies. However, there is always a concern when prescription claims are used as a marker of exposure that the prescription may not be representative of true exposure (meaning the patient may fill the prescription and not take any of

the drug) or not representative of relevant exposure, such as during the critical exposure time period – in this case, first trimester or early pregnancy exposure. We were able to address this concern in our study by setting a more stringent exposure definition where the probability of exposure is certain: ondansetron administered in a medical or hospital setting. By presenting results for both combined medical and prescription claims and medical claims alone, the impact of misclassification of exposure becomes clear, revealing a significant biasing of the risk estimate towards the null – and illustrating the point made by Danielsson and colleagues.[24]

Regarding the timing of exposure, because diagnosis codes for gestational age are not widely utilized, administrative database studies must rely on an estimation of pregnancy duration and first trimester exposure, as is the case with our study. It is common to estimate the date of conception as 270 or 287 days prior to delivery.[21,26] This approach carries with it the limitation that not all pregnancies are equal in length and, therefore, the estimation of the exposure period may be off. For example, for a premature delivery (36 weeks, 252 days), the first trimester would be 252-161 days prior to the date of delivery. Based on our estimation, the relevant exposure period would include 35 days in the pre-conception period and would include 14 days of the second trimester. While this can present a more significant risk of bias for prescriptions that are taken for non-pregnancy indications and may be initiated prior to conception, it's less of a concern for antiemetics that are initiated in response to nausea and vomiting in pregnancy.

In addition, to overcome potential detection bias, whereby offspring may have an underlying birth defect that had not yet been diagnosed, infants in our study were followed for one year post delivery to allow latent diagnosis of birth defects.

However, our study is not without limitations. The inability to control for all potential confounders is a limitation of epidemiological research and of administrative claims databases, in particular. Data were unavailable on maternal sociodemographic variables such as race, education and parity as well as lifestyle risk factors such as smoking, alcohol consumption and over the counter drug use in the pre-conception and early pregnancy periods. Also, because dose response analysis was prohibitive, as antiemetics can be taken on an "as needed" bases, and because days-supply associated with prescriptions is not always uniformly recorded in administrative claims data.[26] However, the prevalence of ondansetron exposure is similar rates d derived from a comparable US-based commercially insured population.[12]

In conclusion, our study is the largest observational study to date on ondansetron safety in pregnancy. By studying a large number of exposed pregnancies, isolating the independent effect of ondansetron on risk, minimizing the risk of exposure misclassification and controlling for potential confounders, we have demonstrated significantly elevated risks for cardiac defects. Birth defects carry a significant burden on individuals, public health, and the health care system. Birth defects are associated with increased risk of,[27]) and many are associated with life-long. It is incumbent upon us as public health professionals and medical practitioners to use the best available data at any given point in time to inform policy and practice in ways that improve

health outcomes and quality of life for the patients and populations we serve. Drug exposures represent a modifiable risk factor, particular for those in which there are alternative therapies available. The confluence of the evidence supports a causal relationship between early pregnancy ondansetron exposure and risk of major structural birth defects in offspring. Previous researchers in the field have called for action in this case: "Irrespective of the mode of action, if an association between use of ondansetron and an increased risk for cardiovascular defects is true, the strongly increasing off label use of the drug at nausea and vomiting in pregnancy must be regarded as unsuitable and should be avoided.[24]

FIGURES/TABLES [see excel spreadsheet]

Figure 1: Study Design / Flow Chart

Table 1: Characteristics of Women Included in the Analysis

Table 2: Association of Ondansetron Exposure with Structural Birth Defects

Table 3: Sensitivity Analyses

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Tab 7

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

IN RE: ZOFRAN® (ONDANSETRON) PRODUCTS LIABILITY LITIGATION	MDL No. 1:15-md-02657-FDS

AFFIDAVIT OF APRIL ZAMBELLI-WEINER, PH.D.
REGARDING RESPONSES TO DOCUMENT REQUESTS

I, APRIL ZAMBELLI-WEINER, PH.D, do state and declare:

a. I am over the age of eighteen and competent to testify to the matters contained in this affidavit.

b. This affidavit is made based on my personal knowledge.

c. Per the Court's ruling on Defendant GSK's Motion to Compel, I hereby submit the following:

1. As for Document Request No. 2(c) of GSK's Amended Notice of Videotaped Deposition, all documents responsive to this Request have been produced and identified as AZW 013-016.

2. Documents AZW 013-016 are the "codes" I refer to in my deposition as being on my company's server.

3. As for Document Request No. 2(d) of GSK's Amended Notice of Videotaped Deposition (and Document Request No. 3 of GSK's Notice of Continued Videotaped Deposition), I am not in possession of any documents responsive to this Request other than what has already been produced.

4. When the Stata output was generated for the study as published in

Reproductive Toxicology, to the best of my recollection the results were copied and pasted into manuscript tables in real time. To my knowledge the Stata output was not printed out or saved electronically in any additional format.

I SOLEMNLY AFFIRM under the penalties of perjury and upon personal knowledge that the statements herein are true and correct to the best of my knowledge, information and belief.

Executed this 6th day of November, 2019.

April Zambelli-Weiner, Ph.D.