Date: November 13, 2007
To: Debra B. Birnkrant, M.D., Division Director
      Division of Anti-Viral Products (DAVP)
      Office of Antimicrobial Products (OAP)
Thru: Ann W. McMahon, MD, MS, Deputy Director
      For Mark I. Avigan, M.D., C.M., Director
      Division of Drug Risk Evaluation (DDRE)
      Office of Surveillance and Epidemiology (OSE)
From: Catherine Dormitzer Ph.D., M.P.H., Epidemiologist
      Andrew Mosholder M.D., M.P.H., Medical Officer
      Division of Drug Risk Evaluation
      Office of Surveillance and Epidemiology
Subject: Epidemiological Analysis of Four Health Claims Database Studies
Drug Name(s): Tamiflu (Oseltamirvir phosphate)
Submission Number: NDA21-087
Applicant/sponsor: Hoffman- La Roche Inc
OSE RCM #: 2007-828
CONTENTS

EXECUTIVE SUMMARY ............................................................................................................. 4
1 BACKGROUND/HISTORY .................................................................................................. 5
2 REVIEW METHODS AND MATERIALS ........................................................................... 6
3 RESULTS OF REVIEW-- STUDY #1 .................................................................................. 7
  3.1 Objectives ..................................................................................................................... .7
  3.2 Design ............................................................................................................................ 8
  3.3 Ethical Review ............................................................................................................... 9
  3.4 Data Source.................................................................................................................... 9
  3.5 Study Time Period(s) ..................................................................................................... 9
  3.6 Population .................................................................................................................... 10
  3.7 Exposure ...................................................................................................................... 11
  3.8 Sample Size and Statistical Power ............................................................................... 12
  3.9 Analyses and Study Results ......................................................................................... 12
4 SUMMARY AND RECOMMENDATIONS -- STUDY #1................................................ 18
5 RESULTS OF REVIEW -- STUDY 2 ................................................................................. 19
  5.1 Objectives .................................................................................................................... 19
  5.2 Design ..........................................................................................................................1 9
  5.3 Ethical Review ............................................................................................................. 20
  5.4 Data Source(s).............................................................................................................. 20
  5.5 Study Time Period(s) ................................................................................................... 20
  5.6 Exposure ...................................................................................................................... 21
  5.7 Disease Outcome of Interest ........................................................................................ 21
  5.8 Sample Size.................................................................................................................. 22
  5.9 Analyses and Study Results ......................................................................................... 22
6 SUMMARY AND RECOMMENDATIONS -- STUDY #2................................................ 23
7 RESULTS OF REVIEW -- STUDY 3 ................................................................................. 23
  7.1 Objectives .................................................................................................................... 23
  7.2 Design ..........................................................................................................................2 3
  7.3 Ethical Review ............................................................................................................. 24
  7.4 Data Source(s).............................................................................................................. 24
  7.5 Study Time Period(s) ................................................................................................... 24
  7.6 Population .................................................................................................................... 25
  7.7 Exposure ...................................................................................................................... 25
  7.8 Disease Outcome of Interest ........................................................................................ 25
EXECUTIVE SUMMARY

The Division of Anti-Viral Products (DAVP) Office of Antimicrobial Products (OAP) requested the Office of Surveillance and Epidemiology, Division of Drug Risk Evaluation (DDRE/OSE) to review for comment four health claims database studies sponsored by Roche that investigate the safety and effectiveness of Tamiflu (oseltamivir phosphate.)

The sponsor submitted the following four studies:


4. Wilcox M, Zhu S. “Neuropsychiatric Events among Influenza Patients” (February 9, 2007)

This consult evaluates each of these four studies separately.


The investigators examined the association that oseltamivir for the treatment of influenza and pneumonia, otitis media, and other respiratory conditions and associated hospitalizations. They examined the effect of patient’s high-risk status or prior influenza vaccination on these rates. Lastly, they examined rates of selected cardiovascular and neuropsychiatric events between patients who received oseltamivir treatment and those did not receive any antiviral treatment.

Overall, they found oseltamivir use reduced the risk of respiratory events, most strongly in the pediatric(0 – 13 years) population. There were however, serious concerns with the investigators’ analysis. Most importantly, patients 13-17 years of age were included in the adult sample and in the age strata, 13 - 49 years of age. These adolescents should have been included in the pediatric sample, not in the adult sample. A request has been made to the sponsor to provide their analyses using more appropriate age strata. The investigators also reported that they found 1,089 events in the psychiatric category. Their analysis did not stratify this analysis by age and included events up to 30 days beyond influenza diagnosis. There was little detail provided on the group of events that were included in the psychiatric events category. A request has been made to the sponsor to provide more detail on what events went into this sub-category, to stratify the results by the following age strata: under 18 years and 18+ years. We also requested the investigators to limit their analysis only to the events that occurred within 14 days after the influenza diagnosis.

The objective of this study was to examine if the risk of mortality, pneumonia and myocardial infarction in the thirty days after an influenza diagnosis is reduced in patients using oseltamivir. This study provides strong evidence that oseltamivir use lowers the risk of pneumonia in a healthy population. It does not provide evidence for a reduction in risk of death and MI. The population under study included an employed healthy population and their dependants, (mean age was 29 years) and all had health insurance, so some caution is needed when applying these results to the general population.


The objective of this study was to examine if the risk of mortality in the thirty days after an influenza diagnosis is reduced in patients using oseltamivir. This study focused on a healthy population (mean age was 29 years) and produced null findings. The sponsor may wish to focus future studies on an older, or at-risk population to examine the effect oseltamivir may have on mortality.

Study 4: Wilcox M, Zhu S. “Neuropsychiatric Events among Influenza Patients” (submitted February 9, 2007)

The objective of this study is to examine if persons who use oseltamivir are less likely to have neuropsychiatric events than influenza patients who do not use antiviral treatment. The main concern of the null finding is that investigators included all events that occurred in the 30 day period after influenza diagnosis, a very long time period for the assessment of acute effects. Secondly, the investigators did not stratify by age group and as a result, these findings cannot be easily interpreted. Another concern is that the outcomes included very diverse CNS events, such as seizures and headache, in the same outcome category, again making clinical interpretation difficult. A request has been submitted to the sponsor asking the investigators to stratify their analysis by the following age strata: <=17 years of age, >= 18 years; and to limit their analysis to events occurring within 14 days of the index date. Lastly, investigators were requested to match the outcomes listed in analysis with the ICD-9 codes they had provided.

In summary, the sponsor submitted four observational studies that used very large health claims databases to examine the association between oseltamivir use and related health outcomes. The sample sizes for all four studies were robust and over 70,000 in the adult samples and over 25,000 in the pediatric sample. The most persuasive findings from these studies relate to protection against pneumonia as a complication of influenza with oseltamivir treatment, but many of the reported results were not strong and some had serious shortcomings. The FDA has already made a request to the sponsor to ask the investigators to address our concerns.

1 BACKGROUND/HISTORY

The Division of Anti-Viral Products (DAVP) Office of Antimicrobial Products (OAP) requested the Office of Surveillance and Epidemiology, Division of Drug Risk
Evaluation (DDRE/OSE) review for comment four health claims database studies sponsored by Roche that investigate the safety and effectiveness of Tamiflu (oseltamivir phosphate.)

This submission was in response to the November 2005 Pediatric Advisory Committee meeting during which Roche offered to evaluate additional study data from the U.S. United Health Care Claims Database and any other applicable databases to gather information on mortality and neuropsychiatric events in oseltamivir treated versus non-antiviral treated patients.

The sponsor submitted the following four studies, which we will number as shown for ease of reference:

- **Study 1**: Thompson/Medstat “Study of the Impact of Oseltamivir on the Risk of Pneumonia and Other Outcomes, 2000 – 2006” (February 2007)
- **Study 2**: Nordstrom B L, Zhu S, Walker AM “Risk of Influenza Complications and Mortality Following Oseltamivir Use: A Retrospective Cohort Study” (April 3, 2006)
  - Full study report in follow-up to abstract by Nordstrom, et al submitted to agency on October 24, 2006
- **Study 4**: Wilcox M, Zhu S. “Neuropsychiatric Events among Influenza Patients” (February 9, 2007)

This consult evaluates each of these four studies separately.

**2 REVIEW METHODS AND MATERIALS**

The sponsor’s four epidemiological studies were evaluated for completeness and whether each study design and data collection achieved the proposed objectives. Because there were four separate studies, each study was evaluated separately and summarized together in the executive summary section.

This evaluation included a description of the following

- Study Objectives
- Research Methods Specified
  - Design
  - Data Sources
  - Ethical Review
  - Study Time Periods
  - Population Selected
  - Exposure Criteria
  - Disease Outcome
3 RESULTS OF REVIEW-- STUDY #1

3.1 OBJECTIVES

3.1.1 Objectives

The first study examined is “Study of the Impact of Oseltamivir on the Risk of Pneumonia and Other Outcomes, 2000 – 2006 -- Final Study Report.” The investigators outlined four study objectives:

1. Do patients receiving oseltamivir for the treatment of influenza have lower rates of pneumonia, otitis media, and other respiratory conditions than patients receiving no antiviral treatment?
   a. Are these results similar in pediatric and adult populations?

2. Do patients receiving oseltamivir for the treatment of influenza have lower rates of hospitalization for pneumonia, otitis media, and other respiratory conditions than patients receiving no antiviral treatment?
   a. Are these results similar in pediatric and adult populations?

3. What is the effect of patient’s high-risk status or prior influenza vaccination on the outcomes detailed in questions 1 and 2?

4. Do patients receiving oseltamivir experience different rates of selected cardiovascular and neuropsychiatric events than patients who were not treated with oseltamivir?

3.1.2 OSE Comments on Objectives

Given that the risk for pneumonia, respiratory conditions and otitis media are complications that arise from influenza and that neuropsychiatric events associated with oseltamivir is a current concern, the investigators’ study objectives are appropriate ones. FDA’s primary interest is objective #4 that addresses the incidence of neuropsychiatric events. Of key concern is the incidence of neuropsychiatric among adolescents and that was not addressed in the study objectives. This study would have been more informative had the investigator included an objective that focused specifically on this population.

Moreover, there were many objectives. The interpretation of the results would have been more straightforward if the investigators had specified one or two outcomes as being of primary interest. Multiple outcomes, in multiple subgroups, create the problem of multiple comparisons.
3.2 Design

3.2.1 Design

The study design was a retrospective cohort study that combined large health claims databases. The treatment group included patients who had an outpatient claim with an influenza diagnosis at an outpatient visit, and a prescription for oseltamivir within one day of diagnosis and that met the inclusion criteria. The control group was selected from a pool of patients who had an influenza claim and did not have a claim for an oseltamivir prescription or any other anti-viral medication and that met the inclusion criteria as well. The outcomes of interest were:

1. Rates of outpatient claims for pneumonia, otitis media and non-pneumonia respiratory conditions
2. Rates of in-patient claims for pneumonia and non-pneumonia respiratory conditions
3. Rates of any cause hospitalization
4. Rates of select safety outcomes
5. Direct healthcare utilization and expenditures (this outcome will not be examined in this consult, given that healthcare expenditures are not under FDA’s purview).

Five study samples were derived: adults (ages 13 and older), pediatrics (under 13 years of age), a safety outcomes sample that included all ages, a sample of patients that had received a prior flu vaccination, and a sample of patients classified as a high risk subgroup by virtue of various comorbidities (including cardiac disease, pulmonary disease, diabetes, renal impairment, and immunosuppression).

Propensity score matching was used to match treatment cases and controls for the adult, pediatric and safety outcomes samples using a “Nearest Neighbor” matching algorithm. The covariates used to compute a propensity score were: age, gender, geographic region, population density, medical co-morbidities, vaccination status, and type of health plan. For each matched analysis, the sample resulted in a 1:1 ratio of treated patients and controls. Given sample size constraints, propensity score matching was not performed on the last two samples: the vaccination and the high-risk group samples.

3.2.2 OSE Comments on Design

The study design chosen by the investigators was an appropriate one, given the data available and the study questions examined, i.e. a retrospective cohort study. At the same time, the study investigators provided very little detail on their justification for choosing propensity score matching to match cases and controls for three of their study samples. Little detail was provided on the covariates used to generate the propensity scores. The investigators presented (in tables 16 & 17) a description of the study samples’ cases and controls and it appears that there are no differences between the study populations based on the selected covariates used to match the samples. Therefore, it appears that appropriately matched controls were selected. However, they did not provide information on if or how the covariates used to generate matches would have affected their results; (i.e., were the covariates selected associated with both the probability of receiving treatment and the outcomes, and if they had not matched on these covariates, would that...
have changed the estimates of interest?). Furthermore, although the investigators provided an abundant number of tables in the Appendices, they did not provide tables that compared the samples prior to propensity score matching and after the match was implemented. It would have been helpful if these tables had been provided with accompanying p values for the covariates of interest.

For the vaccination and the high-risk group samples, covariates were added to the models to adjust for confounders. This is also an appropriate strategy, but there was little information on how the selected covariates affected their point estimates.

### 3.3 Ethical Review

#### 3.3.1 Ethical Review

The investigators used health claims data using MarketScan® Commercial Claims and Encounters and Medicare Supplemental and COB databases. As a result, informed consent was not sought nor obtained.

#### 3.3.2 OSE Comments on Ethical Review

The investigators used a health claims dataset that merged a variety of different sources. It would have been helpful to receive information on what measures were taken to assure all health records were properly anonymized and were HIPPA compliant. Documentation that this study was IRB approved was not provided, so the investigators should provide certification that this study received IRB approval.

### 3.4 Data Source

#### 3.4.1 Data Source

This study utilized the MarketScan Commercial Claims and Encounters and Medicare Supplemental and COB databases.

#### 3.4.2 OSE Comments on Data Sources

The data sources were robust and were appropriate for some of the objectives of the study. Assessing relevant neuropsychiatric events solely on claims data would still be difficult. It is possible that many neuropsychiatric events would not be properly recorded in the claims database, unless affected patients sought medical attention, and that may not always have been the case.

### 3.5 Study Time Period(s)

#### 3.5.1 Study Time Period(s)

The samples were selected from the selected databases for the dates of services for the following flu seasons: Oct 1 – March 31, Years 2001 – 2006. Claims data from six years were combined.
3.5.2 OSE Comments on Study Time Period(s)

Combining six years of data is an appropriate strategy because it increases statistical power; at the same time, the investigators did not provide information that temporal trends, (if any were found) did not affect the associations of oseltamivir use on the outcomes of interest.

3.6 POPULATION

3.6.1 Population

Health insurance claims data from US employers and health plans from the following datasets were used: MarketScan Commercial Claims and Encounters and Medicare Supplemental and COB databases.

Patients meeting the following inclusion criteria were included in the analysis:

- “Presence of a diagnosis of influenza on an outpatient claim (i.e., office visit, ER visit or outpatient clinic visit);
- Continuous enrollment in the health plan for at least three months prior to the date of influenza diagnosis;
- Continuous enrollment in the health plan for at least one month following the date of the influenza diagnosis, except where death occurred; and
- Availability of both medical and pharmacy data”

The following patients were excluded from the study:

- “Presence of pneumonia on the index date;
- Admission to or residence in a health care institution on the index date;
- Evidence of pregnancy on the index date; or
- Drug claim(s) for an antiviral medication other than oseltamivir (amantadine, flumadine, rimantadine, symetrel, zanavir)
- Patients receiving oseltamivir more than 1 day before or after the diagnosis”

Patients who had an oseltamivir claim, but no influenza diagnosis in the same season were not included in the study sample.

3.6.2 OSE Comments on Population

The patient population was appropriate. Given that it includes only patients that have health insurance under selected health systems contributing to the database, it may not be generalizable to the greater population, since patients that have health insurance are more likely to receive and fill a prescription for oseltamivir.

Information was not provided as to whether medical records were validated. If the study investigators did not validate their data, it is difficult to assess the accuracy of their data. It would be helpful if the study investigators could provide more information on how cases were validated. Alternatively, if only the diagnoses reflected in the claims were used for analysis that should be stated.
A subgroup analysis that examined patients receiving oseltamivir, without an influenza diagnosis, and as prophylactic treatment following exposure to influenza, particularly for neuropsychiatric outcomes, might have been informative. It would have been of interest to compare data on other anti-influenza compounds as well.

3.7 Exposure

3.7.1 Exposure
The study protocol defines exposure as having a prescription for oseltamivir within one day either before or after the index date (influenza diagnosis). Influenza diagnosis was defined as having an ICD-9 CM dx code of 487.xx on an outpatient claim.

3.7.2 OSE Comments on Exposure
The exposure outcome of having a recent prescription of oseltamivir is appropriate, although, as previously mentioned, it would have been useful to have studied prophylactic use as well (i.e., without a diagnosis).

3.7.3 Disease Outcome of Interest
The following disease outcome measures were used:
1. Rates of pneumonia, otitis media, and non-pneumonia respiratory conditions
2. Rates of inpatient pneumonia and non-pneumonia respiratory conditions
3. Rates of any cause hospitalizations
4. Direct healthcare utilization and expenditures
5. Rates of select safety outcomes
   a. Cardiac
      i. Acute myocardial infarction
      ii. Arthymias
      iii. CHF
      iv. Other
   b. CNS and Neuropsychiatric Events
      i. Disturbance of consciousness
      ii. Encephalitis
      iii. Abnormal movements
      iv. Psychiatric
      v. Seizure
      vi. Stroke
      vii. Vision Disturbances
      viii. Other

3.7.4 OSE Comments on Disease Outcome of Interest
The disease outcomes pneumonia, otitis media, and non-pneumonia respiratory conditions as well as rates of hospitalization are likely to be captured in health claims databases. The safety outcomes that are cardiac events most likely will be accurately captured in these health claims databases as well, unless they were fatal, in which case no health claim may have resulted, an important limitation.
The safety outcomes that are neuropsychiatric events, which are more variable in their manifestations and the type of clinical treatment received, may be more difficult to capture using these datasets mentioned above.

3.8 SAMPLE SIZE AND STATISTICAL POWER

3.8.1 Sample Size and Statistical Power

The investigators used propensity score matching to match cases and controls for the adult, pediatric and safety outcomes. There were 73,502 patients in the adult sample, 25,248 in the pediatric sample, and 81,411 patients in the safety outcomes sample. All three samples were matched using propensity score matching. There were two samples that were not matched using this method, the high risk group and the vaccination sample. For the high risk group analysis, there were 152,497 non-high risk patients, 5,364 high risk pediatric patients and 19,442 high risk adult patients. For the vaccination analysis, 211,025 patients in the vaccination sample that were divided into four different comparison groups, that ranged from 3,522 patients to 134,472 patients in the reference group.

3.8.2 OSE Comments on Sample Size

The sample sizes produced were large and robust for most of their outcomes. There were some outcomes, such as hospitalizations for the pediatric populations, where the numbers of events were sparse and made precise estimates difficult to obtain. The investigators did not age stratify their safety outcomes; given the large sample size it would have been helpful to see the results by age group.

3.9 ANALYSES AND STUDY RESULTS

3.9.1 Analyses and Study Results

For each outcome measure, multiple regressions were conducted to adjust for differences in baseline characteristics between oseltamivir treated cases and untreated controls. Cox proportional hazards regressions were used to estimate the relative risk of each clinical outcome. Logistic regression was used to evaluate safety outcomes. The covariates used in each model for the clinical (adult and pediatric), vaccination, safety and high risk population were: age, gender, region, urban status, vaccination status and presence of medical comorbidities.

Table 3.1 summarizes the findings of the clinical respiratory outcomes for both propensity score matched adult and pediatric samples. In the adult sample, oseltamivir use was not associated with the relative risk of pneumonia for any of the age strata. Although there was a mild positive association found in the older groups, it was not statistically significant. Oseltamivir use was negatively associated with the overall risk of a respiratory outcome, but was statistically significant for the 13-49 and 50-64 year old age strata. Oseltamivir use was negatively associated with the overall risk of otitis media, but was statistically significant for the 50-64 year age strata, where risk was reduced by close to 50%. The risk of pneumonia and respiratory conditions related hospitalizations
were not reduced with oseltamivir use, but risk of all cause hospitalizations for the 13-49 year age group was reduced by approximately 35%.

In the pediatric sample, oseltamivir use was associated with a decrease in risk of pneumonia for the 6-12 year age strata; there was a mild negative association found among the other age strata that was not statistically significant. Oseltamivir use was negatively associated with respiratory outcomes for all pediatric age strata and was statistically significant. The reduction in the risk of otitis media was found for all age groups and it was statistically significant for the 1-2 and 3-5 year age strata. Pneumonia and respiratory conditions related hospitalizations were too small to provide robust findings, but a reduction for all cause hospitalizations was “borderline significant” for all pediatric age groups combined.

Table 3.2 summarizes the next sample analyzed by the investigators, which was the vaccination sample. Cases were not matched to controls, using propensity score matching methods, due to concerns about the adequacy of the sample size. There were three groups, the vaccinated oseltamivir users, the unvaccinated oseltamivir users and the vaccinated no anti-viral users. All three groups were separately compared to a fourth group, unvaccinated no anti-viral users. Patients were divided into three age strata, pediatric patients, under 13 years of age, adults ages 13-64 and seniors 65+ years.

The vaccinated oseltamivir users had a higher risk of pneumonia in the adult and senior age strata compared to the unvaccinated no-antiviral group. A lower risk of respiratory conditions was found among the pediatric and adult strata when compared to the unvaccinated no-antiviral group. No statistically significant estimates were found with the other outcomes. When comparing the unvaccinated oseltamivir users to unvaccinated no anti-viral users, reductions in risk for pneumonia, respiratory conditions, otitis media and all cause hospitalizations was found among pediatric patients. Reductions in risk for respiratory diagnosis, otitis media and all cause hospitalization were also found for the adult population. Lastly, when comparing vaccinated no anti-viral users to unvaccinated no anti-viral users, an increase in risk was found for pneumonia and otitis media was found among the pediatric group.
Table 3.1: Summary Table of Respiratory Outcomes for Both the Adult and Pediatric Samples

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pneumonia (# of events)</th>
<th>Respiratory (# of events)</th>
<th>Otitis Media (# of events)</th>
<th>Hospitalization, pneumonia (# of events)</th>
<th>Hospitalization, all respiratory (# of events)</th>
<th>Hospitalization, all (# of events)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adult Population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Adults (73,502)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-49 years (52,170)</td>
<td>1.08 (0.95, 1.23)</td>
<td><strong>0.82 (0.79, 0.86)</strong></td>
<td>0.77 (0.65, 0.93)</td>
<td>1.15 (0.82, 1.60)</td>
<td>0.90 (0.59, 1.38)</td>
<td><strong>0.78 (0.67, 0.91)</strong></td>
</tr>
<tr>
<td>50-64 years (17,082)</td>
<td>1.01 (0.84, 1.22)</td>
<td><strong>0.82 (0.78, 0.86)</strong></td>
<td>0.83 (0.68, 1.01)</td>
<td>0.87 (0.52, 1.46)</td>
<td>0.81 (0.38, 1.73)</td>
<td><strong>0.65 (0.52, 0.81)</strong></td>
</tr>
<tr>
<td>65-74 years (2,550)</td>
<td>1.04 (0.84, 1.29)</td>
<td><strong>0.78 (0.73, 0.85)</strong></td>
<td><strong>0.51 (0.30, 0.87)</strong></td>
<td><strong>1.16 (0.65, 5.02)</strong></td>
<td><strong>0.96 (0.50, 1.84)</strong></td>
<td>0.92 (0.71, 1.20)</td>
</tr>
<tr>
<td>75-84 years (1,396)</td>
<td>1.47 (0.95, 2.30)</td>
<td>0.91 (0.75, 1.09)</td>
<td>0.56 (0.13, 2.37)</td>
<td>1.85 (0.68, 5.02)</td>
<td>0.79 (0.29, 2.12)</td>
<td>0.89 (0.56, 1.40)</td>
</tr>
<tr>
<td>85+ years (304)</td>
<td>1.06 (0.63, 1.78)</td>
<td>1.25 (0.96, 1.62)</td>
<td>***</td>
<td><strong>1.66 (0.55, 4.95)</strong></td>
<td><strong>1.45 (0.24, 8.78)</strong></td>
<td><strong>0.78 (0.46, 1.33)</strong></td>
</tr>
<tr>
<td></td>
<td>2.06 (0.64, 6.68)</td>
<td>1.09 (0.64, 1.86)</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>2.05 (0.77, 5.49)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric Population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Pediatric (25,248)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 years (993)</td>
<td><strong>0.55 (0.42, 0.71)</strong></td>
<td><strong>0.69 (0.64, 0.75)</strong></td>
<td><strong>0.74 (0.66, 0.83)</strong></td>
<td><strong>0.85 (0.42, 1.72)</strong></td>
<td><strong>0.38 (0.10, 1.43)</strong></td>
<td><strong>0.66 (0.44, 0.99)</strong></td>
</tr>
<tr>
<td>1-2 years (4,248)</td>
<td>0.65, 0.38, 1.12)</td>
<td><strong>0.70 0.58, 0.83</strong></td>
<td><strong>0.73 (0.60, 0.90)</strong></td>
<td>1.00 (0.27, 3.74)</td>
<td>0.18 (0.02, 1.64)</td>
<td>0.76 (0.38, 1.53)</td>
</tr>
<tr>
<td>3-5 years (6,142)</td>
<td>0.70, 0.42, 1.16)</td>
<td><strong>0.76 (0.64, 0.89)</strong></td>
<td><strong>0.76 (0.61, 0.94)</strong></td>
<td>0.81 (0.25, 2.67)</td>
<td>***</td>
<td>0.77 (0.34, 1.75)</td>
</tr>
<tr>
<td>6-12 years (13,865)</td>
<td><strong>0.48 (0.32, 0.73)</strong></td>
<td><strong>0.68 (0.61, 0.76)</strong></td>
<td>0.82 (0.65, 1.02)</td>
<td>0.82 (0.22, 3.04)</td>
<td>0.36 (0.04, 3.30)</td>
<td>0.58 (0.28, 1.17)</td>
</tr>
</tbody>
</table>

Statistically significant findings are bolded
*** no events among oseltamivir users recorded
### Table 3.2: Summary Table of Respiratory Outcomes for the Vaccinated Samples

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pneumonia</th>
<th>Respiratory Hospitalization, pneumonia</th>
<th>Otitis Media</th>
<th>Respiratory Hospitalization, all respiratory</th>
<th>Hospitalization, all causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated Oseltamivir Users: Unvaccinated No anti-viral Users</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric (&lt;=12 years)</td>
<td>0.76</td>
<td>(0.47, 1.24)</td>
<td>0.82</td>
<td>(0.24, 2.72)</td>
<td>(0.42, 0.85)</td>
</tr>
<tr>
<td>Adult (13-64 years)</td>
<td>1.53</td>
<td>(1.10, 2.13)</td>
<td>0.67</td>
<td>(0.52, 3.13)</td>
<td>(0.59, 0.66)</td>
</tr>
<tr>
<td>Seniors (65+ years)</td>
<td>2.28</td>
<td>(1.21, 4.31)</td>
<td>***</td>
<td>1.06</td>
<td>(0.71, 1.00)</td>
</tr>
<tr>
<td>Unvaccinated Oseltamivir Users: Unvaccinated No Anti-viral Users</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric (&lt;=12 years)</td>
<td>0.62</td>
<td>(0.50, 0.78)</td>
<td>0.71</td>
<td>(0.44, 1.47)</td>
<td>(0.31, 0.67)</td>
</tr>
<tr>
<td>Adult (13-64 years)</td>
<td>0.94</td>
<td>(0.74, 0.79)</td>
<td>0.75</td>
<td>(0.71, 1.27)</td>
<td>(0.69, 0.70)</td>
</tr>
<tr>
<td>Seniors (65+ years)</td>
<td>1.17</td>
<td>(0.92, 1.49)</td>
<td>0.43</td>
<td>(0.73, 2.02)</td>
<td>(0.67, 0.79)</td>
</tr>
<tr>
<td>Vaccinated No Anti-viral Users: Unvaccinated No Anti-viral Users</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric (&lt;=12 years)</td>
<td>1.39</td>
<td>(1.07, 1.81)</td>
<td>1.34</td>
<td>(0.45, 2.11)</td>
<td>(0.99, 1.20)</td>
</tr>
<tr>
<td>Adult (13-64 years)</td>
<td>1.11</td>
<td>(0.84, 1.48)</td>
<td>1.24</td>
<td>(0.61, 2.40)</td>
<td>(1.21, 1.24)</td>
</tr>
<tr>
<td>Seniors (65+ years)</td>
<td>0.85</td>
<td>(0.55, 1.31)</td>
<td>1.10</td>
<td>(0.62, 1.03)</td>
<td>(1.03, 0.73)</td>
</tr>
</tbody>
</table>

Statistically significant findings are bolded
*** no events among oseltamivir users recorded

---

The investigators examined respiratory outcomes for the high-risk population separately. There were 177,303 patients that met the selection criteria for the high-risk sample. Fourteen percent of the study eligible patients met the high risk criteria that were being in the following risk categories: cancer on chemotherapy, cardiac, chronic lung, diabetic renal dysfunction and immunocompromised (included HIV/AIDS, transplant, chemotherapy). As a result, there were 152,497 non-high risk patients, 5,364 high risk pediatric patients and 19,442 high risk adult patients.

Table 3.3 summarizes the findings of the analysis of this high risk sample. Oseltamivir use in the pediatric sample was associated with a decrease in risk of pneumonia, respiratory conditions, otitis media and all cause hospitalizations. When examining the association between oseltamivir use by risk category, statistically significant reductions in risk were found for respiratory conditions among patients with chronic lung disease, diabetes and renal dysfunction. A reduction risk for all cause hospitalizations was found for patients with diabetes as well.
Table 3.3: Summary Table of Respiratory Outcomes for the High Risk Sample

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pneumonia</th>
<th>Respiratory</th>
<th>Otitis Media</th>
<th>Hospitalization, all^^</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric &lt;=12</td>
<td>0.54 (0.31, 0.95)</td>
<td>0.77 (0.46, 0.91)</td>
<td>0.65 (0.46, 0.91)</td>
<td>0.42 (0.20, 0.85)</td>
</tr>
<tr>
<td>(5,364)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult 13+ years</td>
<td>1.02 (0.83, 1.24)</td>
<td>0.85 (0.79, 0.91)</td>
<td>0.81 (0.52, 1.25)</td>
<td>0.78 (0.64, 0.96)</td>
</tr>
<tr>
<td>(19,442)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Pneumonia</th>
<th>Respiratory</th>
<th>Otitis Media</th>
<th>Hospitalization, all^^</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac (n=6,463)</td>
<td>1.20 (0.87, 1.67)</td>
<td>0.88 (0.77, 1.01)</td>
<td>0.53 (0.25, 1.14)</td>
<td>0.94 (0.67, 1.30)</td>
</tr>
<tr>
<td>Chronic Lung (n=5,861)</td>
<td>1.00 (0.72, 1.38)</td>
<td><strong>0.89 (0.81, 0.98)</strong></td>
<td>0.87 (0.42, 1.80)</td>
<td>0.83 (0.58, 1.19)</td>
</tr>
<tr>
<td>Diabetic (n=9,090)</td>
<td>0.87 (0.64, 1.18)</td>
<td><strong>0.83 (0.73, 0.93)</strong></td>
<td>0.96 (0.48, 1.91)</td>
<td><strong>0.70 (0.52, 0.94)</strong></td>
</tr>
<tr>
<td>Renal Dysfunction (n=507)</td>
<td>0.81 (0.33, 2.01)</td>
<td><strong>0.57 (0.34, 0.97)</strong></td>
<td>na</td>
<td>0.39 (0.15, 1.04)</td>
</tr>
<tr>
<td>Immunocompromised (n=1,198)</td>
<td>0.84 (0.41, 1.75)</td>
<td>1.00 (0.99, 1.01)</td>
<td>2.45 (0.26, 22.80)</td>
<td>0.51 (0.00, 21.25)</td>
</tr>
</tbody>
</table>

^^ hospitalizations for all causes were the only hospitalization outcomes that were statistically significant.

Table 3.4 summarizes findings for the sample that focuses on safety outcomes that occurred within 14 days of influenza diagnosis. This sample was a propensity score matched sample of 40,704 oseltamivir users and 40,704 controls. Multiple logistic regression models were conducted to adjust for baseline characteristics between oseltamivir users and non-users. The entire sample was evaluated as one group, and age strata were not used. Both cardiac and CNS/neuropsychiatric events were evaluated. Regarding CNS/psychiatric events, oseltamivir users had a lower risk of events categorized as psychiatric, consciousness and other. Regarding cardiac events, oseltamivir users had a lower risk of arrhythmia and congestive heart failure.
Table 3.4: Summary of Safety Outcomes that occurred within 14 days of Influenza Diagnosis

<table>
<thead>
<tr>
<th>Safety Outcomes (n=81,408)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td></td>
</tr>
<tr>
<td>Any Event</td>
<td>0.75 (0.75, 0.81)</td>
</tr>
<tr>
<td>Any CNS/Neuropsychiatric Event</td>
<td>0.76 (0.68, 0.84)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>0.82 (0.70, 0.96)</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>0.50 (0.04, 5.50)</td>
</tr>
<tr>
<td>Consciousness</td>
<td>0.61 (0.48, 0.76)</td>
</tr>
<tr>
<td>Movement</td>
<td>0.41 (0.12, 1.35)</td>
</tr>
<tr>
<td>Seizure</td>
<td>0.88 (0.60, 1.29)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.72 (0.45, 1.16)</td>
</tr>
<tr>
<td>Other</td>
<td>0.80 (0.67, 0.95)</td>
</tr>
<tr>
<td>Any Cardiac Event</td>
<td>0.73 (0.62, 0.85)</td>
</tr>
<tr>
<td>AMI</td>
<td>0.82 (0.30, 2.28)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0.72 (0.59, 0.90)</td>
</tr>
<tr>
<td>CHF</td>
<td>0.61 (0.43, 0.88)</td>
</tr>
<tr>
<td>Other</td>
<td>0.86 (0.65, 1.13)</td>
</tr>
</tbody>
</table>

3.9.2 OSE Comments on Analyses and Study Results

The investigators examined the association between oseltamivir use and respiratory outcomes among the adult and pediatric populations. Overall, they found oseltamivir use reduced the risk of respiratory events, more so for pediatric patients than for adults. For pediatric patients 6 to 12 years oseltamivir users about 50% less likely to receive a pneumonia diagnosis. The risk of respiratory conditions was reduced approximately 30 percent among all pediatric age groups, and the risk of otitis media was reduced in the younger pediatric patients ages 1-2 and 3-5 years of age.

For the adult population, the risk of respiratory illnesses was lower for the 50-64 age strata. Risk of otitis media was reduced by 50% for the 50-64 year old patients and the risk for all cause hospitalizations was also reduced in the youngest adult age group, 13-49 years of age. These are all important findings.

There are serious concerns with the investigators analysis. Most importantly, patients 13-17 years of age should have been included in the pediatric sample and not in the adult sample. Including these patients in an age strata 13-49 years of age makes it difficult to assess these estimates, because the age range is too broad and include both pediatric and adult patients. Furthermore, the adult population included too many patients in the first age strata while being too fine-grained in the older populations. By dividing the older adult population into the following age categories 65-74, 75-84, 85+, the sample sizes were too small to produce statistically significant results. Had the investigators examined this population as one group, 65+ years of age, there may have been enough statistical power to show an association with some outcomes.
The results from the vaccination sample did not provide strong findings. The investigators pointed out that it is difficult to assess the vaccination status of this study population given that many patients obtain vaccines in non-traditional settings that are not recorded in health claims databases. We would concur with the investigators on this point.

Analysis of the high-risk cohorts revealed lower risk for respiratory illnesses for oseltamivir users for both the pediatric and adult age groups. Again, this study needed to include 13 to 17 year old patients in the pediatric age group rather than the adult population.

Lastly, the investigators reported on events found on a safety outcomes sample. This analysis had many limitations. First, the analysis did not stratify the population by age group. As a result, it provides little information to evaluate the association that oseltamivir use may have on any of the outcomes. Second, the investigators presented their findings on outcomes that occurred within 14 days of influenza diagnosis and within 30 days of diagnosis. We suggest presenting only the estimates for events that occurred within 14 days of influenza diagnosis because events that occurred 15-30 days after influenza diagnosis is too long of a time period for the assessment of these acute effects. The estimates the investigators provided for the fourteen day interval and 30 day interval all had outcomes with confidence intervals that overlapped a great deal. If the investigators had presented their estimates for outcomes that occurred in the 15-30 day interval after influenza diagnosis separately, it would have allowed us to examine the risk difference between the two time intervals and evaluate if the estimates provided in the 14 day interval might be more specifically attributed to oseltamivir use.

The investigators reported that they found 1,089 events in the psychiatric category but provided little detail on what events went into this sub-category. They also did not stratify their outcomes by age groups. As a result, these results are not very informative.

Overall, the investigators provided little detail on the analytic methods used. They stated they used propensity score matching methods using the nearest neighbor algorithm, but it appears that these covariates were added to their multiple regressions model as well. The investigators should have provided more detail on the results of the propensity score methods. For example, it would have been helpful to provide a table that outlined how the propensity score model performed. Secondly, the investigators should have included the estimates of the hazard ratios and relative risks for each of the covariates that were added to the model. This would have allowed others to examine the influence of possible confounders or other influences that explain the associations that oseltamivir use may have on the outcomes of interest.

4 SUMMARY AND RECOMMENDATIONS -- STUDY #1

The investigators examined the association between oseltamivir use and respiratory outcomes among the adult and pediatric populations. Overall, they found oseltamivir use reduced the risk of respiratory events, most strongly in the pediatric population. This finding has biological plausibility given the activity of the drug against influenza illness.

Serious concerns with the investigators’ analyses were found. Most importantly, patients 13-17 years of age should have been included in the pediatric sample and not in the adult sample. A request has been made to the sponsor to provide their analyses using more appropriate age strata.
The investigators reported on events found on a safety outcomes sample and this analysis had many limitations. Most importantly, the analysis did not stratify the population by age group. As a result, it provides little information to evaluate the association of oseltamivir use may have on any of the outcomes, especially in the age group of interest, adolescents. The investigators reported that they found 1,089 events in the psychiatric category. A request has been made to the sponsor to provide more detail on what events went into this sub-category and to stratify by age groups.

The investigators should have provided more detail on the results of the propensity score methods. For example, it would have been helpful to provide a table outlined how the propensity score model performed. Secondly, the investigators should have included the estimates of the hazard ratios and relative risks for each of the covariates that were added to the model to examine possible influences that explain the associations that oseltamivir may have on the outcomes of interest.

5 RESULTS OF REVIEW -- STUDY 2

The next study that the sponsor submitted was titled: “Risk of Influenza Complications and Mortality Following Oseltamivir Use: A Retrospective Cohort Study” (April 3, 2006) by Nordstrom B L, Zhu S, Walker AM. It is a full study report in follow-up to an abstract by Nordstrom et al submitted to agency on October 24, 2006

5.1 OBJECTIVES

5.1.1 Objectives

The objective of this study is to examine if the risk of mortality and pneumonia and myocardial infarction in the thirty days after an influenza diagnosis is reduced in patients using oseltamivir.

5.1.2 OSE Comments on Objectives

The investigator’ intent was to extend the findings of a study that found that mortality was reduced with the use of oseltamivir in one nursing home population. Since influenza causes a substantial number of deaths and since complications such as pneumonia and myocardial infarction are associated with influenza, the objective was an appropriate one.

5.2 DESIGN

5.2.1 Design

The study design was a retrospective cohort study that used the Ingenix Research Data Mart health claims database.

Propensity score matching was used to match treatment cases and controls. Propensity scores were estimated using unconditional logistic regression analysis that incorporated all identified predictors of oseltamivir use as independent variables in the regression and group status

---

(treatment or no treatment) as the outcome. The model included a priori characteristics and empirically derived variables as well. The investigators included all variables where the difference between the two groups had a p-value of less than 0.10 to estimate the propensity score. The covariates used to compute a propensity score were: age, gender, number of office visits, number of drugs, influenza season, month of index date, medical co-morbidities, vaccination status, and class of drugs at diagnosis.

5.2.2 OSE Comments on Design

The study design chosen by the investigators was an appropriate one, given the data available and the study questions examined, i.e. a retrospective cohort study. Propensity score matching was used to match treatment cases to untreated controls. This method allows adjustment for many sources of bias to be addressed simultaneously. The study investigators provided justification for choosing the covariates used to estimate the propensity score to match cases and controls. A review of the tables that describe the study population before and after propensity score matching, reveals that appropriately matched controls were selected. There were approximately 18 controls per case, which is a very high ratio.

5.3 Ethical Review

5.3.1 Ethical Review

The dataset the investigators used was a health claims database. The New England Institutional Review Board approved this study.

5.3.2 OSE Comments on Informed Consent

Given that the investigators obtained IRB approval, FDA has no ethical concerns.

5.4 Data Source(s)

5.4.1 Data Source(s)

This study utilized the Ingenix Research Data Mart health claims database. The data are routinely cleaned and checked and are updated frequently.

5.4.2 OSE Comments on Data Sources

With the exception noted below, health claims data are robust and appropriate given the objectives of the study. Although, the investigators stated that data are routinely cleaned and checked, this information was not validated through medical record review. Therefore, it is difficult to assess the accuracy of their data. Furthermore, it is difficult to evaluate the accuracy of the death outcome given that patients were ascribed a death outcome without validation from the National Death Index nor by another validation method.

5.5 Study Time Period(s)

5.5.1 Study Time Period(s)

The sample was selected for the dates of service for the following influenza seasons: November through March for years 1999-2004. Claims data from six years were combined.
5.5.2 OSE Comments on Study Time Period(s)

Combining six years of data is an appropriate strategy because it increases statistical power; although temporal trends were noted, the investigators adjusted for them.

5.5.3 Population

The study population included patients in the database who were older than one year of age and received an ICD-9 code of influenza (487.*). Exclusions included patients that received another antiviral such as amantadine, rimantadine or zanamivir. Patients that received an influenza diagnosis the same day as an influenza vaccine were also excluded from the study because the investigators did not consider those to be genuine cases of influenza.

Subjects had a minimum of six months of continuous enrollment in the health plan prior to the index date (the date of the influenza diagnosis). Patients who were hospitalized from at least the day before the index date through the day following the index date were excluded.

5.5.4 OSE Comments on Population

The strength of this data is that it is a large robust sample. However, the patient population may not be the most appropriate one. Although the investigators did not provide an age range for their sample, they reported the mean age as 29 years of age, (S.D. = 17) so it is a relatively young population and at a low risk for mortality\(^2\). To examine the risk of myocardial infarction, the investigators did limit their analysis to patients 50 years of age and older and that is a strength of that analysis. Furthermore, given that it includes only patients that have health insurance under the health systems contributing to the database, it may not be generalizable to the greater population, but patients that have health insurance are the ones that are more likely to receive and fill a prescription for oseltamivir.

5.6 EXPOSURE

5.6.1 Exposure

Exposure was defined as having a pharmacy claim for oseltamivir accompanied by an influenza diagnosis. Without a consistent case definition for influenza, “exposure” to the disease will be inconsistent- this would potentially impact on outcomes of interest.

5.6.2 OSE Comments on Exposure

The exposure outcome of having a recent prescription of oseltamivir is an appropriate one.

5.7 DISEASE OUTCOME OF INTEREST

5.7.1 Disease Outcome of Interest

The outcomes of interest were death from any cause, pneumonia and MI occurring during the 30 days following the index date. The occurrence of pneumonia and MI were determined with an appropriate ICD-9 diagnosis code and appropriate physician visit procedure code.

To determine deaths, the investigators examined claims profiles “for all subjects with a diagnosis code of sudden death (798.***), with a hospital discharge status indicating death, or for whom no further claims were submitted later than one month after the index date. Patients lacking a diagnosis or discharge status indicating death were assumed to have died only if the claims clearly indicated terminal medical care in a hospital or ED” [emphasis added].

5.7.2 OSE Comments on Disease Outcome of Interest

Although pneumonia and MI would most likely be appropriately determined, given that this methodology was not validated using medical record review, it is difficult to assess the validity of these outcomes. The methodology the investigators used to determine death may be not always be an accurate one.

5.8 SAMPLE SIZE

5.8.1 Sample Size

There were 37,668 patients with a dispensing of oseltamivir on the date of influenza diagnosis and 131,121 patients with a diagnosis of influenza but no antiviral medications who all met study inclusion criteria. There were 53 deaths and 53 MI events and 4,468 pneumonia events.

5.8.2 OSE Comments on Sample Size

The sample size was large and robust. There were two outcomes, though, death and MI, where the numbers of events were too low to produce reliable estimates.

5.9 ANALYSES AND STUDY RESULTS

5.9.1 Analyses and Study Results

Cox proportional hazards regressions were used to estimate the relative risk of death, pneumonia and MI. The risk of MI was limited to patients 50 years of age and older. Table 5.1 summarizes the findings for each outcome. Oseltamivir use was associated with a lower risk of pneumonia. A non-significant lower risk of death and MI was found in the oseltamivir users as well.

Table 5.1: Summary of Outcomes that occurred within 30 days of Influenza Diagnosis

<table>
<thead>
<tr>
<th>Outcome (# of Events)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death^ (53)</td>
<td>0.35 (0.05, 2.70)</td>
</tr>
<tr>
<td>Pneumonia^ (4,468)</td>
<td>0.70 (0.64, 0.76)</td>
</tr>
<tr>
<td>Myocardial Infarction* (53)</td>
<td>0.76 (0.22, 2.61)</td>
</tr>
</tbody>
</table>

^ n= 168,789
* Analysis includes only patients at least 50 years of age; n= 23,284

5.9.2 OSE Comments on Analyses and Study Results

A lower risk of pneumonia among oseltamivir users appears to be a strong result, and it has biological plausibility given the activity of the drug. It was also reported in a previously
published study of a similar database. There were null findings on deaths and MI, and that may be the result of using a healthy population where the incidences of these events were too low to produce stable estimates; there were only 53 events for each of these outcomes. Based on the tables presented by investigators, it appears that a properly balanced sample was obtained and is likely to have greatly reduced any bias the sample may have had.

6 SUMMARY AND RECOMMENDATIONS -- STUDY #2

This study provides evidence that oseltamivir use lowers the risk of pneumonia in a healthy younger population. It does not provide evidence on risk of deaths and MI in the context of oseltamivir use. That may be the result of a small number of events. The strengths are that this study used a large patient population, and the investigators used appropriate methods to adjust for possible biases that may affect the association between oseltamivir users and non-antiviral users. There are some limitations, first this sample included an employed healthy population and their dependants, all with health insurance. Secondly, the investigators did not provide an age range for this population, though the mean age suggests a relatively young population. Therefore some caution is needed when applying these results to the population at large.

7 RESULTS OF REVIEW -- STUDY 3

The third study the sponsor submitted was titled: “A Retrospective Study of Mortality Following Influenza among Tamiflu Users” (March 1, 2007) by Wilcox M, Nordstrom B, Zhu S et al.

7.1 OBJECTIVES

7.1.1 Proposed/Actual Objective

The primary objective of this study is to examine if persons with a claims diagnosis of influenza who use oseltamivir have lower rates death from respiratory and circulatory causes, all causes and from pneumonia. A secondary objective is to examine the rates of myocardial infarction and pneumonia.

7.1.2 OSE Comments on Objectives

These objectives are similar to study #2; the main difference being the validation of death outcomes (see below). At the same time, influenza causes a substantial number of deaths and complications which themselves may have a death outcome, so the objective was appropriate.

7.2 DESIGN

7.2.1 Design

The study design was a retrospective cohort study that used the Ingenix Research Data Mart health claims database. The study population included patients one year of age or older that received an ICD-9 code of influenza. Propensity score matching was used to match treatment

cases and controls. The primary outcome, death, was determined through the National Death Index (NDI) for fact and cause of death for all patients whose claims ended during the 90 days after influenza diagnosis.

7.2.2 OSE Comments on Design

The study design chosen by the investigators was an appropriate one, given the data available and the study questions examined, i.e. a retrospective cohort study. Propensity score matching was used to match treatment cases to untreated controls. This method allows adjustment for many sources of bias to be addressed simultaneously. The study investigators provided justification for choosing the covariates used to estimate the propensity score to match cases and controls. The authors reported differences in the sample were still found after propensity score matching, so they included propensity score quintiles in each of their regression models. Because they did not provide details of subject characteristics, it was difficult to assess the appropriateness of their model. There were approximately 3.5 controls per case, an acceptable ratio.

7.3 Ethical Review

7.3.1 Ethical Review

The dataset the investigators used was a health claims database. The New England Institutional Review Board approved this study.

7.3.2 OSE Comments on Ethical Review

Given that the investigators obtained IRB approval, FDA has no ethical concerns.

7.4 Data Source(s)

7.4.1 Data Source(s)

This study utilized the Ingenix Research Data Mart health claims database. The data are routinely cleaned, checked and updated frequently.

7.4.2 OSE Comments on Data Sources

Health claims data are robust and appropriate given the objectives of the study. Investigators stated that data are routinely cleaned and checked, but this information was not validated through medical record review. Therefore, it is difficult to assess the accuracy of their data.

7.5 Study Time Period(s)

7.5.1 Study Time Period(s)

The sample was selected for the dates of service for the following influenza seasons: November through March for years 1999-2005. Claims data from seven years were combined.
7.5.2 OSE Comments on Study Time Period(s)

Combining seven years of data is an appropriate strategy because it increases statistical power; the investigators adjusted for temporal trends.

7.6 POPULATION

7.6.1 Population

The study population included patients in the database who were older than one year of age and received an ICD-9 code of influenza (487.*). The mean age was 29 years of age for the oseltamivir users and 25.7 years of age for the non-users. Subjects had a minimum of six months of continuous enrollment in the health plan prior to the index date (the date of the influenza diagnosis). Patients who were hospitalized from at least the day before the index date through the day following the index date were excluded. Patients who received another anti-viral therapy were also excluded.

7.6.2 OSE Comments on Population

The investigators state “the elderly and infirm are under-represented.” This patient population is not the most appropriate one. Mortality due to influenza related complications are rare in this healthy population, and as a result it is difficult to produce statistically significant findings. In addition, given that it includes only patients that have health insurance programs covered in this database, it may not be generalizable to the entire U.S. population. At the same time, patients that have health insurance are the ones that are more likely to receive and fill a prescription for oseltamivir.

7.7 EXPOSURE

7.7.1 Exposure

Exposure was defined as having a pharmacy claim for oseltamivir accompanied by an influenza diagnosis.

7.7.2 OSE Comments on Exposure

The exposure outcome of having a recent prescription of oseltamivir is an appropriate one.

7.8 DISEASE OUTCOME OF INTEREST

7.8.1 Disease Outcome of Interest

“The primary study outcome was death from any respiratory or circulatory cause occurring during the 30 days following the index date. Death outcomes through the end of 2004 were determined through a search of the National Death Index (NDI) for fact and cause of death for all patients whose claims ended during the 90 days after influenza diagnosis. The NDI includes a binary flag indicating likelihood of death. We included all individuals whom the NDI indicated were likely dead.”

“For patients whose claim ended during the risk period in 2005, we reviewed the full chronological sequence of insurance claims…for all patients with a hospital discharge status indicating death, a sudden death diagnosis code, or codes for ambulance services, intubation
or resuscitation near the time of the end of claims for the patient. Patients lacking a diagnosis or discharge status indicating death were assumed to have died only if the claims clearly indicated terminal medical care in a hospital or emergency department, and there were no subsequent claims for medical services. Claims profiles were also reviewed for patients whose claims ended prior to 2005 to allow validation of the profile-review methods of identifying deaths."

Other outcomes included deaths from pneumonia, deaths from influenza, and all-cause mortality. The investigators included any cause of death designated as either underlying or contributing to the death.

Secondary outcomes included pneumonia and myocardial infarction (MI). Both of these outcomes were identified through claims data alone. Patients with a claim for pneumonia or MI during the week preceding the index date were excluded from the analysis of that outcome.

7.8.2 OSE Comments on Disease Outcome of Interest

For determining death, the investigators used one method for the first six years and then a different methodology for the last year of data. Given the large sample size, it would have been preferable that the investigators limit their analysis the years where they could obtain death information exclusively from the NDI.

We do not have concerns about the use of ICD-9 diagnostic codes for pneumonia and MI in this dataset.

7.9 SAMPLE SIZE

7.9.1 Sample Size

There were 60,287 oseltamivir users and 175,933 no antiviral users used for this analysis.

7.9.2 OSE Comments on Sample Size

The sample size was large and robust. However, there were only 33 deaths attributable to respiratory and circulatory causes and 45 deaths attributed to all causes. Given the sparseness of the outcomes, it is difficult to produce a reliable, precise estimate. There were 13 deaths attributable to pneumonia and none that had taken oseltamivir that results in a “zero cell” and so an estimate for that event cannot be computed. There were enough pneumonia events, however, to produce a reliable estimate.

7.10 ANALYSES AND STUDY RESULTS

7.10.1 Analyses and Study Results

Table 7.1 summarizes the findings for each outcome. Multiple logistic regressions were used to estimate the relative risk of death, pneumonia and MI. Oseltamivir use was not associated with a lower the risk of mortality, pneumonia or myocardial infarction.
Table 7.1: Summary of Adjusted Odds Ratios of Mortality and other Outcomes that occurred within 30 days of Influenza Diagnosis

<table>
<thead>
<tr>
<th>Outcome (# of Events)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory or Circulatory Mortality</td>
<td>0.38 (0.08, 1.68)</td>
</tr>
<tr>
<td>Pneumonia or Influenza Mortality*</td>
<td>---</td>
</tr>
<tr>
<td>All cause mortality (45)</td>
<td>0.53 (0.18, 1.58)</td>
</tr>
<tr>
<td>Pneumonia diagnosis (3,339)</td>
<td>1.01 (0.92, 1.11)</td>
</tr>
<tr>
<td>Myocardial Infarction (43)</td>
<td>1.48 (0.68, 3.21)</td>
</tr>
</tbody>
</table>

* no events occurred for oseltamivir users, so an estimate could not be produced

7.10.2 OSE Comments on Analyses and Study Results

The result of these null findings could be the result of the low number of mortality events. Given the median age of this population was 29 years, this is not a surprising finding.

8 SUMMARY AND RECOMMENDATIONS -- STUDY #3

This study focused on a healthy and relatively young population where the mean age was 29 years of age; and so the null findings are not surprising. The numbers of mortality events were low. The sponsor may choose to focus on an older or at-risk population to examine the effect oseltamivir may have on mortality.

9 RESULTS OF REVIEW -- STUDY 4

The last study the sponsor submitted was titled: “Neuropsychiatric Events among Influenza Patients” (February 9, 2007) by Wilcox M, Zhu S

9.1 OBJECTIVES

9.1.1 Objective

The objective of this study is to examine if persons with a claims diagnosis of influenza who use oseltamivir are less likely to have neuropsychiatric events than influenza patients who do not use antiviral treatment.

9.1.2 OSE Comments on Objectives

Given the current concern, of neuropsychiatric events associated with oseltamivir use, the investigators’ study objectives are ones in which the FDA is particularly interested. Of primary concern, is the incidence of neuropsychiatric among adolescents and that was not addressed in these study objectives. This study would have been more informative had the investigators focused specifically on this population.

9.2 DESIGN

9.2.1 Design

The study design was a retrospective cohort study that used the Ingenix Research Data Mart health claims database. The study population included patients one year of age or older that received an ICD-9 code of influenza. Propensity score matching was used to match treatment
cases and controls. The study outcome included claims for neuropsychiatric events that occurred during the 30 days after the index date.

9.2.2 OSE Comments on Design

The study design chosen by the investigators was an appropriate one, given the data available and the study questions examined, i.e. a retrospective cohort study. Propensity score matching was used to match treatment cases to untreated controls. The study investigators provided justification for choosing the covariates used to estimate the propensity score to match cases and controls. As in study #3, the authors reported differences in the sample were still found after propensity score matching, so they included propensity score quintiles in each of their regression models. Because they did not provide details of subject characteristics, it was difficult to assess the appropriateness of their model. It appears that appropriately matched controls were selected. There were approximately 3 controls per case, an acceptable ratio.

9.3 Ethical Review

9.3.1 Ethical Review

The dataset the investigators used was a health claims database. The New England Institutional Review Board approved this study.

9.3.2 OSE Comments on Informed Consent

Given the investigators obtained IRB approval, FDA has no ethical concerns.

9.4 Data Source(s)

9.4.1 Data Source(s)

This study utilized the Ingenix Research Data Mart health claims database. The data are routinely cleaned and checked and are updated frequently.

9.4.2 OSE Comments on Data Sources

Health claims data is robust but neuropsychiatric events, especially without record review, may not be fully captured using health claims data. Furthermore, investigators stated that data are routinely cleaned and checked, but this information was not validated through medical record review. Therefore, it is difficult to assess the accuracy of their data.
9.5 **STUDY TIME PERIOD(S)**

9.5.1 **Study Time Period(s)**

The sample was selected for the dates of service for the following influenza seasons: Influenza seasons November 1, 1999 through April 1, 2005

9.5.2 **OSE Comments on Study Time Period(s)**

*Combining seven years of data is an appropriate strategy because it increases statistical power; the investigators adjusted for temporal trends.*

9.6 **POPULATION**

9.6.1 **Population**

The study population included patients in the database who were older than one year of age and received an ICD-9 code of influenza (487.*). Exclusions included patients that received another antiviral such as amantadine, rimantadine or zanamivir. Patients that received an influenza diagnosis the same day as an influenza vaccine were also excluded from the study because the investigators did not consider those to be genuine cases of influenza. The mean age was 29 years of age for the oseltamivir users and 25.7 years of age for the non-users.

Subjects had a minimum of six months of continuous enrollment in the health plan prior to the index date (the date of the influenza diagnosis). Patients who were hospitalized from at least the day before the index date through the day following the index date were excluded.
9.6.2 OSE Comments on Population

The patient population includes only patients that have health insurance under the health systems contributing to the database, it may not be generalizable to the entire population, but patients that have health insurance are the ones that are more likely to receive and fill a prescription for oseltamivir. The investigators did not provide the age range of this population, but stated that the mean age was approximately 29 years of age for the oseltamivir users and 26 years of age for the non-users; so it is a somewhat younger population and one that the FDA is interested in evaluating for these outcomes.

9.7 EXPOSURE

9.7.1 Exposure

Exposure was defined as having a pharmacy claim for oseltamivir accompanied by an influenza diagnosis.

9.7.2 OSE Comments on Exposure

The exposure outcome of having a recent prescription of oseltamivir is an appropriate one.

9.8 DISEASE OUTCOME OF INTEREST

9.8.1 Disease Outcome of Interest

“The study outcomes included claims for neuropsychiatric events that occurred during the 30 days after the index date. Three comprehensive categories of neuropsychiatric events were identified. ICD-9 Diagnosis Codes were used. The broadest category, which was designated “Any Neuropsychiatric Event” included viral meningitis and viral encephalitis, psychosis, neurotic disorders, epilepsy, migraine, strabismus and stroke.

A more restrictive definition of neuropsychiatric outcomes, “Major Neuropsychiatric Events” excluded chronic disorders, conditions with stated etiology, congenital or hereditary disorders and spinal cord disorders.”

The investigators also created a category of “Neuropsychiatric Events specific to CNS stimulation”, using diagnosis codes intended to represent central nervous system (CNS) stimulation: psychotic reactions, delusion, delirium, confusion, euphoria, hallucination, insomnia, nightmares, night terrors, anxiety, agitation, nervousness, restlessness, irritability, headache, panic states, aggressive behavior, or seizures.

9.8.2 OSE Comments on Disease Outcome of Interest

The investigators examined disease outcomes that occurred within 30 days after the index date. This is a lengthy window of time for assessment of events with a drug that is given for only a few days, and would include events occurring weeks after oseltamivir exposure. A request has been made to the sponsor to have the investigators limit their analysis to events that occurred within 14 days.
It was difficult to assess what criteria the investigators used to classify ICD-9 codes into these three categories. It would have been helpful if the investigators cited a study or other reference that was used to establish these criteria. In our view, the categories are overly broad, because they group together very diverse CNS outcomes (such as seizures and headache, or neurosis and strokes, as examples).

Ideally, medical records would have been reviewed to validate the neuropsychiatric diagnoses, which may be more subtle and variable compared to such outcomes as MI. Furthermore, it is far from certain that neuropsychiatric events of the type that have raised concerns with oseltamivir will be reliably captured by healthcare claims.

9.9 SAMPLE SIZE

9.9.1 Sample Size

There were 60,834 oseltamivir users and 183,786 no antiviral users used for this analysis. There were 10,162 neuropsychiatric events.

9.9.2 OSE Comments on Sample Size

The sample size was large and robust and there were sufficient numbers of events to produce reliable estimates.

9.10 ANALYSES AND STUDY RESULTS

9.10.1 Analyses and Study Results

Logistic regression models were used to examine the association of oseltamivir use on neuropsychiatric outcomes. Six individual diagnoses were excluded because there were fewer than 20 cases: organic psychosis, drug psychosis, schizophrenia, disturbances of conduct not elsewhere classified, organic sleep disorder and visual disturbances.

Table 9.1 summarizes the findings for each outcome. Oseltamivir use was found to be negatively for the three broad categories: “any neuropsychiatric event”, “major neuropsychiatric event” and events “specific to CNS stimulation”.

31
Table 9.1: Summary of Adjusted Odds Ratios of Neuropsychiatric Events that occurred within 30 days of Influenza Diagnosis

<table>
<thead>
<tr>
<th>Outcome (# of events)</th>
<th>aOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any neuropsychiatric event (10,162)</td>
<td><strong>0.89 (0.85, 0.94)</strong></td>
</tr>
<tr>
<td>Major neuropsychiatric event (8,838)</td>
<td><strong>0.89 (0.85, 0.94)</strong></td>
</tr>
<tr>
<td>Specific to CNS stimulation (6,587)</td>
<td><strong>0.88 (0.83, 0.94)</strong></td>
</tr>
<tr>
<td>Transient Mental Disorder/conditions classified elsewhere</td>
<td>0.71 (0.31,1.62)</td>
</tr>
<tr>
<td>Affective psychosis</td>
<td>0.97 (0.83, 1.13)</td>
</tr>
<tr>
<td>Other non-organic psychosis</td>
<td>0.94 (0.45, 1.93)</td>
</tr>
<tr>
<td>Anxiety, dissociative &amp; somatoform disorder</td>
<td>0.94 (0.83, 1.07)</td>
</tr>
<tr>
<td>Special syndromes/syndromes not elsewhere classified</td>
<td><strong>0.65 (0.45, 0.93)</strong></td>
</tr>
<tr>
<td>Epilepsy &amp; recurrent seizures</td>
<td>1.19 (0.79, 1.78)</td>
</tr>
<tr>
<td>Migraine</td>
<td>0.93 (0.79, 1.10)</td>
</tr>
<tr>
<td>Other brain conditions</td>
<td>0.58 (0.23, 1.44)</td>
</tr>
<tr>
<td>General Symptoms</td>
<td><strong>0.84 (0.74, 0.97)</strong></td>
</tr>
<tr>
<td>Symptoms - nervous/musculoskeletal</td>
<td>1.13 (0.61, 2.09)</td>
</tr>
<tr>
<td>Symptoms involving the neck</td>
<td><strong>0.82 (0.73, 0.92)</strong></td>
</tr>
<tr>
<td>Other unknown causes</td>
<td>0.56 (0.20, 1.54)</td>
</tr>
</tbody>
</table>

9.10.2 OSE Comments on Analyses and Study Results

The investigators reported that there was evidence of a protective effect on some of the CNS outcomes. The main concern of these finding is that investigators included all neuropsychiatric events that occurred in the 30 day period after influenza diagnosis. That is too long of a time period. Secondly, the investigators did not stratify by age group and as a result, these findings are difficult to interpret. In addition, the overly broad outcome categories selected make clinical inferences difficult from these data.

10 SUMMARY AND RECOMMENDATIONS -- STUDY #4

A request has already been submitted to the sponsor asking the investigators to stratify their analysis by the following age strata: <=17 years of age, >= 18 years and to limit their analysis to events occurring within 14 days of the index date. Lastly, investigators were requested to match the outcomes listed in their analysis with ICD-9 codes they had provided in their report. Although a mild negative association was found with oseltamivir use and some neuropsychiatric events, given the time period used to evaluate these events and the fact that the events were not stratified by age, the findings as reported are not persuasive.