# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 021246Orig1s045 and 021087Orig1s062

# MEDICAL REVIEW(S)

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 21-246/S-045** **Applicant: Hoffmann-La Roche Inc.** **Stamp Date: June 21, 2012**

**Drug Name: TAMIFLU® (oseltamivir phosphate)** **NDA/BLA Type: Priority Review**

On initial overview of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| **FORMAT/ORGANIZATION/LEGIBILITY** | | | | | |
| 1. | Identify the general format that has been used for this application, e.g. electronic CTD. | X | | | Electronic submission |
| 2. | On its face, is the clinical section organized in a manner to allow substantive review to begin? | X | | | |
| 3. | Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin? | X | | | |
| 4. | For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)? | X | | | |
| 5. | Are all documents submitted in English or are English translations provided when necessary? | X | | | |
| 6. | Is the clinical section legible so that substantive review can begin? | X | | | |
| **LABELING** | | | | | |
| 7. | Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies? | X | | | |
| **SUMMARIES** | | | | | |
| 8. | Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)? | X | | | |
| 9. | Has the applicant submitted the integrated summary of safety (ISS)? | X | | | Also contains CTD Summary of Clinical Safety |
| 10. | Has the applicant submitted the integrated summary of efficacy (ISE)? | X | | | Also contains CTD Summary of Clinical Efficacy |
| 11. | Has the applicant submitted a benefit-risk analysis for the product? | X | | | |
| 12. | Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug? | | X | | 505(b)(1) supplement |
| **DOSE** | | | | | |
| 13. | If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?<br><br>Study Number: CASG 114 (WP20749)<br>Study Title: "A Pharmacokinetic/Pharmacodynamic and Safety Evaluation of Oseltamivir (Tamiflu®) for the Treatment of Children Less than 24 Months of Age with Confirmed Influenza Infection."<br>Sample Size: 68 subjects<br>Location in submission: Section 5.3.5.3. | X | | | |

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| | Study Number: WP22849<br>Study Title: "An Open-Label, Prospective, Pharmacokinetic/Pharmacodynamic, and Safety Evaluation of Oseltamivir (Tamiflu®) in the Treatment of Infants 0 to < 12 Months of Age with Confirmed Influenza Infection."<br>Sample Size: 65 subjects (54 in 2010/2011 influenza season, 11 in 2011/2012 influenza season)<br>Location in submission: Section 5.3.5.3. | | | | |
| **EFFICACY** | | | | | |
| 14. | Do there appear to be the requisite number of adequate and well-controlled studies in the application?<br><br>Pivotal Study #1: CASG 114 (WP20749)<br>Indication: Treatment of influenza in pediatric patients (including infants with a post conceptional age of at least 36 weeks) who have been symptomatic for no more than 2 days.<br><br>Pivotal Study #2: WP22849<br>Indication: Treatment of influenza in pediatric patients (including infants with a post conceptional age of at least 36 weeks) who have been symptomatic for no more than 2 days. | | X | | Not an initial NDA, adequate for sNDA for additional population.<br><br>Controlled study not requested; PK and safety study requested and will rely on extrapolation from adult efficacy. The studies are not the standard Phase 3 trials usually submitted for an NDA. |
| 15. | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | X | | | |
| 16. | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. | X | | | Product is approved. sNDA is submitted for approval of expanding target population using bridging PK and safety data. Studies are not standard Phase 3 trials usually submitted for an NDA. |
| 17. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | | X | | |
| **SAFETY** | | | | | |
| 18. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division? | X | | | See #9 above. |
| 19. | Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)? | | | X | Product is approved. sNDA is submitted for approval of a new patient population. |
| 20. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | | | X | |

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| 21. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious? | | | X | |
| 22. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | X | | | |
| 23. | Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms? | | X | | |
| 24. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | | | X | The drug is approved. |
| 25. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | X | | | Provided in the complete study reports (CSRs). |
| **OTHER STUDIES** | | | | | |
| 26. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | | | X | Product is approved; no special studies were requested. |
| 27. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)? | | | X | |
| **PEDIATRIC USE** | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | X | | | |
| **ABUSE LIABILITY** | | | | | |
| 29. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | | | X | |
| **FOREIGN STUDIES** | | | | | |
| 30. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | | X | | |
| **DATASETS** | | | | | |
| 31. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | X | | | |
| 32. | Has the applicant submitted datasets in the format agreed to previously by the Division? | X | | | |
| 33. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | X | | | |
| 34. | Are all datasets to support the critical safety analyses available and complete? | X | | | |
| 35. | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | X | | | |

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| **CASE REPORT FORMS** | | | | | |
| 36. | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | X | | | |
| 37. | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? | X | | | |
| **FINANCIAL DISCLOSURE** | | | | | |
| 38. | Has the applicant submitted the required Financial Disclosure information? | X | | | |
| **GOOD CLINICAL PRACTICE** | | | | | |
| 39. | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | X | | | |

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

**We note that you have decided not to include in the pooled analysis data from the 11 subjects who developed influenza during the 2011/2012 season. Given the small number of pediatric subjects studied, complete information is always preferable. Please explain your reasoning for not including these 11 subjects. In addition, please submit before September 3, 2012 the datasets for these 11 subjects, and we will incorporate the data into our own analyses. Please submit also the summary of conclusions you have made from these data, including information on demographics, PK parameters, and any additional information that you have collected.**

**In your proposed draft labeling, you are seeking to expand the indication for treatment of influenza with Tamiflu down to (b) (4) weeks of age. You appear to have data available for children younger than this age limit, and we believe younger infants represent an unmet need. Please explain why you have chosen (b) (4) weeks as the cut-off, and why your proposed indication does not extend to younger age groups.**

**Please indicate where in the submission the coding dictionary is located, or submit the dictionary for our review. Alternatively, please explain your procedures for converting verbatim terms to MedDRA terms.**

Tafadzwa Vargas-Kasambira, M.D., M.P.H. 7/31/2012

Reviewing Medical Officer Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | |
|---|---|
| Linda Lewis, M.D. | 7/31/2012 |
| Clinical Team Leader | Date |

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

TAFADZWA S VARGAS-KASAMBIRA
11/28/2012

LINDA L LEWIS
11/28/2012
Inadvertent late entry.  I concur with assessment.

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | sNDA |
| Application Number(s) | NDA 21-246/SDN-045<br>NDA 21-087/SDN-062 |
| Priority or Standard | P |
| Submit Date(s) | June 21, 2012<br>August 10, 2012 |
| Received Date(s) | June 21, 2012<br>August 10, 2012 |
| PDUFA Goal Date | December 21, 2012 |
| Division / Office | DAVP/OAP |
| Reviewer Name(s) | Tafadzwa Vargas-Kasambira, M.D., M.P.H. |
| Review Completion Date | November 13, 2012 |
| Established Name | Oseltamivir phosphate |
| (Proposed) Trade Name | TAMIFLU® |
| Therapeutic Class | Antiviral |
| Applicant | Hoffmann-La Roche Inc. |
| Formulation(s) | Dry powder for Oral Suspension or compounded 75 mg Capsule |
| Dosing Regimen | Weight dependent (b) (4) daily dosing |
| Indication(s) | Treatment of Influenza in pediatric patients (including |

| | |
|---|---|
| | infants with a post-conceptional age of at least (b) (4) weeks who have been symptomatic for no more than 2 days |
| Intended Population(s) | Infants less than 1 year of age |

Template Version: March 6, 2009

# Table of Contents

# Table of Tables

# Table of Figures

# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

NDA 21-246 (supplement 045) and NDA 21-087 (supplement 062) containing pharmacokinetic, pharmacodynamic, and safety data from pediatric clinical trials CASG114/WP20749 and WP22849, support the selection of a Tamiflu dose of 3 mg per kilogram twice daily for five days for treatment of influenza A and B in infants less than one year of age. The safety data submitted in support of this application supports the use of Tamiflu in this age group. This reviewer recommends the approval of the supplemental NDAs for the dose selected. These open-label, single treatment arm trials which lacked control arms were not designed to assess efficacy, but the dose proposed for approval is based upon extrapolation of the pharmacokinetic data in older age groups. This reviewer recommends approval of the applicant's proposal for expanding the indication of the trial drug and labeling Tamiflu specifically for treatment of influenza in infants. The recommendation is made for infants greater than two weeks of age, rather than (b) (4) weeks post-conceptional age, as the applicant proposed.

Through the review of these supplemental NDAs, no deficiencies that would preclude the approval of this submission for dosage determination were identified. Tamiflu® (oseltamivir phosphate) was studied in two separate and similarly designed trials in pediatric subjects less than one year of age. CASG114 was a Phase I/II prospective, open-label, age-stratified pharmacokinetic/pharmacodynamic and safety evaluation of Tamiflu in which 87 pediatric subjects were enrolled (70 evaluable subjects less than one year of age), and received Tamiflu doses ranging from 3 to 3.5 mg per kilogram twice daily for five days. Enrolled children less than two years of age with confirmed influenza were stratified into five age cohorts: 12 to 23 months at 30 mg twice daily; 12 to 23 months at 3.5 mg/kg twice daily; 9 to 11 months at 3 mg/kg twice daily; 9 to 11 months at 3.5 mg/kg twice daily; 6 to 8 months at 3 mg/kg twice daily; 3 to 5 months at 3 mg/kg twice daily; and 0 to 2 months at 3 mg/kg twice daily. Only infants less than one year were evaluated for this clinical review. The drug formulation used was that approved at the time, Tamiflu oral suspension at 12 mg/mL (currently approved suspension concentration is 6 mg/mL).

Similarly,WP22849 was a Phase 1b prospective, open-label, pharmacokinetic/pharmacodynamic and safety evaluation of Tamiflu in which 65 pediatric subjects less than one year of age received Tamiflu doses ranging from 2 to 3 mg/kg twice daily for five days. Enrolled children were stratified into three age cohorts: 90 to < 365 days of age at Tamiflu 3 mg/kg twice daily; 31 to 90 days of age at 2.5 mg/kg twice daily; and 0 to 30 days of age at 2 mg/kg twice daily. The drug formulation used was the approved 75-mg capsule compounded to a final concentration of 10 mg/mL.

### 1.2 Risk Benefit Assessment

There are currently no antiviral agents approved for treatment of influenza in pediatric patients less than one year of age. Tamiflu is marketed for treatment and prophylaxis of influenza in children one year of age and older. This expansion of the treatment population would make Tamiflu the first viable option for treatment of the disease in infants.

The data provided in CASG114 and WP22849 represent a comprehensive PK/PD and safety database in influenza-infected infants less than one year of age. There are few other trials that have allowed for a thorough assessment of PK, PK/PD, and PK/safety in this population of young patients.

Although unable to identify a relationship between exposure and either PD or safety parameters, the applicant sought to bridge the infant PK data to that achieved at doses known to be safe and efficacious in older populations (children ≥ 1 year of age). Several dosing levels were simulated in a population PK model that the applicant developed to describe both the PK of oseltamivir and its metabolite oseltamivir carboxylate, based on pooled data. The 3 mg/kg twice daily regimen was predicted to provide oseltamivir exposures across the entire cohort of infants less than one year of age, within the range of those known to be safe and effective in other, older populations. The applicant selected a single dose (3 mg/kg) across the age range in preference to age-based dosing as this approach minimizes dosing errors while ensuring appropriate dosing.

Tamiflu at the recommended dose was safe and well-tolerated. The safety profile was similar among age cohorts in infants less than one year of age, with the most common adverse events being pyrexia, vomiting, and dermatitis (diaper and allergic). Given the range of adverse events seen in this population, this profile does not differ substantially from that seen in pediatric patients ≥ 1 year of age (adverse events such as diaper dermatitis, RSV bronchiolitis and oral candidiasis are examples of events that occur more frequently in infants less than one year).

Morbidity (and mortality) from influenza infection is significant in younger pediatric subjects, and therefore the fact that most of these subjects with influenza who were less than one year of age were admitted to hospital, is expected and appropriate. Influenza-associated hospitalizations are substantially higher among younger children, particularly among those less than two years of age, and highest in infants less than six months of age. In addition, the use of the drug in this age group would be of particular importance in the case of influenza outbreaks in environments such as neonatal intensive care units or newborn nurseries in hospitals, where there is presently no option for treatment of young infants who are infected with influenza following exposure.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) will not be required for this study.

### 1.4 Recommendations for Postmarket Requirements and Commitments

There will be no postmarket requirements or commitments requested of the applicant.

# 2 Introduction and Regulatory Background

### 2.1 Product Information

- Name: Oseltamivir phosphate (Tamiflu®)
- Description: Dry powder reconstituted to a concentration of 6 mg/mL, and 30, 45, and 75 mg capsules
- Chemical Class: (3R,4R,5S) -4-acetylamino-5-amino-3(1-ethylpropxy)-1-cyclohexene-1-carboxylic acid, ethyl ester phosphate (1:1)
- Chemical Formula: $C_{16}H_{28}N_2O_4$ (free base)
- Pharmacological Class: Selective inhibitor of influenza A and B neuraminidases
- Proposed Indication and Dosing: Treatment of pediatric patients (including infants with a post-conceptional age of at least (b) (4) weeks who have been symptomatic for no more than 2 days. Recommended dosage – Oseltamivir 3 mg/kg BID in infants less than one year of age.

### 2.2 Tables of Currently Available Treatments for Proposed Indications

The current indications for oseltamivir are for the treatment and prophylaxis of influenza. The currently approved drugs for these indications are described specifically in Table 1. There are no currently approved and marketed drugs to treat influenza in infants < 1 year of age.

Table 1. Currently Available Antiviral Drugs for Influenza

| Available Treatment | Indication |
|---|---|
| **Tamiflu (oseltamivir phosphate)** | Treatment (5 days) of uncomplicated acute illness due to influenza A and B infection in adults, adolescents and children 1 year and older who have been symptomatic for no more than 2 days. Prophylaxis of influenza in adults and adolescents for up to 6 weeks, during community outbreaks, and in patients 1 year or older after known exposure (10 days). |
| **Relenza (zanamivir)** | Treatment of uncomplicated acute illness due to influenza A or B in adults and children 7 years and older who have been symptomatic for no more than 2 days. Prophylaxis of influenza in adults and children 5 years and older. |
| **Symmetrel (amantadine hydrochloride)** | Treatment and prophylaxis of signs and symptoms of infection caused by various strains of influenza A virus |

| Available Treatment | Indication |
|---|---|
| **Flumadine (rimantadine hydrochloride)** | Treatment and prophylaxis of illness caused by various strains of influenza A in adults. Prophylaxis against influenza A in children. |

### 2.3 Availability of Proposed Active Ingredient in the United States

Oseltamivir phosphate, the active ingredient in Tamiflu, is available in the United States by prescription only.

### 2.4 Important Safety Issues With Consideration to Related Drugs

Not applicable.

### 2.5 Summary of Presubmission Regulatory Activity Related to Submission

*March 19, 2012*: The applicant requested feedback on the format and content of the sNDA (IND 53,093/SDN-0549). The questions concerned general format of the proposed sNDA, nonclinical and CMC issues.

*April 17, 2012*: Agency comments were received by the applicant. The Agency found most of the applicant's proposals acceptable.

*May 14, 2012*: Formal response to Agency comments were submitted by the applicant.

*May 8, 2012*: Formal Agency agreement to applicant's comments was received.

*Pandemic Preparedness*: The U.S. Department of Health and Human Services recognized the gap in the availability of influenza antivirals for pediatric patients as part of the influenza pandemic preparedness plan in 2006. The CASG144 trial, conducted by NIAID under its own IND (71,826), was undertaken to address this critical knowledge gap. The trial began in 2007, and had already accrued a significant number of infants when the 2009 H1N1 pandemic began. Interim data from this trial were requested by the FDA during the 2009 H1N1 influenza pandemic by the FDA, as well as by the European and Japanese agencies, and served as the basis for Emergency Use Authorization (EUA) dosing recommendations for oseltamivir in children under one year of age in the United States.

### 2.6 Other Relevant Background Information

None.

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality and Integrity

The applicant submitted the sNDA in accordance with FDA guidelines. The quality and integrity of the submission were adequate.

## 3.2 Compliance with Good Clinical Practices

The applicant states that all investigators certified that they agreed to conduct the studies according to all stipulations of the protocols, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. research sites. These trials were conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and the applicable regulatory requirements. CASG114 was conducted under IND 71,826 with NIAID/DMID as the sponsor. WP22849 was fully sponsored by Roche.

## 3.3 Financial Disclosures

The applicant submitted financial information pertinent to the application. FDA Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) was completed and submitted. No clinical investigators were full or part-time employees of (b) (4) No disclosable financial information was reported by any of the clinical investigators participating in the trials.

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

Tamiflu is an FDA-approved drug with approved age-appropriate formulations, and CMC did not, therefore, review this sNDA submission.

## 4.2 Clinical Microbiology

In both trials CASG114 and WP22849, infection was confirmed by culture or rapid test at screening (≤ 96 hours before enrollment). Nasopharyngeal swabs were collected periodically, and virus was quantified by RT-PCR and culture. Genotypic (sequencing of HA and NA culturable isolates) and phenotypic (NAI assay) resistance analyses were conducted.

Results for CASG114 showed that the youngest children (0 to 2 months) may have taken slightly longer to neutralize influenza A virus compared with the 6 to 8 month old infants. There were otherwise no statistically significant differences in time to undetected viral load between trial cohorts or virus type or subtype (using RT-PCR or viral culture). The resistance rate was at least 8% (3/37 subjects) for the 2009 pandemic strain of A/H1N1, although the analyses used (including population sequencing and NAI of cell culture amplified isolates) tended to be biased against detection of resistant isolates. In trial WP22849, the resistance rate was at least 22% (7/32 subjects) for H1N1 and at least 10% (1/10) among subjects infected with influenza A/H3N2. Also observed was the potential emergence of a novel NA A245D in an influenza B isolate. No resistance was observed among the influenza B isolates. Lastly, subjects with detectable levels of resistant virus may have taken slightly longer to attain undetectable viral loads. These resistance rates are consistent with those observed in other trials.

Refer to the Microbiology/Virology review by Damon Deming, PhD for further details.

## 4.3 Preclinical Pharmacology/Toxicology

Tamiflu is an FDA-approved drug and no new pharmacology/toxicology data were submitted, and Pharmacology/Toxicology did not, therefore, review this submission.

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

Oseltamivir phosphate is an ethyl ester prodrug that requires ester hydrolysis for conversion to the active form, oseltamivir carboxylate. Oseltamivir carboxylate is an inhibitor of influenza virus neuraminidase, affecting the release of viral particles from the cell.

### 4.4.2 Pharmacodynamics

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate, and is converted extensively by hepatic esterases (among other enzymes) to oseltamivir carboxylate. Exposure to oseltamivir is less than 5% of the total exposure after oral dosing. Protein binding is low (3%). Neither oseltamivir nor oseltamivir carboxylate is a substrate for, or inhibitor of, cytochrome P450 isoforms. Absorbed oseltamivir is primarily eliminated by conversion to oseltamivir carboxylate (> 90%). The half-life of oseltamivir is approximately 1 to 3 hours in most subjects (6 to 10 hours for oseltamivir carboxylate). Oseltamivir carboxylate is not further metabolized and is eliminated renally in the urine. Less than 20% of an oral radiolabeled dose is eliminated in feces.

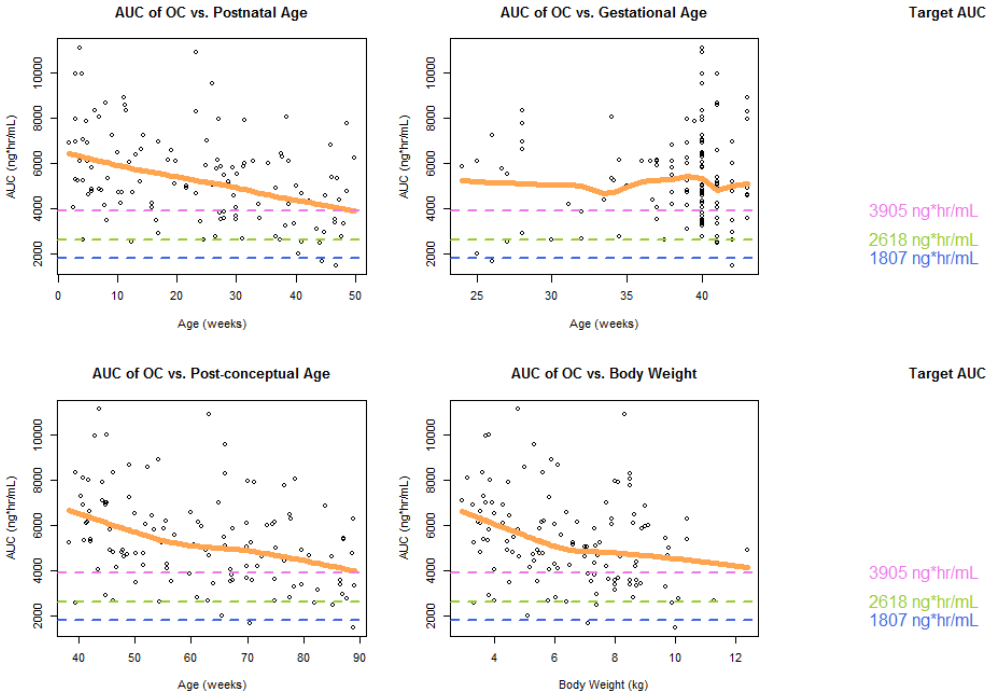
### 4.4.3 Pharmacokinetics

The applicant found no evidence of an association between exposure to the trial drug and either PD or safety parameters, nor was there a relationship found between PK and PD secondary endpoints, including fever, viral kinetics, and emergence of resistance. In the absence of such associations, the applicant was unable to determine a dosing recommendation for oseltamivir for infants less than one year of age, based directly on trial observations.

The doses studied in these trials were selected based on achieving a target exposure that had previously been associated with efficacy for treatment of influenza in adults. CASG114 targeted a higher exposure with the aim of minimizing emergence of resistance (associated dose was the 150 mg dose studied in adults), while WP22849 targeted a dose that was closer to the adult AUC that was associated with the approved 75 mg BID dose. Due to the fact that the trials studied different doses, the sponsor conducted modeling simulation in order to determine the optimal dose. A population model incorporating key covariates was devised. This model was designed to describe the PK of the prodrug oseltamivir, as well as that of the active metabolite oseltamivir carboxylate, based on data pooled from both trials. The model was also qualified for simulation and the provision of post-hoc individual exposures for 122 infants with evaluable PK data. Please see the Clinical Pharmacology review by Jee Eun Lee, PhD for further details.

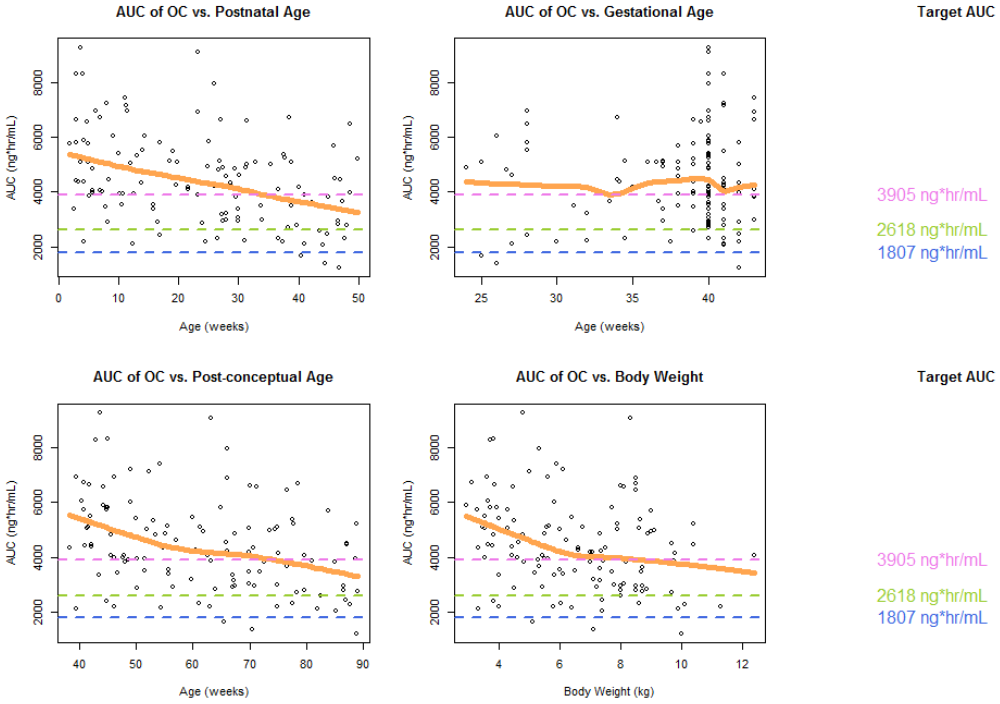
The modeling was performed by the applicant, and corroborated by the Division's Pharmacometrics team, as noted in the Clinical Pharmacology review of this submission.

Figure 1. AUC of Oseltamivir Carboxylate Following Oseltamivir 3 mg/kg.




Source: Clinical Pharmacology review

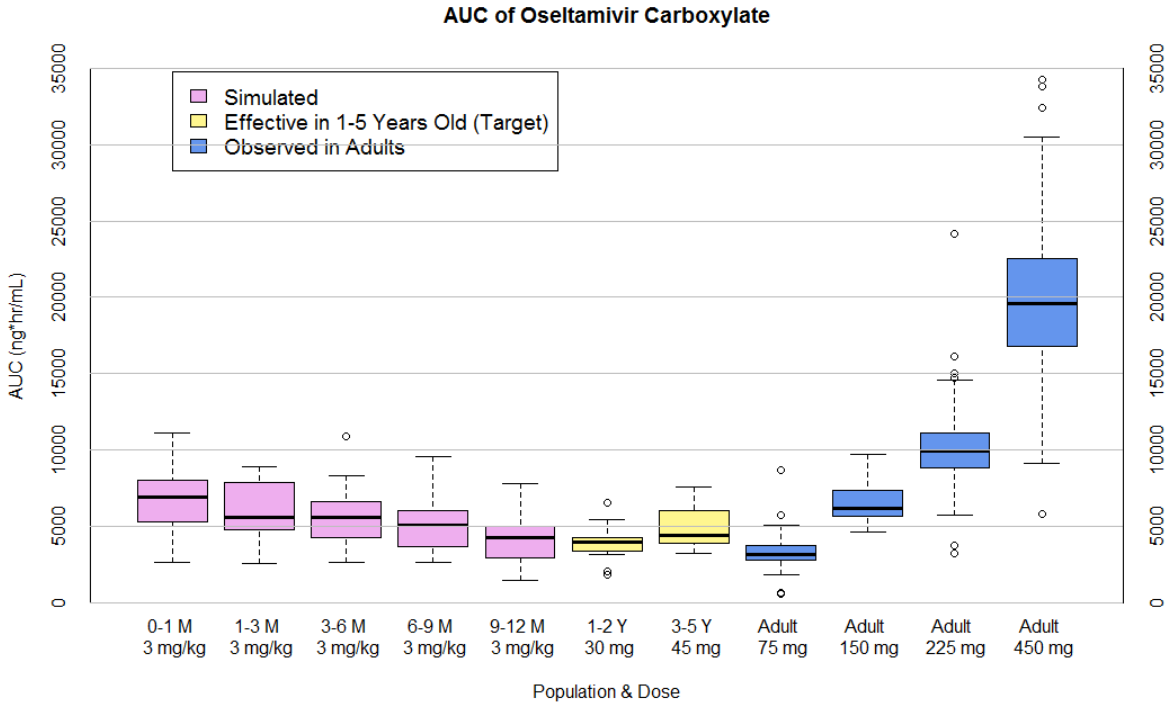
Figure 2. AUC of Oseltamivir Carboxylate Following Oseltamivir 2.5 mg/kg.




Source: Clinical Pharmacology review

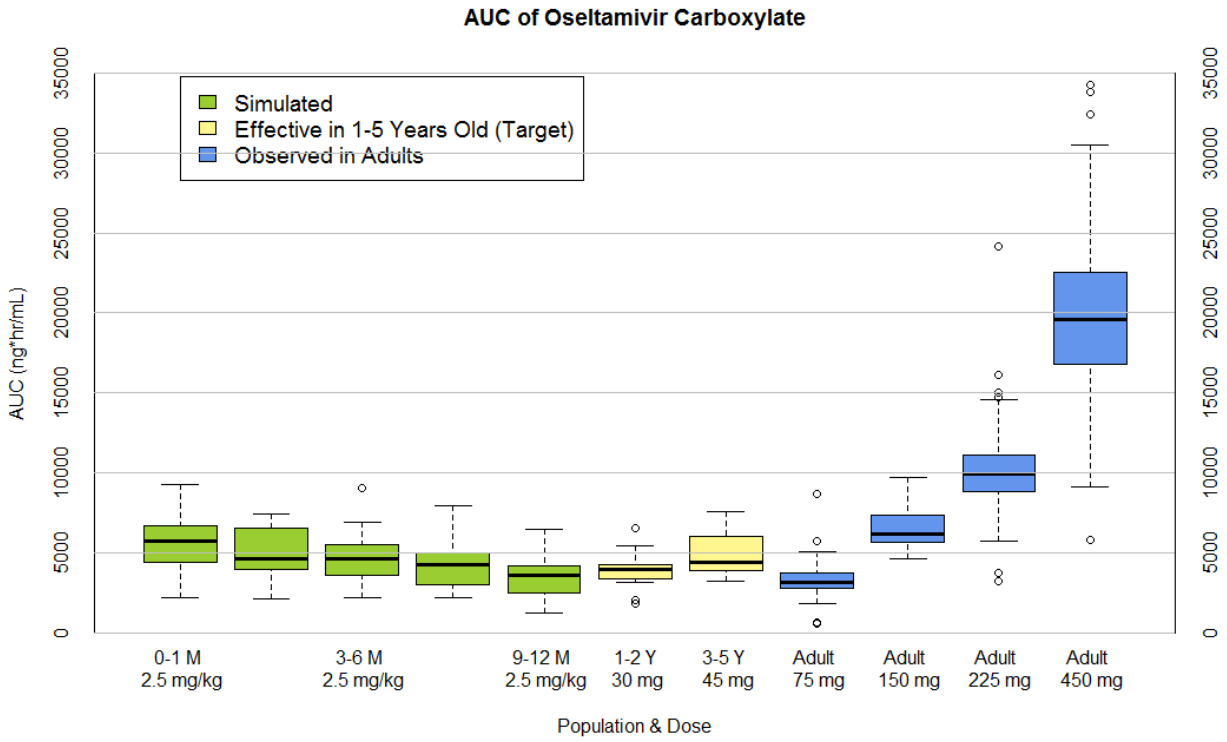
These results are presented in comparison with observed AUC of Oseltamivir Carboxylate in subjects greater than one year of age in Figure 3 and Figure 4.

Figure 3. Model-predicted AUC of Oseltamivir Carboxylate in < 1 Year of Age following 3 mg/kg BID




Source: Clinical Pharmacology review

Figure 4. Model-predicted AUC of Oseltamivir Carboxylate in < 1 Year of Age following 2.5 mg/kg BID




Source: Clinical Pharmacology review

The 3 mg/kg BID dose was found to be safe and well-tolerated, as noted by the applicant, and appeared to be reasonable for younger infants who may be at risk of potential resistance and treatment failure due to underexposure of oseltamivir carboxylate at lower doses and potential for high viral burdens. This dose is in alignment with current dosing recommendations for infants at one year of age where a typical infant of 10 kg would receive 30 mg BID.

See section 6.1.2., Analysis of Primary Endpoint, for a summary of the exposure/response analyses.

# 5 Sources of Clinical Data

## 5.1 Tables of Studies/Clinical Trials

See section 5.3, Discussion of Individual Studies/Clinical Trials, and section 6.1, Methods, for summaries of trials CASG114 and WP22849.

### 5.2 Review Strategy

The clinical information provided by the applicant for this study was reviewed. The materials that were submitted included the CASG114/WP20749 and WP22849 Complete Study Reports (CSR) and Data Sets. Case Report Forms (CRFs) were submitted for all subjects who died, for all subjects who withdrew from the trials due to related or unrelated adverse events, and for all subjects who experienced SAEs during study drug dosing. In addition, narratives were provided for all subjects who experienced deaths, SAEs, and drug-related AEs leading to withdrawal.

### 5.3 Discussion of Individual Studies/Clinical Trials

The submission comprised clinical summaries of two separate trials: CASG114/ WP20749 and WP22849.

Summary of CASG114/WP22849 Trial Design

The trial was titled*: "A pharmacokinetic/pharmacodynamics and safety evaluation of oseltamivir (Tamiflu®) for the treatment of children less than 24 months of age with confirmed influenza."* The primary goal was to define the PK following administration of an oral dose of oseltamivir using a targeted area-under-the-concentration-curve (AUC) approach.

A total of 87 subjects were enrolled in the trial, of whom 72 were aged less than one year. Two subjects were withdrawn from the analysis population (see footnote, Table 24), leaving a total of 70 subjects that were evaluable. See section 6.1 for inclusion/exclusion criteria and screening procedures.

The subjects were divided into one of five cohorts based on age (see section 6.1.1.). Safety was assessed by evaluating the number and types of AEs, including those AEs thought to be associated with trial product. Exploratory analyses included the correlation of clearance of virus and viral RNA with PK parameters and subject age, and the correlation of the development of resistance with PK and subject age.

Summary of WP22849 Trial Design

The trial was titled: *"An open-label, prospective, pharmacokinetic/pharmacodynamics and safety evaluation of oseltamivir in the treatment of infants 0 to < 12 months of age with confirmed influenza in the 96 hours prior to the first dose."* The primary goal was to define the PK of oseltamivir and oseltamivir carboxylate in children up to one year of age with confirmed influenza.

The applicant conducted the safety analysis based on 54 subjects who were enrolled and completed the trial during the 2010-2011 influenza season. There were additional data from 11 subjects enrolled in the 2011-2012 influenza season that the applicant provided upon request

following the initial submission. Therefore, there was a total of 65 subjects whose data were analyzed by this Medical Officer.

The trial divided subjects into three cohorts (see section 6.1.1.). Safety was assessed throughout the trial with evaluation of AEs, vital signs, physical examination, and laboratory testing.

An overview of trial design and subject disposition for both trials is provided in Table 2.

Table 2. Overview of Pivotal Trials Providing Main Trial Safety Data of Oseltamivir

| Protocol | Population | Total Subjects Enrolled | Total Subjects Exposed | Safety Population | Duration (Follow-up) | Region | Season | Recruitment Strata | Age (years) |
|---|---|---|---|---|---|---|---|---|---|
| **WP20749** | Confirmed influenza | 72* | 71 | 70§ | 30 days | USA | 2006-2010 | Age | < 1 (cohorts II-V) |
| **WP22849** | Confirmed influenza# | 65† | 65 | 65 | 30 days | EU | 2010-2011 | Age | < 1 |

* 15 patients were enrolled in the oldest cohort ≥ 1 to < 2 years of age (Cohort I). Data from these subjects were not analyzed by the sponsor for this submission. The 72 subjects refer to those < 1 year of age.
§ One subject in Cohort IIB (Patient 45) did not return for follow-up visit, and it could not be confirmed if trial drug was administered. The subject was included in baseline demographic assessment, but not in the safety assessment. Therefore, 71 subjects were exposed to oseltamivir treatment, but an additional subject (Patient 234) failed to return for follow-up after withdrawal of consent, and was removed from the safety analysis. Therefore, the safety population included only 70 subjects.
† In WP22849, 54 subjects were recruited in the 2010-2011 influenza season, and 11 subjects were recruited in the 2011-2012 influenza season. For the FDA analysis, the total population of 65 subjects was analyzed.
# Confirmed by rapid diagnostics test or PCR in local laboratory, but not confirmed by central laboratory.

# 6 Review of Efficacy

The two trials were not designed to assess efficacy of oseltamivir for the subject population in question (no placebo groups were enrolled for comparison), and therefore no efficacy parameters were examined. The objectives of CASG114 and WP22849 were to determine the PK, PD, PK/PD relationship, and safety of oseltamivir in infants less than one year of age.

The analyses discussed in this section focus on the pharmacokinetic and pharmacodynamics assessments that were conducted. They were exploratory in nature, with the aim of supporting efficacy. Pharmacokinetics were examined in order to conduct bridging to children older than those studied, as well as adults, and relied on extrapolation of efficacy from those populations. Refer to section 4.4.3., Pharmacokinetics, for a discussion of the process of dose selection and standard PK analysis.

## 6.1 Indication

The proposed indication under evaluation is oseltamivir for use in the treatment of influenza in pediatric patients under the age of one year.

### 6.1.1 Methods

Trial CASG114

The trial was a prospective, age-stratified, open-label PK/PD and safety evaluation of oseltamivir therapy in children less than one year of age with confirmed influenza infection. At the onset of the protocol, a minimum of 48 children with confirmed influenza were to be enrolled into one of five age cohorts:

- Cohort IA: 12 to 23 months – received oseltamivir 30 mg BID
- Cohort IB: 12 to 23 months – received oseltamivir 3.5 mg/kg BID
- Cohort IIA: 9 to 11 months – received oseltamivir 3.0 mg/kg BID
- Cohort IIB: 9 to 11 months – received oseltamivir 3.5 mg/kg BID
- Cohort III: 6 to 8 months – received oseltamivir 3.0 mg/kg BID
- Cohort IV: 3 to 5 months – received oseltamivir 3.0 mg/kg BID
- Cohort V: 0 to 2 months – received oseltamivir 3.0 mg/kg BID

Confirmed laboratory diagnosis of influenza was by viral culture or rapid influenza diagnostic test within 96 hours prior to trial enrollment. The duration of influenza symptoms could be ≤ 96 hours. The predefined AUC target was the dose which was expected to result in $AUC_{12}$ values for oseltamivir carboxylate between 2,600 ng.hr/mL and 7,700 ng.hr/mL. The first nine subjects enrolled in each included cohort received a proposed starting dose of 30 mg BID (toddlers 12 to 23 months of age) or 3 mg/kg BID (neonates and infants between 0 and 11 months of age) for five days (total 10 doses). Doses were adjusted by predetermined rules (Cohorts IA and IIB) to achieve the targeted exposure ($AUC_{12}$).

Both outpatient and hospitalized children with influenza were eligible to be enrolled. At trial outset, Cohorts I, II, and III were enrolled simultaneously. Cohorts IV and V were enrolled sequentially by decreasing age groups, predicated upon PK and safety data from the preceding cohort. Dosing information was reviewed in real time by the Data and Safety Monitoring Board (DSMB), which would recommend opening the consecutively younger cohorts as data became available and doses were verified in the older age cohorts. The DSMB would recommend modifying the dose in the ongoing cohorts, based upon the available data. Following the outbreak of the H1N1 pandemic in 2009, the protocol was amended to allow either 1) the opening of enrollment into younger age cohorts before completion of the initial dataset in the previous age cohort, or 2) over-enrollment in any age cohort upon the advice of the DSMB, FDA, or NIAID.

The intent-to-treat (ITT) population was considered to be all subjects who received at least one dose of trial medication. These subjects were included in all summaries regarding subject accrual, baseline information, and safety parameters. Only subjects with the specimens obtained at the required intervals for PK measurements were included in the PK/PD analysis. Frequencies of AEs were summarized by body system, grade, and causality by using frequencies and percentages.

Trial WP22849

The trial was a prospective, open-label study of the PK/PD and safety of oseltamivir therapy in three cohorts of infants with influenza infection, according to postnatal age:

- Cohort I: Infants 91 to < 365 days – received oseltamivir 3 mg/kg BID
- Cohort II: Infants 31 to 90 days – received oseltamivir 2.5 mg/kg BID
- Cohort III: Infants 0 to 30 days – received oseltamivir 2 mg/kg BID

Confirmed laboratory diagnosis of influenza was by PCR or rapid influenza diagnostic test within 96 hours prior to first dose. Also similar to the other trial was the acceptable duration of influenza symptoms, which could be ≤ 96 hours prior to the dose. All cohorts received oseltamivir at 12 hour intervals for five days (a total of 10 doses). Dosing could continue for a further 5 days (an additional 10 doses) if the specimen collected on Day 6 was positive for influenza or if the subject had symptoms consistent with ongoing viremia. The maximum possible number of doses was twenty.

The PK parameters of oseltamivir and OC were estimated from plasma drug concentrations by non-compartmental methods. PD assessments were aimed at deriving relationships between drug exposure and virologic and selected clinical responses to treatment and AEs. Adverse events were listed by subject and summarized by age cohort, by body system, and by preferred term within each body system.

### 6.1.2 Demographics

The demographic characteristics of the pooled trial population are shown in Table 3. In general, there were slightly more male subjects (55%), and the majority of subjects were non-Hispanic (74%) and White/Caucasian (79%). The mean age of the subjects at enrolment was 165 days; most of the subjects had a gestational age over 37 weeks (76%), and a post-conceptional age greater than or equal to 38 weeks (81%).

Table 3. Demographic Characteristics – Pooled Data

| | I | II | III | IV | V | TOTAL |
|---|---|---|---|---|---|---|
| | **≤ 1 month (≤ 30 days) N=13** | **1-3 months (31-90 days) N=34** | **3-6 months (91-180 days) N=23** | **6-9 months (181-270 days) N=35** | **>9 months (≥ 271 days) N=30** | **All N=135** |
| **Sex** | | | | | | |
| **Male** | 9 (69%) | 20 (59%) | 13 (57%) | 20 (57%) | 12 (40%) | 74 (55%) |
| **Female** | 4 (31%) | 14 (41%) | 10 (43%) | 15 (43%) | 18 (60%) | 61 (45%) |
| **Race** | | | | | | |
| **Amer Indian/ Alaska Native** | 0 | 0 | 1 (4%) | 0 | 0 | 1 (1%) |
| **Asian** | 0 | 0 | 1 (4%) | 1 (3%) | 0 | 2 (1%) |
| **Black/African American** | 0 | 3 (9%) | 3 (13%) | 2 (6%) | 6 (20%) | 14 (10%) |
| **White/Caucasian** | 12 (92%) | 27 (79%) | 18 (79%) | 28 (80%) | 21 (70%) | 106 (79%) |
| **Nat Hawaiian/Pac Islander** | 0 | 2 (6%) | 0 | 0 | 1 (3%) | 3 (2%) |
| **Other*** | 1 (8%) | 2 (6%) | 0 | 4 (11%) | 2 (7%) | 9 (7%) |
| **Ethnicity** | | | | | | |
| **Hispanic** | 9 (69%) | 8 (24%) | 5 (22%) | 11 (31%) | 2 (7%) | 35 (26%) |
| **Non-Hispanic** | 4 (31%) | 26 (76%) | 18 (78%) | 24 (69%) | 28 (93%) | 100 (74%) |
| **Age (days) at enrollment** | | | | | | |
| **Mean** | 23.5 | 57.2 | 134.9 | 216.9 | 310.8 | 165 |
| **SD** | 5.1 | 18.1 | 27.2 | 28.2 | 24 | 105.1 |
| **Median** | 23 | 55.5 | 133 | 210 | 314.5 | 171 |
| **Range** | 13 - 30 | 32 - 88 | 92 - 175 | 182 - 269 | 271 - 349 | 13 - 349 |
| **Weight (kg)** | | | | | | |
| **Mean** | 3.8 | 4.8 | 6.2 | 7.7 | 8.5 | 6.49 |
| **SD** | 0.49 | 0.9 | 1.7 | 1.7 | 1.4 | 2.14 |
| **Median** | 3.8 | 4.9 | 6.4 | 7.7 | 8.5 | 6.2 |
| **Range** | 2.9 – 4.8 | 3.1 – 6.5 | 3.5 - 9 | 4.6 – 12.4 | 5.1 – 10.7 | 2.9 – 12.4 |
| **Gestational Age** | | | | | | |
| **≤ 37 weeks** | 1 (8%) | 4 (12%) | 8 (35%) | 11 (31%) | 9 (30%) | 33 (24%) |
| **>37 weeks** | 12 (92%) | 30 (88%) | 15 (65%) | 24 (69%) | 21 (70%) | 102 (76%) |
| **Post-conceptional Age** | | | | | | |
| **≤ 37 weeks** | 1 (8%) | 4 (12%) | 5 (22%) | 10 (29%) | 6 (20%) | 26 (19%) |
| **≥ 38 weeks** | 12 (92%) | 30 (88%) | 18 (78%) | 25 (71%) | 24 (80%) | 109 (81%) |

Baseline characteristics of the pooled population are shown in Table 4. The majority of the subjects were inpatients (52%) but were not admitted to the ICU. A sizable number were treated as outpatients (39%), while only 9% were treated in the inpatient ICU. A higher percentage of the youngest subjects (≤ 30 days) were admitted as non-ICU inpatients, and this percentage decreased the older the subjects became.

*Medical Officer's comments: It is significant that most of these pediatric subjects under one year of age were admitted to hospital when influenza was suspected, presumably due to the presenting symptoms of the patients, or the perceived sequelae of the infection. Morbidity (and mortality) from influenza infection is significant in younger pediatric subjects, and therefore admission is likely the most appropriate action for those ill subjects who are not sick enough to be admitted to the ICU. Of note, a higher proportion of the subjects under 3 months of age were admitted to the ICU, which might be expected. Influenza-associated hospitalizations are substantially higher among younger children, particularly among those less than two years of age, and highest in infants less than six months of age*[1].

A slight majority of subjects was not febrile at baseline (58%), while the symptoms of most of the subjects lasted for ≤ 48 hours (62%). The most prevalent influenza virus type in the trial population, commiserate with the general population, was influenza type A (80%), while 14% of isolates were identified as type B, and 6% were unknown.

Table 4. Baseline Characteristics – Pooled Data

| | I | II | III | IV | V | TOTAL |
|---|---|---|---|---|---|---|
| | **≤ 1 month (≤ 30 days) N=13** | **1-3 months (31-90 days) N=34** | **3-6 months (91-180 days) N=23** | **6-9 months (181-270 days) N=35** | **>9 months (≥ 271 days) N=30** | **All N=135** |
| **Location of Subjects** | | | | | | |
| **Inpatient ICU** | 2 (15%) | 6 (17%) | 1 (4%) | 0 | 3 (10%) | 12 (9%) |
| **Inpatient non-ICU** | 11 (85%) | 23 (68%) | 11 (48%) | 13 (37%) | 12 (40%) | 70 (52%) |
| **Outpatient** | 0 | 5 (15%) | 11 (48%) | 22 (63%) | 15 (50% | 53 (39%) |
| **Febrile at Baseline** | | | | | | |
| **Yes** | 6 (46%) | 13 (38%) | 9 (39%) | 16 (46%) | 13 (43%) | 57 (42%) |
| **No** | 7 (54%) | 21 (62%) | 14 (61%) | 19 (54%) | 17 (57%) | 78 (58%) |
| **Duration of Symptoms** | | | | | | |
| **≤ 48 hours** | 9 (69%) | 26 (76%) | 11 (48%) | 22 (63%) | 16 (53%) | 84 (62%) |
| **>48 hours** | 3 (31%) | 8 (24%) | 12 (52%) | 13 (37%) | 14 (47%) | 51 (38%) |
| **Influenza** | | | | | | |

1 Standling JF, Nika A, Tsagris V et al. Oseltamivir pharmacokinetics and clinical experience in neonates and infants during an outbreak of H1N1 influenza A virus infection in a neonatal intensive care unit. Antimicrob Agents Chemo. 2012. 56(7):3833-3840

| | I | II | III | IV | V | TOTAL |
|---|---|---|---|---|---|---|
| | **≤ 1 month (≤ 30 days) N=13** | **1-3 months (31-90 days) N=34** | **3-6 months (91-180 days) N=23** | **6-9 months (181-270 days) N=35** | **>9 months (≥ 271 days) N=30** | **All N=135** |
| **Virus Type** | | | | | | |
| **Type B** | 2 (15%) | 1 (3%) | 3 (13%) | 5 (14%) | 8 (27%) | 19 (14%) |
| **Type A** | 10 (77%) | 29 (85%) | 19 (83%) | 30 (86%) | 20 (67%) | 108 (80%) |
| **Unknown** | 1 (8%) | 4 (12%) | 1 (4%) | 0 | 2 (6%) | 8 (6%) |

As discussed previously, the applicant included data from the 2010-2011 influenza season in the initial sNDA submission on June 21, 2012, but the data for the 2011-2012 influenza season (as well as a summary of the findings from the 11 included subjects) were submitted on August 10, 2012. Although this Medical Officer combined the data from both influenza seasons so that the pooled population included all subjects (N=135), a comparison between the demographic and baseline characteristics was made in order to determine if there were any significant differences. None were discovered. It should be noted that this comparison was purely descriptive (Table 5).

Table 5. Comparison of Subjects from 2010-2011 and 2011-2012 Influenza Seasons – Trial WP22849

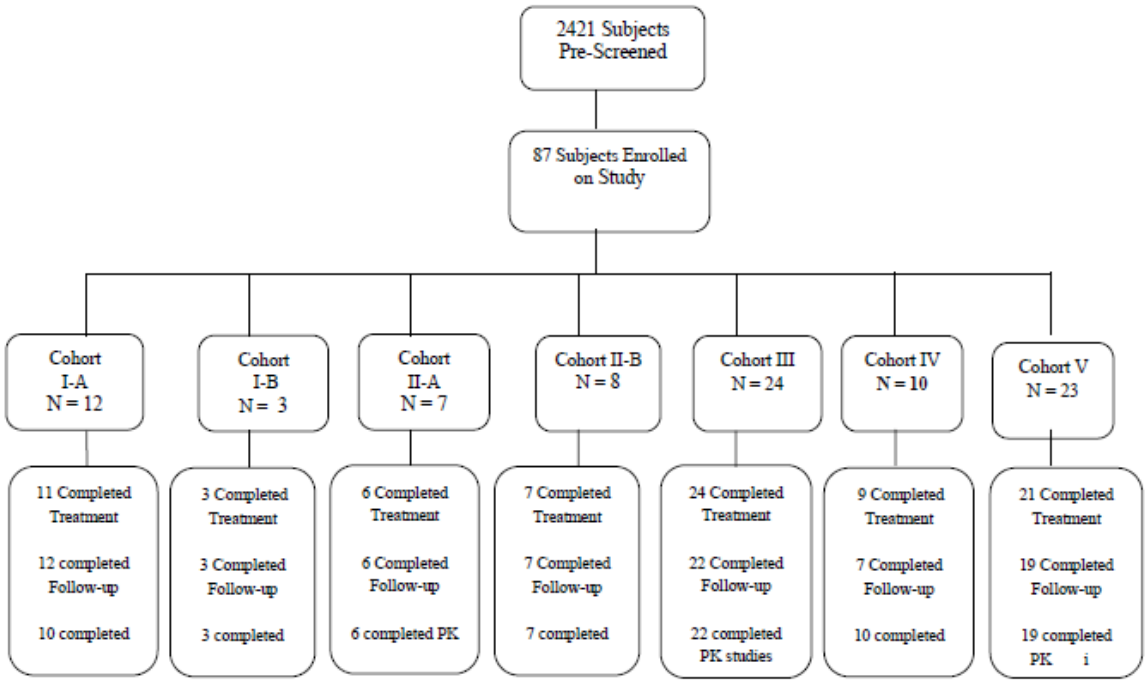
| | **2010-2011 Influenza Season N=54** | **2011-2012 Influenza Season N=11** | **TOTAL N=65** |
|---|---|---|---|
| **Sex** | | | |
| **Male** | 31 (57%) | 5 (45%) | 36 (55%) |
| **Female** | 23 (43%) | 6 (55%) | 29 (45%) |
| **Race** | | | |
| **Amer Indian/Alaska Native** | 0 | 0 | 0 |
| **Asian** | 0 | 0 | 0 |
| **Black/African American** | 2 (4%) | 0 | 2 (3%) |
| **White/Caucasian** | 50 (92%) | 11 (100%) | 61 (94%) |
| **Nat Hawaiian/Pac Islander** | 0 | 0 | 0 |
| **Other*** | 2 (4%) | 0 | 2 (3%) |
| **Ethnicity** | | | |
| **Hispanic** | 3 (6%) | 0 | 3 (5%) |
| **Non-Hispanic** | 51 (94%) | 11 (100%) | 62 (95%) |
| **Age (days) at enrollment** | | | |
| **Mean** | 162.5 | 129.1 | 156.8 |
| **SD** | 102.8 | 119.8 | 105.6 |
| **Median** | 156.5 | 71 | 133 |
| **Range** | 18 - 349 | 32 - 347 | 18 - 349 |
| **Weight (kg)** | | | |
| **Mean** | 6.6 | 6.1 | 6.49 |
| **SD** | 2.1 | 2.0 | 2.1 |
| **Median** | 6.6 | 5.4 | 6.4 |
| **Range** | 2.9 – 12.4 | 4.1 – 10.3 | 2.9 – 12.4 |
| **Height (cm)†** | | | |
| **Mean** | 64.1 | 62.4 | 63.5 |
| **SD** | 8.7 | 9.8 | 8.8 |
| **Median** | 64 | 59 | 64 |
| **Range** | 47 – 80 | 48 – 77 | 47 – 80 |
| **Gestational Age** | | | |
| **≤ 37 weeks** | 7 (13%) | 0 | 7 (11%) |
| **>37 weeks** | 47 (87%) | 11 (100%) | 58 (89%) |
| **Febrile at Baseline** | | | |
| **Yes** | 31 (57%) | 8 (73%) | 39 (60%) |
| **No** | 23 (43%) | 3 (27%) | 26 (40%) |
| **Duration of Symptoms** | | | |
| **≤ 48 hours** | 39 (72%) | 5 (45%) | 44 (68%) |
| **>48 hours** | 15 (28%) | 6 (55%) | 21 (32%) |
| **Viral Type** | | | |
| **Type B** | 16 (30%) | 0 | 16 (25%) |
| **Type A** | 32 (59%) | 10 (91%) | 42 (65%) |
| **Unknown** | 6 (11%) | 1 (9%) | 7 (10%) |
| **Location of Subjects** | | | |
| **Inpatient ICU** | 4 (7%) | 1 (9%) | 5 (8%) |
| **Inpatient non-ICU** | 33 (61%) | 7 (64%) | 40 (61%) |
| **Outpatient** | 17 (32%) | 3 (27%) | 20 (31%) |

### 6.1.3 Subject Disposition

In trial CASG114, a total of 87 subjects were enrolled from 16 US centers, with the University of Texas-Southwestern enrolling the most (N=25, or 29%). All subjects except one definitely received at least two doses of trial medication, and all but three received at least seven doses. Ten trial sites were activated but did not enroll any subjects.

Figure 5 shows the disposition of subjects in trial CASG114. A total of 81 subjects (93%) completed at last 8 doses of treatment, while 68 (78%) had at least 10 doses. Seventy-six subjects (87%) completed follow-up.

Figure 5. Disposition of Subjects - CASG114




Source: CSR, CASG114, Page 155

A total of five subjects (6%) less than one year of age withdrew prematurely from treatment. The reasons are shown in Table 6. Subject #45 received one dose ("Other" category) and no further contact with the subject was had, while subject #43 ("Other" category) did not return for visits or return phone calls. Subject #234 withdrew consent due to too many blood draws, and subject #236 was deemed non-complaint with trial visits.

Table 6. Withdrawals from Trial Treatment - CASG114

| **Number of Subjects Withdrawn Prematurely** | N=5 |
|---|---|
| | |
| **Reasons for Withdrawal** | |
| Non-compliant | 1 |
| Adverse Event | 1* |
| Investigator recommended | 1 |
| Parent/Legal Guardian Withdrew Consent | 1 |
| Other | 2 |

*Subject PID 114-3-25 had two reasons for withdrawal: adverse event (hypersensitivity) and investigator recommendation

In trial WP22849, a total of 65 subjects was enrolled from 11 centers in Europe, with the University of Medicine of Berlin, Germany, enrolling the most (N=35, or 54%). Fifty-four subjects were enrolled during the 2010-2011 influenza season, while eleven subjects were enrolled during the 2011-2012 influenza season into Cohorts I and II only.

No subjects were withdrawn prematurely from treatment.

6.1.4 Analysis of Primary Endpoint(s)

The primary objective of trial WP22849 was to define the PK of oseltamivir and oseltamivir carboxylate in children with confirmed influenza up to one year of age, while the primary objective of trial CASG114 was the same, except that the subject population was up to age two years (though the only data analyzed for this review were for subjects less than one year of age.) The data from the two trials were pooled for the analysis.

There was a total of 122 subjects (excluding data from the 11 subjects from the 2011-2012 influenza season, as the applicant submitted PK parameters estimated in these 11 subjects, but not their raw PK data) who contributed data for the PK/PD analysis. The range of oseltamivir dose used was 2 to 3.5 mg/kg BID. Most subjects had five PK samples collected, yielding a total of 556 with oseltamivir phosphate samples, and 594 with oseltamivir carboxylate samples.

Published studies have found that children who are symptomatic for longer periods shed virus for longer, while asymptomatic children with influenza shed virus for shorter periods of time[1]. This trend was not seen in these trials. As has been noted in the literature[2], younger infants develop resistance to oseltamivir more readily than older infants because they have a higher viral burden and longer duration of viral shedding, allowing more opportunity for resistance to develop.

2 Loeb M, Singh PK, Fox J et al. Longitudinal study of influenza molecular viral shedding in Hutterite communities. JID 2012;206:1078-84

The applicant identified several key findings. They concluded that the administered doses (including 3 mg/kg across the entire age range) were safe and well-tolerated with no evidence of an exposure-related trend in the tolerability profile. Age did not have an effect on either the time to resolution of fever, or cessation of viral shedding. Infants under three months of age had more treatment emergent resistance to the trial drug. The applicant also found that infants over the age of six months had a higher percentage of secondary illness.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary objectives were the same for both trials, namely:

- To describe the frequency of all adverse events among treated children
- To assess the clearance of virus and viral ribonucleic acid
- To determine the potential for the development of resistance to oseltamivir

The frequency of adverse events is discussed in section 7, Review of Safety. Please see the Clinical Virology review by Damon Deming, PhD for assessment of viral clearance and viral resistance to oseltamivir.

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

Subpopulation analyses were not conducted.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Tamiflu is an approved drug, and most of the clinical data submitted concerned safety rather than efficacy. Dosing recommendations were made based on the PK/PD data and simulation modeling conducted by the applicant and corroborated by the Division. Please see the Clinical Pharmacology review by Jee Eun Lee, PhD for further analyses that form the basis of the oseltamivir dosing recommendation for infants less than one year of age.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy and/or tolerance was not assessed in these trials.

6.1.10 Additional Efficacy Issues/Analyses

In conclusion, efficacy of oseltamivir for treatment of influenza in infants less than one year of age was not assessed in trials CASG114 and WP22849. The trials were open label, single arm

studies with no control arm for comparison of outcomes. As such, conclusions about the effectiveness of the trial drug for treating influenza in this age group cannot directly be made,

The PK and PD parameters of oseltamivir in infants < 1 year of age were evaluated in order to determine the appropriate dose of the drug for treatment of influenza in this age group. Using population modeling, the applicant (with results corroborated by the Division) determined an oseltamivir dose that would be effective in infants less than one year of age, based upon efficacy previously shown in adult trials. This dose increased oseltamivir carboxylate exposure in younger infants, but was selected after weighing the risks and benefits; a lower dose would decrease exposure, but would place these infants at risk of experiencing under-dosing and therefore potential treatment failure or resistance development.

It should be noted that recommendations released by the Centers for Disease Control and Prevention and the World Health Organization for dosing of oseltamivir in infants < 1 year are already available[3,4], although antiviral medications for influenza are not currently approved for use in this age group. . Extrapolation of doses from older subjects is complicated by rapid organ and drug-metabolizing enzyme maturation in young infants. Metabolism of prodrug oseltamivir to its metabolite oseltamivir carboxylate, is mediated primarily by human carboxylesterase 1 (HCE1), an enzyme that is expressed in the liver[5]. During the first year of life, the expression of HCE1 increases rapidly, which suggests that neonates may produce smaller amounts of the active metabolite, oseltamivir carboxylate. Oseltamivir carboxylate is renally eliminated through both glomerular filtration and tubular secretion processes. Both reach adult capacity by about 6 to 12 months of age[6]. In addition, neonates may experience decreased renal clearance of drugs and their metabolites, as well as variations in oral bioavailability, which may also affect drug absorption.

The PK/PD results from this analysis indicate that the youngest subjects had the highest exposure to oseltamivir carboxylate, suggesting the aforementioned trend with renal clearance and/or absorption. Similarly, as previously discussed, the higher dose of 3 mg/kg BID yielded the highest oseltamivir carboxylate AUC in younger infants, while the lower dose of 2.5 mg/kg BID yielded mean AUCs in younger infants comparable to those in children greater than one year of age, reflecting the trends in metabolism of this age group.

3 Centers for Disease Control and Prevention. Antiviral agents for the treatment and chemoprophylaxis of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recommend. 2011. Rep. 60:1-24
4 World Health Organization. WHO Guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses. 2010. World Health Organization, Geneva, Switzerland
5 Shi D, Yang D, Prinssen EP, et al. Surge in expression of carboylesterase 1 during the neonatal stage enables a rapid gain of the capacity to activate the anti-influenza prodrug oseltanivir. J Infect Dis. 2011. 203:937-942
6 Kearns GL, Abdel-Rahman SM, Alander SW et al. Development pharmacology – drug disposition, action, and therapy in infants and children. N Engl J Med 2003;349:1157-1167

# 7 Review of Safety

## 7.1 Methods

Safety data for this NDA supplement were provided by the applicant in the form of electronic datasets that contained tables of clinical adverse events. Data from the 2010-2011 influenza season for 54 subjects were initially submitted on June 21, 2012, and subsequently data from the 2011-2012 influenza season were submitted on August 9, 2012 for an additional 11 subjects. A summary assessment of the pooled data was provided, but the datasets were not combined by the applicant. The applicant provided an Integrated Summary of Safety (ISS) that incorporated relevant integrated analyses.

Narrative summaries and case report forms were provided for all subjects who experienced serious adverse events (SAEs), both those deemed to be drug-related and those deemed not to be. Narratives were provided for all subjects who died, had SAEs, and for those who withdrew from either of the trials due to drug-related AEs. JMP Statistical Discovery Software (SAS Institute, Inc.) was used to compile tabulations of AEs, SAEs, and trial drug interruptions or discontinuations.

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety evaluation was conducted using the data generated from the two trials under review: CASG114 and WP22849.

### 7.1.2 Categorization of Adverse Events

On-treatment AEs were events reported during treatment with oseltamivir up to 3 days from the last treatment dose. AEs were summarized by System Organ Class (SOC) and causality.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of data was conducted with trials CASG114 and WP22849. Table 7 shows age and dose information of the pooled data, including the data from WP22849 separated by influenza season (2010-2011: 54 subjects; 2011-2012: 11 subjects).

Table 7. Pooled Trials CASG114 and WP22849 - Age and Dose Information by Trial

| | I | II | III | IV | V | TOTAL |
|---|---|---|---|---|---|---|
| | **≤ 1 month (≤ 30 days)** | **1-3 months (31-90 days)** | **3-6 months (91-180 days)** | **6-9 months (181-270 days)** | **>9 months (≥ 271 days)** | |
| **CASG 114 (dose)** | N=8 (3 mg/kg) | N=14 (3 mg/kg) | N=10 (3 mg/kg) | N=22 (3 mg/kg) | N=16 (3 or 3.5 mg/kg) | 70 |

| | I | II | III | IV | V | TOTAL |
|---|---|---|---|---|---|---|
| | **≤ 1 month (≤ 30 days)** | **1-3 months (31-90 days)** | **3-6 months (91-180 days)** | **6-9 months (181-270 days)** | **>9 months (≥ 271 days)** | |
| | | | | | | |
| **WP22849 – 54 pts (dose)** | N=5 (2 mg/kg) | N=20 (2.5 mg/kg) | N=13 (3 mg/kg) | N=13 (3 mg/kg) | N=14 (3 mg/kg) | 65 |
| | | | | | | |
| **Totals by Age group** | 13 | 34 | 23 | 35 | 30 | 135 |

## 7.2 Adequacy of Safety Assessments

In light of the fact that Tamiflu is an approved drug for which a significant amount of safety data are available from previously reviewed treatment protocols, the monitoring of clinical and safety parameters in these trials was considered to be adequate. In addition, laboratory parameters were not monitored in these trials, given the fact that few laboratory abnormalities had been identified in other age groups previously, in comparison to placebo.

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall Exposure of Trial Population

Pooling of the safety data from both trials under review yielded a total trial population of 135 subjects (Table 8). A total of 119/135 (88%) subjects across all age groups received 9 to 10 doses of oseltamivir (considered to be a full course of treatment), while 16 subjects (12%) received less than 9 doses of oseltamivir.

Table 8. Extent of Exposure - Pooled Trial Data

| | **I** | **II** | **III** | **IV** | **V** | **TOTAL** |
|---|---|---|---|---|---|---|
| **Total Number of Doses** | **≤ 1 month (≤ 30 days) N=13** | **1-3 months (31-90 days) N=34** | **3-6 months (91-180 days) N=23** | **6-9 months (181-270 days) N=35** | **>9 months (≥ 271 days) N=30** | **All N=135** |
| **1 – 2** | -- | -- | -- | -- | 1 (3%) | 1 (1%) |
| **5 – 6** | 1 (8%) | -- | -- | -- | -- | 1 (1%) |
| **7 – 8** | -- | -- | 2 (9%) | -- | -- | 2 (1%) |
| **9 - 10** | 12 (92%) | 32 (94%) | 18 (78%) | 35 (100%) | 22 (73%) | 119 (88%) |
| **>10** | | 2 (7%) | 3 (13%) | -- | 7 (23%) | 12 (9%) |

Source: Applicant's Clinical Overview

Demographics of Target Population

Demographics of the study population is described in section 6.1.2. Demographics.

7.2.2 Explorations for Dose Response

The exploratory PK/PD analyses are described in section 4.4.3., Pharmacokinetics.

7.2.3 Special Animal and/or In Vitro Testing

Tamiflu is an approved medication for treatment of influenza, and no additional animal or *in vitro* testing was therefore conducted for this supplement.

7.2.4 Routine Clinical Testing

No routine clinical testing was conducted.

7.2.5 Metabolic, Clearance, and Interaction Workup

The primary objective of trials CASG114 and WP22849 was to define the PK of oseltamivir and oseltamivir carboxylate in children up to one year of age with confirmed influenza. See section 6.1.4. for details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There were no evaluations for potential adverse events for similar drugs in the same drug class as oseltamivir.

## 7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported from either study CASG114 or WP22849.

7.3.2 Nonfatal Serious Adverse Events

A total of 12 subjects (10%) experienced 13 SAEs (including both on- and off-treatment); one subject suffered from respiratory syncytial virus (RSV) bronchiolitis and ventricular septal defect (VSD), while the 11 other subjects experienced only one SAE each. Narratives of the SAEs were provided by the applicant, and these are summarized in Table 9.

Table 9. Summary of Narratives of All Serious Adverse Events - Pooled Data

| Serious Adverse Event (SAE) | Feeder Trial/ Subject # | Age/Sex of Subject | Significant Past Medical History | Day of Tamiflu at Onset of SAE | Medical Course | Resolution of SAE | Relationship of SAE to Tamiflu |
|---|---|---|---|---|---|---|---|
| Hypersensitivity | CASG114 Subj 25 | 10 m M | *S. pneumoniae* and empyema | Day 2 | Generalized, pruritic rash with associated cough and difficulty breathing | Diphenhydramine HCl, steroids. Resolution by Day 31. | Related |
| Pyrexia | CASG114 Subj 23 | 7 m F | None | Day 1 | Tmax 104.2°F on Day 7 with associated cough, diarrhea, vomiting. | Diagnosis: otitis media, Amox started. Fever resolution Day 13. | Not related |
| Influenza | CASG114 Subj 3 | 6 m M | Congenital lobar emphysema left upper lobectomy at 6 weeks | Day 2 | Increased work of breathing, low oxygen saturation. Briefly on ceftriaxone due to suspected lung infiltrate. | Placed on oxygen, then weaned to room air. | Not related |
| Worsening oxygen desaturation | CASG114 Subj 7 | 9 m F | Former 25-week preemie | Day (b) (6) | Decrease in $O_2$ sats to 88-89%, supplemental oxygen started. | Weaned to room air by Day (b) (6) | Not related |
| Respiratory distress | CASG114 Subj 302 | 4 m M | None | Completed | Wheezing, admitted Day (b) (6) or bronchiolitis. Treated with albuterol. | Discharged Day (b) (6) | Not related |
| Reactive airway disease | CASG114 Subj 30 | 11 m F | Former 26-week preemie | Completed | Hospitalized on Day (b) (6) Viral resp panel negative. | Weaned to room air | Not related |
| Diarrhea | WP22849 Subj 1704 | 118 days F | Former 26-week preemie | Day 3 | Prolonged hospitalization with decrease | Diarrhea resolved without therapy by Day (b) (6) | Not related |

| Serious Adverse Event (SAE) | Feeder Trial/ Subject # | Age/Sex of Subject | Significant Past Medical History | Day of Tamiflu at Onset of SAE | Medical Course | Resolution of SAE | Relationship of SAE to Tamiflu |
|---|---|---|---|---|---|---|---|
| | | | | | in weight. Stool studies negative. | | |
| Orbital cellulitis | WP22849 Subj 2004 | 174 days M | Former 35-week preemie | Completed | Developed Day 7. Left eye swab positive for *H. influenza*. | Treated, resolved by Day 14. | Not related |
| Respiratory syncytial virus bronchiolitis | WP22849 Subj 3002 | 321 days M | Former 36-week preemie | Day 6 | Fever, cough, rhinorrhea. Hospitalized for dyspnea on Day (b) (6) RSV positive. Symptomatic treatment. | Resolved Day (b) (6) | Not related |
| Pyrexia | WP22849 Subj 4214 | 92 days F | Tet of Fallot, congenital abnormalities | Completed (to Day 11) | Hospitalized Da (b) (6) or fever and drop in $O_2$ sats. Treated with Amp/Gent for 9 days (reason unclear). | Resolved Day (b) (6) | Not related |
| Fever, rash | WP22849 Subj 4220 | 340 days M | Former 26-week preemie, PDA ligation, RSV bronchiolitis | Completed (to Day 11) | Norovirus infection on Day 3, RSV on Day 6, fever to Tmax 39.2°C on Day 18, rash on Day 24 | Treatment for suspected *Mycoplasma*. Fever resolved on Day 32, rash resolved Day 41. | Not related |
| Respiratory syncytial virus bronchiolitis, VSD | WP22849 Subj 2005 | 70 days M | RSV bronchiolitis | Completed | VSD detected Day 10. RSV diagnosed Day 3, CPAP in PICU. | Surgery for VSD on Day 74. RSV testing negative Day 17. | Not related |

The most frequently reported SAEs were in the Infections and Infestations class: two subjects (1%) experienced respiratory syncytial virus (RSV) bronchiolitis, and one subject each experienced orbital cellulitis (1%), viral upper respiratory tract infection (1%), and influenza (1%). The explanation for why the latter subject was reported to have influenza as an SAE when all enrolled subjects were suspected to have the infection appears to be due to the complications that developed secondary to the infection.

There was a single SAE (hypersensitivity) that was considered by the investigator to be related to the trial medication, occurring in Subject 25, from Cohort II in trial CASG114. This was a ten month old male who was treated for Streptococcus pneumonia and empyema up to four days prior to enrollment. The subject developed a generalized, erythematous, pruritic rash on Day 2 of the trial after having received a single dose of trial medication on Day 1. The rash worsened after the second dose of trial drug. Associated symptoms included cough and difficulty breathing, for which summoned paramedics gave a single dose diphenhydramine HCl, leading to clinical improvement. Trial medication was discontinued after the second dose. Diphenhydramine HCl was continued for three more days, and was followed by a five-day course of prednisolone. The rash resolved by Day 31, off oseltamivir therapy.

The features of this case support the conclusion that the SAE was related to administration of the trial medication. The rash developed one day after the initial dose, and worsened after the second dose was given. In addition to this manifestation of hypersensitivity, the second dose precipitated worsening in the form of associated symptoms usually associated with anaphylaxis (difficulty breathing, cough). These symptoms responded to administration of an antihistamine drug. The subject had been taking clindamycin and ceftriaxone for the empyema, but it is unlikely that these antibiotics were associated with the AE as they were discontinued five days prior to the onset of the rash. Of note, cases of anaphylaxis and serious skin reactions have been reported in postmarketing experience with Tamiflu, as included in the label. For these reasons, this Medical Officer agrees with the applicant's assessment of this SAE as being related to the trial medication.

The low frequency of SAEs overall in these two trials reflects the trend noted in other trials of oseltamivir that have been reviewed by the Division. Two SAEs in particular, namely serious skin and hypersensitivity reactions, and neuropsychiatric events, have been noted with clinical experience with oseltamivir use for influenza treatment in adults and pediatric patients > 1 year of age. As noted, there were two subjects who developed rash and/or hypersensitivity reactions in trials CASG114 and WP22849. There were no reports of neuropsychiatric SAEs, though it should be noted that such reactions might be difficult to diagnose in children in general, and in infants < 1 year of age in particular, unless significant.

### 7.3.3 Dropouts and/or Discontinuations

Refer to section 6.1.3., Subject Disposition.

7.3.4 Significant Adverse Events

Sixty-five subjects (48%) experienced a total of 95 on-treatment AEs. The majority of adverse events reported were mild or moderate (87 or 95%) in intensity. Four subjects experienced AEs severe in intensity (hypersensitivity, RSV bronchiolitis, pyrexia, and neutropenia). The case of neutropenia was considered life-threatening, but was deemed by the investigator not to be related to trial treatment; the AE resolved with no dose adjustment and the subject continued on trial treatment.

Relation to Study Medication

Of the 95 adverse events reported, few were determined to be related to trial medication (11, or 8%). The remainder were considered to be unrelated. Categorization for the two trials differed, with WP22849 using the categories "possible", "probable", or "remote" to denote an association with trial medication, while CASG114 used "related" and "unrelated". This Medical Officer combined the three terms for WP22849 to assign causal relationship.

CASG114 reported four subjects who experienced four AEs that were related to the trial medication: two subjects experienced vomiting (1%), one subject experienced diaper dermatitis (1%), and another experienced rash (1%). In trial WP22849, seven subjects experienced seven AEs that were deemed associated with trial medication: two subjects displayed vomiting (1%), two subjects experienced diarrhea (1%), two subjects displayed pyrexia (1%), and one subject experienced gastroenteritis secondary to norovirus (1%).. Vomiting and diarrhea (etiology undifferentiated) have been reported in treatment trials in pediatric subjects ≥ 1 year of age, as noted in the label. Rash, as discussed previously, is noted in the label as a potential SAE with use of oseltamivir for treatment of influenza. Pyrexia is not noted as a common AE in the label, although it may be surmised that some pediatric subjects develop fever during the influenza disease, and differentiating between coincident fever and influenza-associated fever might be difficult. In addition, it appears that pyrexia was reported as an infrequent AE for children ≥ 1 year of age, while it was much more commonly reported for the trials under study in infants < 1 year of age, perhaps because fever is often considered to be a more critical piece of the diagnostic picture in younger children. Irritability is not noted in the label as a common AE in older patients.

7.3.5 Submission Specific Primary Safety Concerns

None.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

On-treatment AEs were events reported during treatment with oseltamivir up to three days from the last treatment dose. There was a total of 65/135 (48%) of subjects who experienced at least one adverse event. There were 95 on-treatment adverse events overall. The most commonly reported AEs in the pooled subject data were vomiting (10%), diarrhea (7%), and diaper dermatitis (7%). A summary of AEs reported through the trial period by body system and preferred term is shown in Table 10:

Table 10. On-Treatment Adverse Events by System Organ Class (SOC) and Preferred Term - Pooled Data

| **Body System**<br>**Preferred Term** | **ALL**<br>**N=135** |
|---|---|
| **Number of subjects with at least one AE** | **65 (48%)** |
| **Gastrointestinal Disorders** | **28 (21%)** |
| Vomiting | 14 (10%) |
| Diarrhea | 9 (7%) |
| Regurgitation | 3 (2%) |
| Flatulence | 1 (<1%) |
| Hematochezia | 1 (<1%) |
| Teething | 1 (<1%) |
| Anal fissure | 1 (<1%) |
| Constipation | 1 (<1%) |
| **Skin and Subcutaneous Tissue Disorders** | **21 (16%)** |
| Dermatitis diaper | 9 (7%) |
| Rash | 3 (2%) |
| Rash macular | 2 (<1%) |
| Rash papular | 1 (<1%) |
| Rash maculopapular | 1 (<1%) |
| Erythema | 1 (<1%) |
| Skin erosion | 1 (<1%) |
| Skin edema | 1 (<1%) |
| Dermatitis contact | 1 (<1%) |
| Dermatitis allergic | 1 (<1%) |
| Seborrheic dermatitis | 1 (<1%) |
| **Infections and Infestations** | **16 (12%)** |
| RSV bronchiolitis | 3 (2%) |
| Otitis media | 3 (2%) |
| Oral candidiasis | 2 (1%) |
| Rotavirus infection | 3 (2%) |
| Cellulitis orbital | 1 (<1%) |
| Gastro – Norovirus | 1 (<1%) |
| Urinary tract infection | 1 (<1%) |
| Influenza | 1 (<1%) |
| Candida nappy rash | 1 (<1%) |
| Candidiasis | 1 (<1%) |
| Pneumococcal infection | 1 (<1%) |
| Staphylococcal infection | 1 (<1%) |
| **General Disorders and Administration Site Conditions** | **7 (5%)** |
| Pyrexia | 4 (3%) |
| Irritability | 2 (1%) |
| Crepitations | 1 (<1%) |
| **Respiratory, Thoracic and Mediastinal Disorders** | **3 (2%)** |
| Cough | 1 (<1%) |
| Tachypnea | 1 (<1%) |
| Dyspnea | 1 (<1%) |
| Rhonchi | 1 (<1%) |
| **Eye Disorders** | **3 (2%)** |
| Conjunctivitis | 3 (2%) |

| **Body System**<br>**Preferred Term** | **ALL**<br>**N=135** |
|---|---|
| **Blood and Lymphatic System Disorders** | **2 (1%)** |
| Neutropenia | 2 (1%) |
| **Metabolism and Nutrition Disorders** | **2 (1%)** |
| Dehydration | 1 (<1%) |
| Fluid imbalance | 1 (<1%) |
| **Investigations** | **1 (<1%)** |
| Oxygen saturation decreased | 1 (<1%) |
| **Immune System Disorders** | **1 (<1%)** |
| Hypersensitivity | 1 (<1%) |
| **Nervous System Disorders** | **1 (<1%)** |
| Lethargy | 1 (<1%) |
| **Psychiatric Disorders** | **1 (<1%)** |
| Staring | 1 (<1%) |
| **Renal and Urinary Disorders** | **1 (<1%)** |
| Urine odor abnormal | 1 (<1%) |

*Gastrointestinal disorders:*
Twenty-eight (21%) subjects experienced AEs of this category. These included vomiting in 14 (10%) subjects, diarrhea in 9 (7%) subjects, and regurgitation in 3 (2%) subjects each. Vomiting and diarrhea are labeled AEs resulting from oseltamivir use, as previously discussed. Gastroenteritis is not labeled, but the symptoms of this condition often include vomiting and/or diarrhea. Categorization of this AE, therefore, may have differed between investigators.

*Skin and Subcutaneous Tissue Disorders:*
A total of 21 (16%) subjects were reported to have experienced AEs in this category. The most commonly reported AEs included diaper dermatitis in 10 (7%) subjects, rash in 3 (2%) of subjects, and erythema in 1 (<1%) subject. Combining the AEs under the assigned preferred term of "rash" (including rash, rash macular, rash maculopapular, and rash generalized) would yield a total of 7 subjects with this AE. Rash is a labeled AE associated with oseltamivir use, and hypersensitivity, which is also labeled, may include allergic or skin dermatitis. The association between diaper dermatitis and oseltamivir use is a difficult one to conclude in very young infants as diaper dermatitis is common in this age group. In addition, the condition may be exacerbated by diarrhea, which was frequently reported in these trials, again making the conclusion of an association difficult.

*Infections and infestations :*
A total of 16 (12%) subjects were reported to have experienced AEs in this SOC category. The most common of these AEs included RSV infection/bronchiolitis and oral candidiasis in 3 (2%) subjects each. RSV is not included in the oseltamivir label as being a common AE with use of the drug, at least in children down to age ≥ 1 year of age. This may be partially explained by the fact that infection or bronchiolitis secondary to RSV is more commonly diagnosed in infants < 1 year of age.

*Neurologic/Psychiatric Disorders*
The single reported nervous system event was lethargy that occurred in a 195-day old female infant. The episode lasted for one day, was classified as moderate in intensity, resolved without sequelae, and was deemed not to be associated with the trial medication.

The psychiatric disorders event was classified as "staring," clarified in the AE investigator text as a "2-3 second staring episode." The event occurred in a 210-day old female infant and was classified as mild and not associated with trial medication. There is no narrative of this single event, and it is therefore impossible to know if there were associated characteristics that might further elucidate the nature of the staring. Such a brief event would arguably not be that much cause for concern in such a young infant unless the investigator noted others signs that the event might represent a more serious condition, such as an absence seizure.

There were no reported neurologic or psychiatric events such as those described in the Warnings and Precautions section of the label that have been noted with post-marketing experience.

The remainder of the common AEs seen are noted in Table 12.

#### 7.4.2 Laboratory Findings

Laboratory testing was not required in either trial CASG114 or WP22849. Three subjects in study CASG114 (Subjects 3, 63, and 222) had laboratory tests (CBC, chemistries) completed for specific AEs or SAEs. These were largely unremarkable.

#### 7.4.3 Vital Signs

The only vital signs reported in the trials under review were heart rate and respiratory rate. The median change in heart rate from baseline to the final day of the trials was 10 (SD 26) beats per minute for all subjects. This change is not substantial. The median change in respiratory rate from baseline to the final day of the trials was -2 breaths per minute for all subjects. As with heart rate, this change in respiratory rate was not substantial.

Temperature was measured, but was treated as a PD (efficacy) parameter.

#### 7.4.4 Electrocardiograms (ECGs)

ECGs were not obtained as a routine part of the assessments conducted in these trials.

#### 7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted.

#### 7.4.6 Immunogenicity

Influenza antibody titers were not measured in the trials. No immunogenicity studies were conducted.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

This aspect was not assessed.

7.5.2 Time Dependency for Adverse Events

Adverse events were assessed throughout the on-treatment period. No specific time-dependency was identified.

7.5.3 Drug-Demographic Interactions

There were 25 males and 40 females who developed at least one AE whilst on treatment.

7.5.4 Drug-Disease Interactions

Drug-disease interactions were not explored during the trials.

7.5.5 Drug-Drug Interactions

Most subjects were not on medications prior to enrollment in the two trials, while some subjects (such as several former premature infants) were on medications. No formal assessment was made of the drug interactions between Tamiflu and these other drugs.

**7.6 Additional Safety Evaluations**

7.6.1 Human Carcinogenicity

Not applicable.

7.6.2 Human Reproduction and Pregnancy Data

Not applicable.

7.6.3 Pediatrics and Assessment of Effects on Growth

This effect of oseltamivir use on growth was not one of the goals of the trials. Treatment was given for only five days at most, and there was no long term follow-up, making assessment of oseltamivir's effect on growth impractical.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

### 7.7 Additional Submissions / Safety Issues

Safety data from the 11 subjects enrolled in WP22849 during the 2011-2012 influenza season were submitted as an amendment to the NDA as noted. There are no additional submissions that have been received from the applicant. There are no further safety issues other than those that have been previously discussed.

In conclusion, Tamiflu in infants < 1 year of age used at a dose ranging from 2 to 3 mg/kg twice daily was found to be safe and well-tolerated. The safety profile was acceptable from infants age 1 year, down to those who were two weeks old. The safety results of the trials appeared to be fairly consistent with the known safety profile of oseltamivir. No update in the safety information of the label is warranted.

# 8 Postmarket Experience

DAVP and OSE are continuously monitoring postmarketing AEs and reviewing specific events as needed. No specific OSE review of postmarketing AEs was conducted for this review.

# 9 Appendices

Use of Extrapolation in Pediatric Trial Review:

1. TITLE IV—PEDIATRIC RESEARCH EQUITY ACT OF 2007 ‘‘(B) SIMILAR COURSE OF DISEASE OR SIMILAR EFFECT OF DRUG OR BIOLOGICAL PRODUCT.— (i) IN GENERAL.—If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric subjects, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric subjects, such as pharmacokinetic studies. (ii) EXTRAPOLATION BETWEEN AGE GROUPS.—A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group. (iii) INFORMATION ON EXTRAPOLATION.—A brief documentation of the scientific data supporting the conclusion under clauses (i) and (ii) shall be included in any pertinent reviews for the application under section 505 of this Act or section 351 of the Public Health Service Act (42 U.S.C. 262).

## 9.1 Literature Review/References

1. Loeb M, Singh PK, Fox J et al. Longitudinal study of influenza molecular viral shedding in Hutterite communities. JID 2012;206:1078-84

2. Centers for Disease Control and Prevention. Antiviral agents for the treatment and chemoprophylaxis of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recommend. 2011. Rep. 60:1-24

3. World Health Organization. WHO Guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses. 2010. World Health Organization, Geneva, Switzerland

4. McPherson C, Warner B, Hunstad DA et al. Oseltamivir dosing in premature infants. JID 2012;206:847-50

5. Shi D, Yang D, Prinssen EP, et al. Surge in expression of carboylesterase 1 during the neonatal stage enables a rapid gain of the capacity to activate the anti-influenza prodrug oseltanivir. J Infect DIs. 2011. 203:937-942

6. Standling JF, Nika A, Tsagris V et al. Oseltamivir pharmacokinetics and clinical experience in neonates and infants during an outbreak of H1N1 influenza A virus infection in a neonatal intensive care unit. Antimicrob Agents Chemo. 2012. 56(7):3833-3840

7. Kearns GL, Abdel-Rahman SM, Alander SW et al. Development pharmacology – drug disposition, action, and therapy in infants and children. N Engl J Med 2003;349:1157-1167

### 9.2 Labeling Recommendations

The following draft labeling recommendations are to be sent to the applicant. These recommendations are based on the findings of trials CASG114 and WP22849. The exact language for the labeling is still being decided, but the following sections are expected to be revised.

INDICATIONS AND USAGE

Section 1.1: Treatment of Influenza

TAMIFLU should be indicated for the treatment of uncomplicated acute illness due to influenza infection in patients 2 weeks of age and older who have been symptomatic for no more than 2 days.

DOSAGE AND ADMINISTRATION

(b) (4) Pediatric Patients (b) (4)

(b) (4): The recommended oral dose of TAMIFLU for treatment of influenza in pediatric patients 1 to 12 years of age (b) (4) (b) (4) The recommended oral dose of TAMIFLU for treatment of influenza in pediatric patients is recommended from age 2 weeks to 1 year of age at 3 mg/kg twice daily for 5 days (shown in Table. ). (b) (4)

(b) (4)

| Weight (kg) | Treatment Dosing for 5 days | Prophylaxis Dosing for 10 days | Volume of Oral Suspension (6 mg/mL) for each Dose** | Number of Bottles of Oral Suspension to Dispense | Number of Capsules and Strength to Dispense‡‡ |
|---|---|---|---|---|---|
| (b) (4) | | | | | |
| (b) (4) | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 15 kg or less | 30 mg twice daily | 30 mg once daily | 5 mL | 1 bottle | 10 Capsules 30 mg |
| (b) (4) kg thru (b) (4) kg | 45 mg twice daily | 45 mg once daily | 7.5 mL | 2 bottles | 10 Capsules 45 mg |
| (b) (4) kg thru (b) (4) kg | 60 mg twice daily | 60 mg once daily | 10 mL | 2 bottles | 20 Capsules 30 mg |
| (b) (4) kg or more | 75 mg twice daily | 75 mg once daily | 12.5 mL† | 3 bottles | 10 Capsules 75 mg |

*TAMIFLU is not approved for prophylaxis of patients less than 1 year of age
** A 10 mL oral dosing dispenser is provided with the oral suspension. In the event that the dispenser provided is lost or damaged, another dosing dispenser may be used to deliver the volumes.
†Delivery of this TAMIFLU for Oral Suspension dose requires administering 10 mL followed by another 2.5 mL.
‡‡Oral Suspension is the preferred formulation for patients (b) (4) who cannot swallow capsules.

First, the dose of TAMIFLU for the patients (b) (4) [see Dosage and Administration (2)] then the total volume of an oral suspension needed to be compounded (b) (4), based on the Table. (b) (4)

Table. Volume of an Oral Suspension (6 mg/mL) Needed to be Compounded Based Upon the Patient's TAMIFLU Dose

| TAMIFLU Dose* | Total Volume to Compound per Patient (mL) |
|---|---|
| 15mg or less | 37.5mL |
| 30 mg | 75 mL |
| 45 mg | 100 mL |
| 60 mg | 125 mL |
| 75 mg | 150 mL |

* If the TAMIFLU dose is between the doses listed, the total volume of oral suspension to compound should default to the next greater dose listed.

Second, the number of capsules and the amount of water and vehicle (Cherry Syrup, Ora-Sweet® SF, or simple syrup) that are needed to prepare the total volume (from Table: 37.5mL, 75 mL, 100 mL, 125 mL, or 150 mL) of compounded oral suspension (6 mg/mL) (see Table) (b) (4)

Table. Number of TAMIFLU 75 mg Capsules and Amount of Vehicle (Cherry Syrup, Ora-Sweet® SF, or Simple Syrup) Needed to Prepare the Total Volume of a Compounded Oral Suspension (6 mg/mL)

| | | | | | |
|---|---|---|---|---|---|
| Total Volume of Compounded Oral Suspension to be Prepared | 37.5mL | 75 mL | 100 mL | 125 mL | 150 mL |
| Number of TAMIFLU 75 mg Capsules* | 3 capsules (225mg oseltamivir) | 6 capsules (450 mg oseltamivir) | 8 capsules (600 mg oseltamivir) | 10 capsules (750 mg oseltamivir) | 12 capsules (900 mg oseltamivir) |
| Amount of Water | 2.5mL | 5 mL | 7 mL | 8 mL | 10 mL |
| Volume of Vehicle Cherry Syrup (Humco®) OR Ora-Sweet® SF (Paddock Laboratories) OR simple syrup | 34.5mL | 69 mL | 91 mL | 115 mL | 137 mL |

*Includes overage to ensure all doses can be delivered

Dosing of the Compounded Suspension (6 mg/mL)
Refer to Dosage and Administration sections 2.2, 2.3, 2.4 and Table. for the proper dosing instructions for the pharmacy label.

Section 5.4: Limitations of Populations Studied

(b) (4)
(b) (4). (b) (4)

Section 6.1: Clinical Trials Experience

*Treatment Studies in Infants (Less than 1 year of age)*

The following information from the two trials will be included (text added by Division underlined): Assessment of adverse reactions is based on two open label studies that included 135 influenza-infected (b) (4) (including premature infants at least 36 weeks post conceptional age) exposed to TAMIFLU at doses ranging from 2 to 3.5 mg/kg twice daily for 5 days. The safety profile was similar across the age range studied, with vomiting, diarrhea and diaper rash being the most frequently reported adverse reactions. (b) (4)
(b) (4)

Section 8.4: Pediatric Use

Safety and efficacy of TAMIFLU for treatment (b) (4) in (b) (4) less than two weeks of age has not been established. Safety and efficacy of TAMIFLU for prophylaxis of influenza (b) (4) not been established for (b) (4) less than 1 year of age.

Section 12.3: Pharmacokinetics

(b) (4)

The following text is proposed by the applicant, and is largely agreed to by the Division (text added by the Division is underlined): The pharmacokinetics of oseltamivir and oseltamivir

carboxylate have been evaluated in two open-label studies of (b) (4) less than one year of age (n=122) infected with influenza. Apparent clearance of the active metabolite decreases with decreasing age in (b) (4) less than one year of age; however the oseltamivir and oseltamivir carboxylate exposure following a 3 mg per kg dose in (b) (4) under 1 year of age is (b) (4) to be within the observed exposure in adults and adolescents receiving between 75 mg twice daily and 150 mg twice daily.

Section 14: CLINICAL STUDIES

Section 14.1: Treatment of Influenza

(b) (4)

The following information was recommended, with updated percentages based on the total subject population (text added by the Division underlined): Two open label (b) (4) evaluated the safety and pharmacokinetics of oseltamivir and oseltamivir carboxylate in influenza infected (b) (4) less than 1 year of age (including premature infants at least 36 week post-conceptional age). (b) (4) received TAMIFLU at doses ranging from 2 to 3.5mg/kg twice daily for 5 days. These clinical trials were not designed to evaluate clinical efficacy or virologic response.

Of the 135 patients under the age of 1 year enrolled in the (b) (4), the majority of the subjects were male (56%), white (79%), non-Hispanic (74%), full term (76%) and infected with influenza A (80%). Pharmacokinetic data indicated that a dose of 3 mg/kg twice daily in pediatric (b) (4) (b) (4) provided TAMIFLU concentrations similar to or higher than those observed in older (b) (4) and adults receiving the approved dose and, by extrapolation, is expected to provide similar efficacy.

### 9.3 Advisory Committee Meeting

There will be no Advisory Committee meeting convened for this sNDA.

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

TAFADZWA S VARGAS-KASAMBIRA
12/10/2012

LINDA L LEWIS
12/10/2012
I concur with this review.  See CDTL for this supplement.