CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021246Orig1s045 and 021087Orig1s062

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW MEMORANDUM

NDA: 21246/S45, 21087/S62	**Submission Date: 6/21/2012**
Brand Name: Tamiflu®	**Generic Name: Oseltamivir**
Clinical Pharmacology Reviewer:	**Jenny H. Zheng, Ph.D.**
Clinical Pharmacology Team Leader:	**Shirley Seo, Ph.D.**
OCP Division:	**Clinical Pharmacology IV**
OND Division:	**Division of Antivial Products (DAVP)**
Sponsor: Hoffmann La Roche Inc.	**Relevant NDA NDA 21087, IND53093**
Formulation; Strength(s):	**Powder for suspension**
Route of Administration:	**Oral**
Proposed Indication:	**Treatment of influenza in children less than 1 year old of age**
Approved Indication:	**Treatment and Prophylaxis of influenza in adults and adolescents**

This memorandum is to summarize and assess the results from the inspection conducted by Division of Bioequivalence and GLP Compliance, Office of Scientific Investigations (OSI/DBGC), which was pending when the Clinical Pharmacology review was finalized.

The sites listed in the Appendix were the major clinical and analytical sites for Studies WP22849 and WP20749 (CASG 114) that were inspected. Please see the OSI review for details of the inspection results. Form FDA 483 was issued for Dr. Sanchez at University of Texas Southwestern Medical Center at Dallas Children's Medical Center Parkland Health and Hospitals Systems, Dallas, TX. The OSI/DBGC reviewers assessed Dr. Sanchez's response and deemed the response as adequate. Form FDA 483 was also issued for one of the analytical sites: (b) (4) However, the OSI/DBGC reviewers deemed that this observation had no consequences on data quality.

Following the above inspections, the DBGC reviewers recommend the following:

- The clinical pharmacology reviewer should evaluate the possible impact of ferrous sulfate, palivizumab, and oxacillin on pharmacokinetics of oseltamivir and its metabolite, for subjects #222, 226, 402, 642, and 643.
- The clinical pharmacology review should consider the pre-study dose of oseltamivir when evaluating pharmacokinetic data for subject #236.
- All other data from these studies are acceptable for review.

After careful evaluation, the clinical pharmacology reviewer concludes that the impact of ferrous sulfate, palivizumab, and oxacillin on pharmacokinetics of oseltamivir and its metabolite, for subjects #222, 226, 402, 642, and 643 is minimal and would not change the pharmacokinetic results and final conclusion. In addition, the pre-study dose of oseltamivir in subject #236 should not affect the steady-state pharmacokinetics of oseltamivir and its metabolite. Therefore, the conclusion in the clinical pharmacology review is not changed.

Appendix:

Study #1	
Study Number	WP22849
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

☒ Inspection Request - Clinical Site	☒ Inspection Request - Analytical Site
Facility #1 Name: Charité -Universitätsmedizin Berlin Address: Augustenburger Platz 1 Klinik für Pädiatrie mit Schwerpunkt Pneumologie und Immunologie Berlin, Germany 13353	Facility #1 Name: (b) (4) (b) (4) Address: (b) (4) (b) (4)

Study #2	
Study Number	WP20749 (CASG 114)
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

☒ Inspection Request - Clinical Site	☒ Inspection Request - Analytical Site
Facility Name/Address: 1) UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390 2) Children's Medical Center, 1935 Medical District Drive, Dallas, TX 75235 3) Parkland Health and Hospital Systems, 5201 Harry Hines Blvd., Dallas, TX 75235	Facility Name: (b) (4) Address: (b) (4)
Facility #2 Name/Address: (if applicable) 1) The Children's Hospital of Alabama, 1600 7th Avenue South, Birmingham, AL 35233 2) The University of Alabama Hospital, 619 19th Street, Birmingham, AL 35249 (Tel) (Fax)	Facility #2 Name: (if applicable) Address: (Tel) (Fax)

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

/s/

HUIMIN ZHENG
11/30/2012

SHIRLEY K SEO
11/30/2012

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:21246/S45	**Submission Date: 6/21/2012**
Brand Name	**Tamiflu®**
Generic Name	**Oseltamivir**
Clinical Pharmacology Reviewer	**Jenny H. Zheng, Ph.D.**
Clinical Pharmacology Team Leader	**Shirley Seo, Ph.D.**
Pharmacometrics Reviewer	**Jee Eun Lee, Ph.D.**
Pharmacometrics Team Leader	**Yaning Wang, Ph.D.**
OCP Division	**Clinical Pharmacology IV and Pharmacometrics**
OND Division	**Division of Antivial Products (DAVP)**
Sponsor	**Hoffmann La Roche Inc.**
Relevant NDA	**NDA 21087, IND53093**
Formulation; Strength(s)	**Powder for suspension**
Route of Administration	**Oral**
Indication	**Treatment of influenza in children less than 1 year old of age**
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1 Executive Summary

Tamiflu® (oseltamivir) was approved for the treatment and prophylaxis of influenza in children older than 1 year of age and adolescents/adults. The approval for the use in children older than 1 year of age was based on clinical trials conducted in children 1-12 years of age and these studies demonstrated safety and efficacy. Although the use of Tamiflu® in children younger than 1 year of age has not been approved, there is a need for the treatment of influenza in this population since the mortality rate associated with influenza was highest in children younger than 1 year of age.

A clinical trial (Collaborative Antiviral Study Group 114 clinical trial: CASG114 or Roche study WP20749) was conducted to provide emergency dosing guidelines for this age group in response to the swine flu pandemic in 2009. Those guidelines were based on provisional analyses of pharmacokinetics (PK)/pharmacodynamics (PD) and safety data from the CASG114 which was conducted in children 0-2 year of age. Additionally the sponsor conducted a prospective, open-label, multicenter study (WP22849) evaluating pharmacokinetics, pharmacodynamics, and safety of oseltamivir in infants less than one year of age with influenza diagnosed in the 96 hours prior to the first dose.

The dosing recommendation for infants less than 1 year of age is based on predicted pharmacokinetic exposures that are comparable to the exposures observed from children older than 1 year of age, adolescents and adults, following administration of effective dosing regimens. This method was chosen as the final approach after conducting a series of analyses of PK, PD and PK/PD of individual clinical studies including population approaches for pooled data from both studies. Upon completion of analyses, the sponsor proposes a 3 mg/kg twice daily (BID) dosing regimen for all ages of infants younger than 1 year of age.

The proposed indication for Tamiflu in infants younger than 1 year of age is for the treatment of influenza only. The indication for prophylaxis of influenza is not proposed for this population.

1.1 Recommendation

The Office of Clinical Pharmacology/Divisions of Clinical Pharmacology IV (OCP/DCPIV) and Pharmacometrics (OCP/DPM) has reviewed NDA21246/S45 submitted on June 21, 2012. The overall Clinical Pharmacology information submitted to support this sNDA is acceptable.

1.2 Postmarking requirement/Commitments

None

1.3 Clinical Pharmacology Summary

Doses used in clinical trials

Study CASG114, a prospective, age-stratified, open-label study was conducted to characterize PK/PD and safety of oseltamivir in children younger than 24 months of age (n=87) with confirmed influenza infection. Eighty-seven patients were enrolled in five cohorts by age (Cohort I: 12-23 months, Cohort II: 9-11 months, Cohorts III: 6-8 months, Cohorts IV: 3-5 months, Cohorts V: 0-2 months). The predefined AUC target was AUC_{0-12} values for oseltamivir carboxylate between 2,660 ng*hr/mL and 7,700 ng*hr/mL. The lower limit of the target was derived from mean exposure minus one standard deviation predicted for infants following 3 mg/kg in an analysis using 3 pediatric studies (JV16284, WV15758, and PP16251) and the upper limit was derived from observed mean exposure plus two standard deviations in adults following 150 mg BID. Doses were adjusted by predetermined rules to achieve the target exposure.

Study WP22849, a prospective, open label study was conducted to evaluate PK/PD and safety in infants 0-12 months of age (n=54) with confirmed influenza infection. Fifty-four patients were enrolled in three cohorts by age (Cohort I: 91-365 days, Cohort II: 31-90 days, Cohort III: 0-30 days).

Note: The sponsor uses different notation for age count interchangeably for an age group in each study and labeling: "6-9 months" equals to "6-8 months old". This happens because the upper limit of the age is exclusive but still included to signify the cutoff. "3-6 months" should be also interpreted as "3-5 months old" in the same fashion. Furthermore, the codes for age cohort used in individual study and in analyses with pooled data are different: Cohort I is for infants 12-23 months of age in CASG114 but is used for infants ≤ 1 month of age in the analysis with pooled data (Table 1). In this review, the codes defined in the analyses with pooled data will be used.

The doses that were given to each age group in the two studies are summarized in Table 1.

Table 1. Doses in each age group

	I	II	III	IV	V
Age Cohort	≤ 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)
CASG114 [a]	n = 8 (3 mg/kg)	n = 15 (3 mg/kg)	n = 10 (3 mg/kg)	n = 23 (3 mg/kg)	n = 16 (3 or 3.5 mg/kg)
WP22849 [a]	n = 5 (2 mg/kg)	n = 13 (2.5 mg/kg)	n = 12 (3 mg/kg)	n = 13 (3 mg/kg)	n = 11 (3 mg/kg)
Total	13	28	22	36	27

Since the CASG114 study included patients older than 1 year of age, the subset of data for infants younger than 1 year of age from CASG114 (n=68) and the PK evaluable data from WP22849 (n=54) were pooled for an integrated PK/PD analysis (Table 2).

Table 2. Total number of infants younger than 1 year of age included in the analysis

Age range	CASG114	WP22849	Total
3 to < 12 months	47	36	83
1 to < 3 months	13	13	26
< 1 month	8	5	13
Total	68	54	122

Formulation for infants younger than 1 year of age

The approved formulation, powder for suspension 6 mg/mL upon reconstitution is proposed for infants younger than 1 year old but different formulations of Tamiflu® were utilized in the two studies. In WP22849, the administered formulation was a pharmacy preparation of a dispersion of Tamiflu capsule contents to 10 mg/mL in water containing 0.1% of sodium benzoate. In CASG114 a 12 mg/mL oral suspension, which was previously marketed, was used. Bioequivalence across the formulation was established in the original submission. Furthermore, the population pharmacokinetics analysis showed no effect of formulation on the exposures of oseltamivir and oseltamivir carboxylate.

Pharmacokinetics of oseltamivir and oseltamivir carboxylate

The PK of oseltamivir in adults has been characterized prior to the current submission. Oseltamivir is an ethyl ester prodrug which is absorbed from the gastrointestinal tract after oral administration and primarily (~90%) converted by hepatic carboxyl esterases (predominantly in the liver) to the active metabolite, oseltamivir carboxylate (OC). The active metabolite is excreted by the kidney through tubular secretion. The plasma half-lives of oseltamivir and oseltamivir carboxylate are 1-3 hours and 6-10 hours, respectively.

2 Question Based Review

2.1 General Attributes

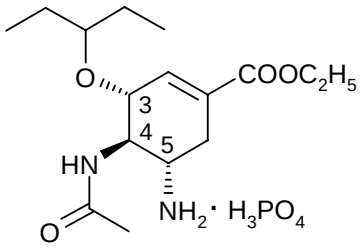
2.1.1 What is Tamiflu®?

Tamiflu (oseltamivir phosphate) is available as capsules containing 30 mg, 45 mg, 75 mg oseltamivir for oral use, in the form of oseltamivir phosphate, and as a powder for oral suspension, which when constituted with water as directed contains 6 mg/mL oseltamivir

base. Oseltamivir phosphate is a white crystalline solid with the chemical name (3R,4R,5S)-4-acetylamino-5-amino-3(1-ethylpropoxy)-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1).

Chemical formula: $C_{16}H_{28}N_2O_4$ (free base)
Molecular weight: 312.4 (free base); 410.4 (phosphate salt)

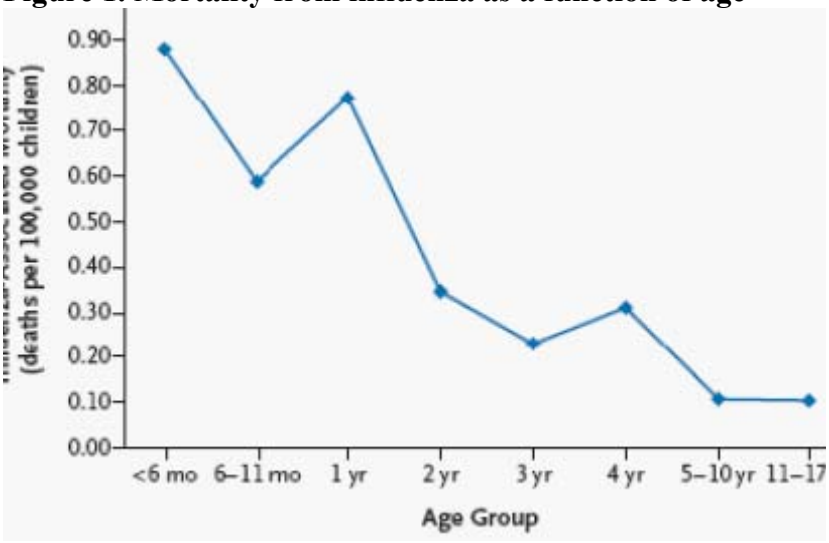
Chemical Structure:



2.1.2 What is regulatory history leading to this supplement?

Influenza infection in infants can develop into croup, bronchiolitis or pneumonia and has significant morbidity. In the US, the average excess hospitalization associated with influenza in infants < 6 months of age was found to approach 1000 per 100,000. As shown in Figure 1, infants under 1 year of age are at greatest risk.

Figure 1. Mortality from influenza as a function of age



Transplacentally acquired protective antibodies (predominantly IgG) begins at 28 weeks of gestation, increasing until the time of birth. The term neonate's serum level of

antibodies is believed to be similar to that of the mother's serum. Antibody levels decline rapidly after birth but generally persist up to the age of six months. After 6 months, the transplacental immunity is not expected to be present. .Tansplacental immunity may not exist for new pandemic strains of influenza virus.

Tamiflu is approved for the treatment and prophylaxis of children > 1 year of age. The recommended dosing regimens in the approved labeling are shown in Table 3.

Table 3. Treatment and prophylaxis dosing of oral Tamiflu for influenza in patients 1 to 12 year of age based on body weight (*Source: Tamiflu® labeling***)**

Weight (kg)	**Weight (lbs)**	**Treatment Dosing for 5 days**	**Prophylaxis Dosing for 10 days**
15 kg or less	33 lbs or less	30 mg **twice** daily	30 mg **once** daily
15.1 kg thru 23 kg	33.1 lbs thru 51 lbs	45 mg **twice** daily	45 mg **once** daily
23.14 kg thru 40 kg	51.1 lbs thru 88 lbs	60 mg **twice** daily	60 mg **once** daily
40.1 kg or more	88.1 lbs or more	75 mg **twice** daily	75 mg **once** daily

The recommended dosing for infants younger than 1 year of age has not been established even though they are at greater risk. The US 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. To provide emergency dosing guidelines for infants younger than 1 year of age, the interim data from clinical trial CASG114 (Collaborative Antiviral Study Group 114 clinical trial, or Roche study WP20749) in children 0-2 year of age was used to support the dosing guidelines for this age group and to establish PK/PD and safety profiles of oseltamivir and oseltamivir carboxylate. To support the indication for infants younger than 1 year of age, the sponsor conducted a prospective, open-label, multicenter study (WP22849) evaluating pharmacokinetics (PK), pharmacodynamics (PD), and safety of oseltamivir in infants less than one year of age with influenza diagnosed in the 96 hours prior to the first dose, in additional to Study CASG114.

2.2 Key review questions

2.2.1 What Clinical Pharmacology related information has been submitted to support this NDA supplement?

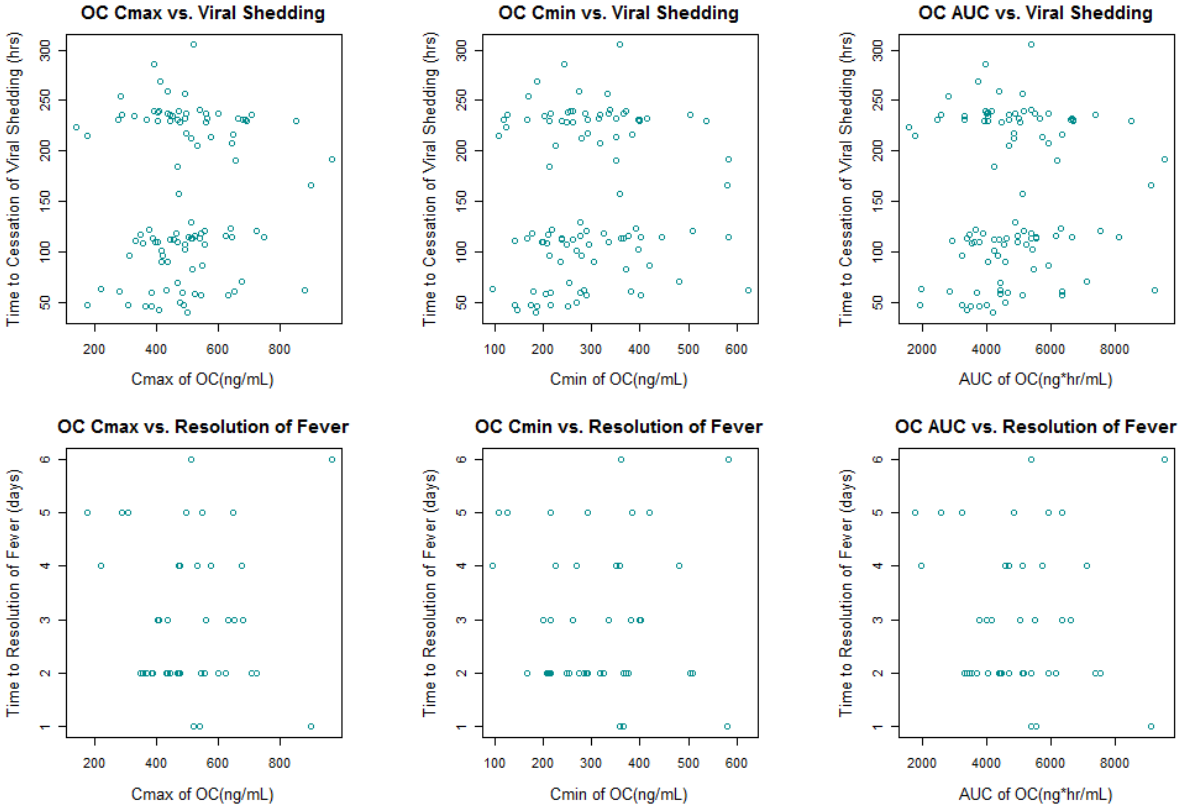
The current supplement includes studies where pharmacokinetics, pharmacodynamics and safety profiles in infants younger than 1 year of age are evaluated. Two studies (CSAG114 and WP22849) were submitted, where PK/PD samples were collected from 136 patients 0-1 year of age following administration of 2.0-3.5 mg/kg BID of Tamiflu. Other than the clinical study reports (CSR) from these two studies, the sponsor submitted a report for integrated PK-PD analysis with pooled dataset from the two studies, a report

for population pharmacokinetics analysis, and a report for simulation to support the dosing regimen in infants younger than 1 year of age.

2.2.2 What are characteristics of the exposure-response relationships for efficacy/safety?

There is no distinctive relationship between exposure of oseltamivir or oseltamivir carboxylate and PD endpoints including time to cessation of viral shedding or time to event to resolution of fever within the studied exposure ranges. This is not surprising since the range of doses administered to the infants 0-1 year of age was narrow and doses were chosen to target an effective exposure range.

Figure 2. Scatter plots of time to resolution of fever and time to cessation of viral shedding and AUC, Cmax and Cmin of oseltamivir carboxylate (*Source: reviewer's analysis using the sponsor's dataset***)**



2.2.3 What are the pharmacokinetic parameters of oseltamivir and oseltamivir carboxylate in infants younger than 1 year of age?

The clearance by each age cohort in infants < 1 year of age is summarized in **Table 4**. The median values of apparent clearance of oseltamivir and oseltamivir carboxylate estimated from a noncompartmental analysis for data from 9 infants who received 30 mg fixed dosing regimen in CASG114 is used for comparison, which were 81.3 L/hr (the median body weight normalized clearance of oseltamivir was 7.14 L/hr/kg and the median body weight was 11.39 kg) and 11.6 L/hr, respectively (*Source: For Cohort 1A in Table 4 on page 71 and Table 12A and 12B on page 122 of CASG114 CSR*).

Table 4. Clearance of oseltamivir and oseltamivir carboxylate in infants < 1 year of age (*Source: reviewer's analysis using the sponsor's final model, mean and standard deviation are reported*)

	0-1 MONTHS (N=13)	**1-3 MONTHS (N=26)**	**3-6 MONTHS (N=22)**	**6-9 MONTHS (N=35)**	**9-12 MONTHS (N=26)**
Oseltamivir	51.3 (18.9)	64.6 (27.2)	74.8 (23.6)	72.7 (30.3)	85.4 (31.8)
Oseltamivir carboxylate	2.6 (2.2)	2.8 (1.0)	4.1 (1.8)	5.5 (2.5)	6.2 (2.4)

2.2.4 Are there other clinical data from infants younger than 1 year of age outside and in the US?

Yes.

Prior to the studies submitted under the current supplement, several prospective and retrospective studies have been conducted in infants outside the US. The summary of those studies are provided in Table 5.

Table 5. Summary of Studies Conducted in Infants < 1 Year of Age Outside the US

Study Title	Dosage prescribed	No. of oseltamivir-treated infants < 1 year
Japanese prospective interventional study	4 mg/kg/day	47
Japanese retrospective study (Retrospective survey)	Majority received 4 mg/kg/day (0.4 – 6.4 mg/kg/day)	771
Japanese prospective surveillance study (Prospective survey)	4 mg/kg/day (b.i.d. dosing)	1284
Japanese retrospective study evaluating encephalopathy	Not provided	103
German study (Retrospective analysis)	2 mg/kg b.i.d.	157
Total		**2362**

Furthermore, the sponsor collected post-marketing drug safety database for infants younger than 1 year of age up to 2/29/2012. After exclusion of cases included in the two studies submitted under the current supplement, a total of 218 cases comprising 331 AEs are reported. The majority of the cases were reported from Japan (n=92), UK (n=43), and USA (n=32). These cases comprised:

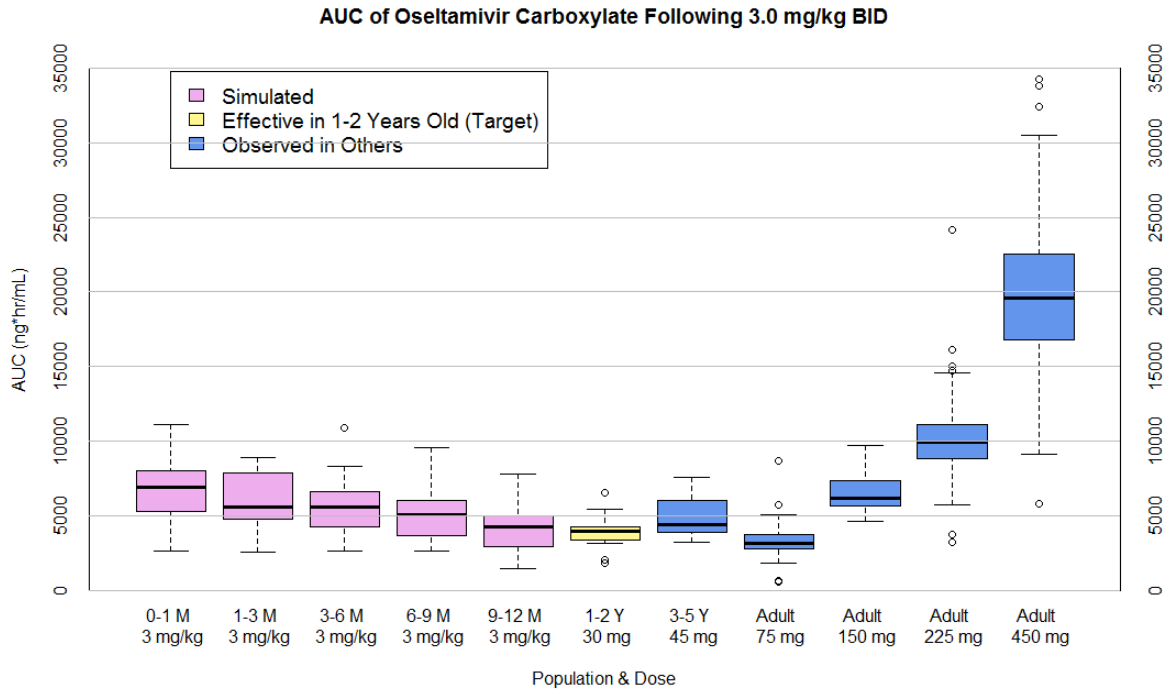
- 35 infant 0 to < 3 months of age (including 12 babies < 1 month of age)
- 43 infants aged 3 to < 6 months of age
- 75 infants aged 6 to < 9 months of age
- 65 infants aged 9 to < 12 months of age

2.2.5 Is the proposed dosing regimen in infants younger than 1 year of age appropriate for Tamiflu®?

Yes.

The simulated AUCs of oseltamivir carboxylate following 3.0 mg/kg BID in infants 0-1 year of age show higher than the exposures observed from children 1-2 years old following 30 mg BID, the approved dosing regimen for children 1-2 years of age (Figure 3). This dose of 30 mg BID was also effective with no resistance in the study PP16351 and thus the exposures from this study were used to derive the target exposure. Furthermore, the simulated AUC following 3.0 mg/kg BID was between the exposure in adults following 75 mg BID and 150 mg BID. Both doses were safe and efficacious in clinical trials of the original drug development.

Figure 3. Simulated AUCs of oseltamivir carboxylate in infants 0-1 year of age following 3.0 mg/kg BID of Tamiflu in comparison with other populations (*Source: reviewer's simulation using the sponsor's final model***)**



2.2.6 Should lower dose be recommended in younger infants 0-3 months of age in whom lower clearance due to immaturity of renal function was observed?

Not necessarily.

During the original clinical development program, 21 Japanese children aged 1-2 years of age received 2 mg/kg dose in study JV16284 and resistance was developed in some subjects. Resistance was also observed in study WV15758, where approximately 80 children 1-2 years of age received 2 mg/kg BID. In another study (WV16193), children 1-2 years of age received 30 mg BID (eq. approximately 3 mg/kg since the median body weight for this age group is 10 kg) did not show any resistance.

Resistance is believed to occur faster and more frequently in pediatric populations and mortality associated with influenza in the youngest infants is of great concern. As a result, the higher exposure of oseltamivir carboxylate in this population is rather desirable than lower exposure. Furthermore, safety concern is believed to be more associated with exposure of oseltamivir rather than the exposure of oseltamivir carboxylate and the simulated Cmax of oseltamivir show that exposure of oseltamivir following 3.0 mg/kg Tamiflu is less than the observed exposure of oseltamivir in adults following administration of 150 mg of Tamiflu which was believed to be safe in Phase 3 clinical trial in the original development.

2.2.7 Did the sponsor use validated bioanalytical assays to generate the study data?

Yes. Oseltamivir and its carboxylate metabolite were analyzed in human plasma by two validated methods. Plasma was analyzed using either solid-phase extraction (Study CASG114 (WP20749)) or protein precipitation (Study WP22849) followed by high-performance liquid chromatography (HPLC) and detection using electrospray tandem mass spectrometry (MS; LC/MS/MS).

Clinical Study Number	Assay Range (ng/mL)	Matrix	Lab	Accuracy (%)	Precision (% CV)	Stability
CASG114	1.00−250 (oseltamivir) R^2> 0.992	Human plasma	BASi UK	101.0 to 103.0	4.4 to 9.0	≥ 29 hrs at room T ≥376 days at 5°C and < -65°C At least 2 freeze/ thaw cycles
	10.0−10,000 (oseltamivir carboxylate) R^2> 0.990			99.5 to 100.0	3.3 to 7.2	
WP22849	1.00−250 (oseltamivir) R^2> 0.998	Human plasma	PRA International	99.6 to 102.0	3.5 to 4.7	≥24 hrs at room T ≥376 days at -20°C and -70°C At least 5 freeze/ thaw cycles
	10.0−10,000 ng/mL (oseltamivir carboxylate) R^2> 0.994			100.3 to 103.9	3.8 to 6.0	

The standard curve and QC data indicated that the plasma assay method for oseltamivir and oseltamivir carboxylate were precise and accurate. All study samples were analyzed within their documented long-term stability.

In addition, analytical site and clinical site inspections were conducted to ensure the validity of the oseltamivir and oseltamivir carboxylate exposures. For this submission, approval is based on bridging oseltamivir and oseltamivir carboxylate exposures in pediatrics to those observed in children older than 1 year of age and adults. Therefore, the validity of the oseltamivir and oseltamivir carboxylate pharmacokinetic evaluation is pivotal for approval of oseltamivir use in pediatric patients. The inspection results are pending.

3 Results of Sponsor's analysis

3.1.1 Population Pharmacokinetics and Modeling and Simulation

The analysis dataset included 556 oseltamivir and 594 oseltamivir carboxylate quantifiable plasma samples from 122 subjects (69 male, 53 female) administered 2.0 to 3.5 mg/kg of oseltamivir in studies CASG114 and WP22849. Mean age was 24.0 weeks (1.9 ~ 49.9 weeks). Mean body weight was 6.5 kg (2.9~12.4 kg). Among them, there were 95 (77%) White, 14 (11.5%) Black, 12 (9.8%) Other, and 2 (1.6%) of Unknown

races. There were 13 (10.7%) of subjects 0-1 month of age, 26 (21.3%) of subjects 3-6 months of age, 35 (28.7%) of subjects 6-9 months of age, and 26 (21.3%) of subjects 9-12 months of age.

A total of 22 (3.8%) of oseltamivir concentrations that were below the quantification limit (BQL) were excluded from the analysis. Since number of concentrations of BQL takes a small portion of the data, imputation of BQL was not attempted. A total of 3 quantifiable oseltamivir concentrations that were inconsistent with the concentration-time profiles were excluded from the analysis. By visual assessment, exclusion of those outliers seems reasonable.

The sponsor's base model to describe the data was a two-compartment model for oseltamivir with additional compartment for active metabolite. The final model included clearance and volume of distribution parameters that were allometrically scaled as $(WT/8)^{0.75}$ and $WT/8)^{1}$, respectively where WT is weight in kilogram. Age dependence was described by the linear function: $CL_M/F=\theta_6\times(WT/8)^{0.75}\times(1+\theta_{10}\times(Age/24-1))$; $V_M/F=\theta_7\times(WT/8)^{1}\times(1+\theta_{10}(Age/24-1))$ where the unit for Age is week. The model-estimates for the parameters are summarized in Table 6.

Table 6. PK parameters estimated from the final population PK model (*Source: Report "Simulation to support oseltamivir dose selection in infants less than one-year old" page 13***)**

Parameter		Estimate (95%CI)	%RSE	Bootstrap Median (95%CI)	Variability	Shrinkage
k_a (1/hr)	θ_1	0.894 (0.673 - 1.11)	12.6	0.902 (0.798 - 1.04)		
CL/F (L/hr)	θ_2	79.4 (71.3 - 87.5)	5.2	79.2 (73.4 - 85.2)		
V_2/F (L)	θ_3	171 (125 - 216)	13.6	171 (138 - 212)		
Q/F (L/hr)	θ_4	20.1 (17.5 - 22.6)	6.47	20.1 (16.1 - 25.4)		
V_3/F (L)	θ_5	317 (174 - 460)	23.0	316 (182 - 477)		
CL_M/F (L/hr)	θ_6	4.82 (4.4 - 5.24)	4.43	4.83 (4.52 - 5.17)		
V_M /F (L)	θ_7	42.1 (38.4 - 45.9)	4.55	42.2 (38.0 - 46.8)		
σ_{OP}	θ_8	0.481 (0.429 - 0.532)	5.43	0.479 (0.441 - 0.516)	CV=48.1%	9.9%
σ_{OC}	θ_9	0.176 (0.168 - 0.184)	2.27	0.176 (0.152 - 0.2)	CV=17.6%	11.3%
$CL_{M,AGE}$	θ_{10}	0.335 (0.264 - 0.406)	10.9	0.332 (0.221 - 0.429)		
ω^2_{CL}	$\Omega(1,1)$	0.138 (0.091 - 0.185)	17.4	0.135 (0.0933 - 0.19)	CV=37.2%	8.3%
$R\omega_{CL}\omega_{V2}$	$\Omega(2,1)$	0.0813 (-0.003 - 0.165)	52.7	0.0791 (-0.00525 - 0.166)	R=0.259	
ω^2_{V2}	$\Omega(2,2)$	0.714 (0.391 - 1.04)	23.1	0.687 (0.447 - 1.05)	CV=84.5%	9.5%
$R\omega_{V2}\omega_{CLM}$	$\Omega(3,2)$	0.164 (0.11 - 0.217)	16.6	0.155 (0.0604 - 0.284)	R=0.547	
ω^2_{CLM}	$\Omega(3,3)$	0.125 (0.0931 - 0.157)	13.1	0.121 (0.0792 - 0.19)	CV=35.4%	2.7%

PE: Parameter Estimate; SE: Standard Error: RSE: Relative Standard Error, RSE=100·SE/PE.
95% CI: 95% confidence interval.
SD: Standard Deviation; CV: coefficient of variation, CV = 100*SD %.

Note: $V_{M,AGE}$ is not included in the table but the same parameter (θ10) was used for both $CL_{M,AGE}$ and $V_{M,AGE}$.

From the analysis, the sponsor concluded for the oseltamivir prodrug, body-weight alone through allometric scaling was adequate to describe the variability of clearance. For oseltamivir carboxylate, age was an additional covariate in describing a significant proportion of the unexplained variability in both apparent clearance and volume of distribution. The rapid maturation of renal function (glomerular filtration rate and tubular secretion) over the first year of life can be an explanation for the increase in apparent clearance as age increases up to 1 year. The impact of age on apparent volume of distribution (increasing volume of distribution with increasing age) could be explained by changes in effectiveness of intra-hepatic trapping and enzymatic system as well as changes in total body water during the first year of life.

From the covariate analysis, the use of post-conceptual age instead of postnatal age did not improve the model. The formulation (which differed in the two studies) did not have impact on oseltamivir or oseltamivir carboxylate PK. No effect of race or gender on oseltamivir or oseltamivir carboxylate PK was identified either.

Since no evidence for the correlation between PK exposures and PD endpoints has been identified within the studied PK exposure ranges, the sponsor attempted to bridge the simulated exposures to target exposure from other populations to support recommended dosing regimen in infants younger than 1 year of age. As described in CASG114 CSR (see the summary of individual study report in Appendix), there is indirect evidence from younger children that emergence of resistance may be related to underexposure of oseltamivir carboxylate. Resistance was observed from studies (WV15758, NP15826) where 2 mg/kg BID was administered to children 1 to 2 years of age, and no resistance was observed in a study (PP16351) where children 1 to 2 year of age received 30 mg BID. The target exposure was thus derived from PP16351 where approved dosing regimen, 30 mg fixed dose BID (eq. to 3 mg/kg for the median body weight of 10 kg for the age group) was administered to children 1 to 2 years of age. The AUC values for individual patient are described in Table 7. This target exposure was within the range of exposure demonstrated as safe and efficacious in the adult phase III pivotal trials, in which regimens of 75 mg and 150 mg BID were investigated (AUC_{0-12} 2700 ng*hr/mL and 5500 ng*hr/mL, respectively).

Table 7. AUC_{inf} values in infants 1 to 2 year of age following 30 mg single dose of oseltamivir from PP16351 (*Source: Clinical Pharmacology Summary page 43***)**

Patient	Body-weight	Age (years)	Oseltamivir Carboxylate AUC_{∞} (hr*ng/mL)
20	10.4	1	4334
22	10.8	1	2016
23	11	1	6557
25	11.8	1	5409
26	12.4	1	3591
30	11.3	1	4035
21	11.4	2	4155
24	10.9	2	4061
27	12.2	2	3822
28	17.2	2	3150
29	15.9	2	3927
31	13.2	2	1807
		Average	3905
		Average minus 1 SD	2618
		Minimum	1807
		Maximum	6557

This target exposure was set as follows for bridging purpose:

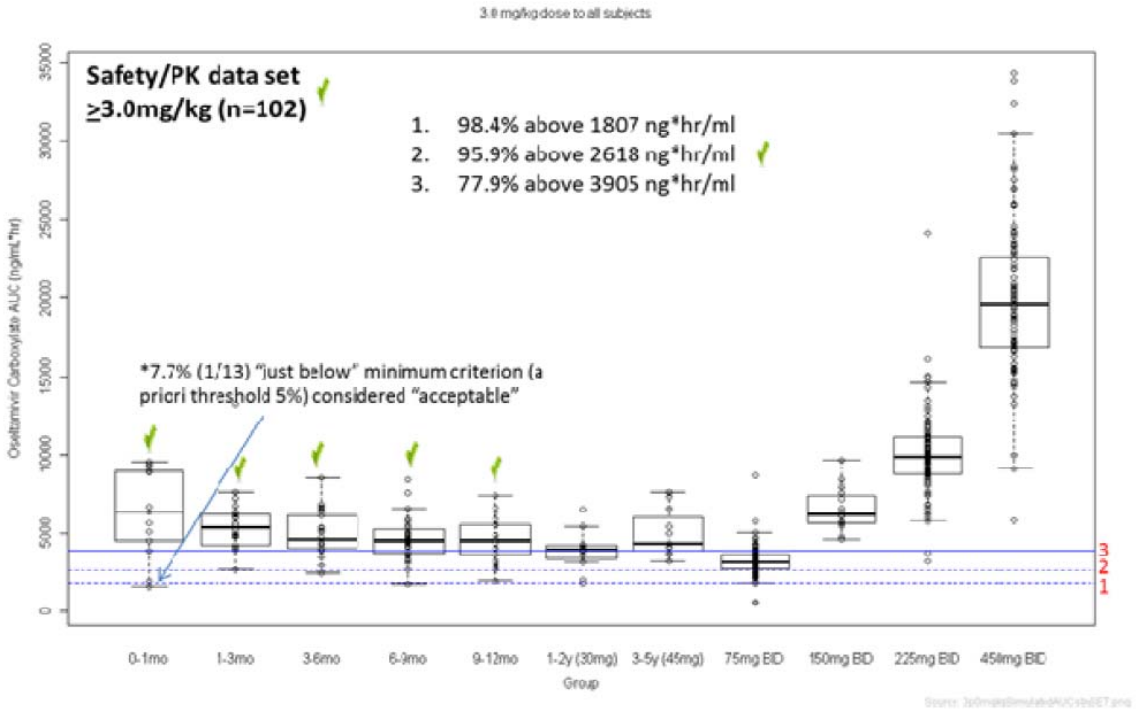
1. At least 95% of infants should have a steady-state $AUC_{0-\tau} > 1807$ hr*ng/mL ("minimum")
2. At least 85% of infants should have a steady-state $AUC_{0-\tau} > 2618$ hr*ng/mL ("average minus 1 SD")
3. At least 50% of infants should have a steady-state $AUC_{0-\tau} > 3905$ hg* ng/mL ("average")

While no PK-safety relationship was identified, the safety margin was based on the nonclinical evidence to support an association between drug exposure and safety/tolerability. According to the nonclinical overview submitted under the current supplement, the projected safety margins in infants for Cmax and AUC for oseltamivir phosphate were greater than 83× and 120×, respectively, in comparison to juvenile rats and greater than 83× and 22000× compared to data in juvenile marmosets. The margins for Cmax and AUC for oseltamivir carboxylate were greater than 14× and 11×, respectively, compared to juvenile rats and greater than 8× and 3,500× compared to juvenile marmosets.

As shown in Figure 4, the simulated steady-state oseltamivir carboxylate AUCs in all age groups of infants younger than 1 year of age are above the target exposure and well

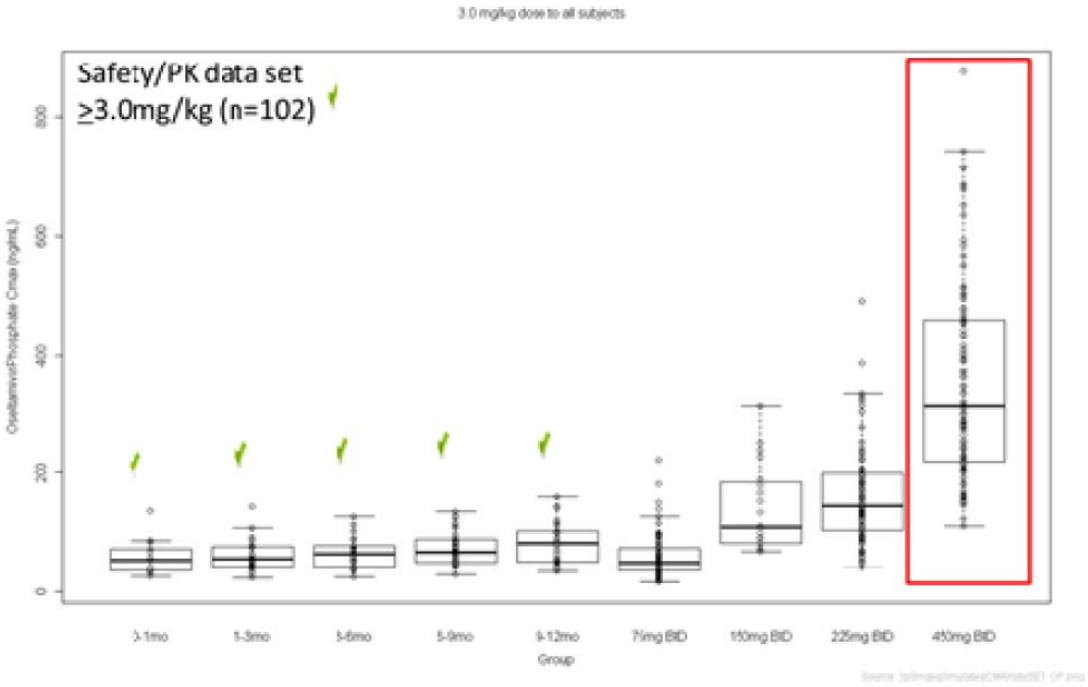
aligned with exposures observed from other populations including adults who received 75 mg or 150 mg. The simulated oseltamivir Cmax values following 3 mg/kg BID (Figure 5) are below the observed Cmax in adults following 150 mg for which safety and efficacy were shown in clinical trials during the original drug development.

Figure 4. Comparison of simulated steady-state oseltamivir carboxylate AUCs by age following 3 mg/kg BID versus AUCs observed in other populations (*Source: Clinical Pharmacology Summary page 48***)**



Note: Green tick indicates pre-specified criteria met; Blue line indicates nominated thresholds; Insert indicates target attainment for entire < 1 year of age population

Figure 5. Comparison of simulated steady-state Cmax by age following 3 mg/kg BID versus Cmax observed in other populations



Note: Green tick indicates pre-specified criteria met; Red box highlights conservative exposure ceiling

Based on the simulation results, the sponsor recommends 3 mg/kg BID dosing regimen for infants younger than 1 year of age. The rationale is following:

- 3mg/kg BID safeguards those few younger infants who may be at risk of potential consequences for underexposure of OC at lower doses (resistance and failure), even though 3 mg/kg BID yields modestly increased median OC AUCs in younger infants.
- A 3 mg/kg BID dose has been demonstrated to be safe and well tolerated, in infants from < 1 month to < 1 year of age from CASG114 and WP22849
- A 3 mg/kg BID regimen is in alignment with current dosing recommendations for infants at 1 year of age where a typical infant of 10 kg already receives 30 mg BID (i.e., 3 mg/kg BID)
- A 3 mg/kg BID regimen across the < 1 year of age cohort provides less potential for medication errors than separate doses for different age cohorts

4 Reviewer's analysis

4.1 Introduction

The sponsor's recommended dosing was based on the simulation to match exposures in the target population to the safe and effective exposures in other populations using a population PK model. An independent analysis was conducted to explore potential PK-PD relationships and to consider an alternative model

where power values of the allometric scaling for PK parameters are estimated instead of being fixed as the sponsor practiced in the modeling process.

4.2 Objectives

Analysis objectives are:

1. To evaluate potential relationship between PK and PD
2. To evaluate alternative population PK model where power values for allometric scaling for clearance and/or volume of distribution are estimated
3. To evaluate the simulated exposures using the population PK model in comparison with observed values in other populations including those in children 1-2 years of age

4.3 Method

4.3.1 Data sets

Data sets used in the analysis are summarized in Table 8.

Table 8. Analysis data sets

Study Number	Name	Link to EDR
Study-wp22849	pkpd.xpt ppar.xpt	\\cdsesub1\evsprod\NDA021246\0032\m5\datasets\wp22849\analysis
Population PK	poppk.xpt	\\cdsesub1\evsprod\NDA021246\0032\m5\datasets\model-simulation\analysis
Integrated PK-PD	pk.xpt pkquart.xpt effpkpt.xpt	\\cdsesub1\evsprod\NDA021246\0032\m5\datasets\integrated-iss-ise-analysis-report\analysis
Additional PK-PD data for 11 subjects not included in interim analysis for WP22849	ockeypkcomp.csv opkeypkcomp.csv	\\cdsesub1\evsprod\NDA021246\0043\m5\datasets\model-simulation\analysis

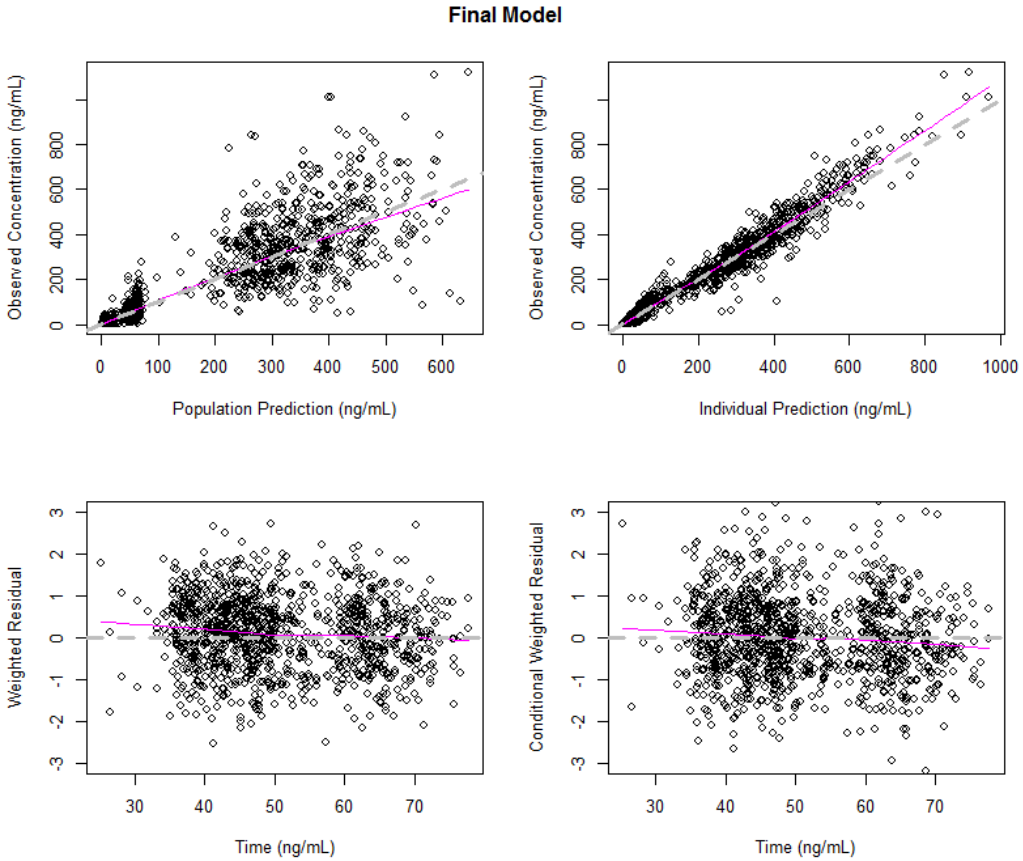
4.3.2 Software

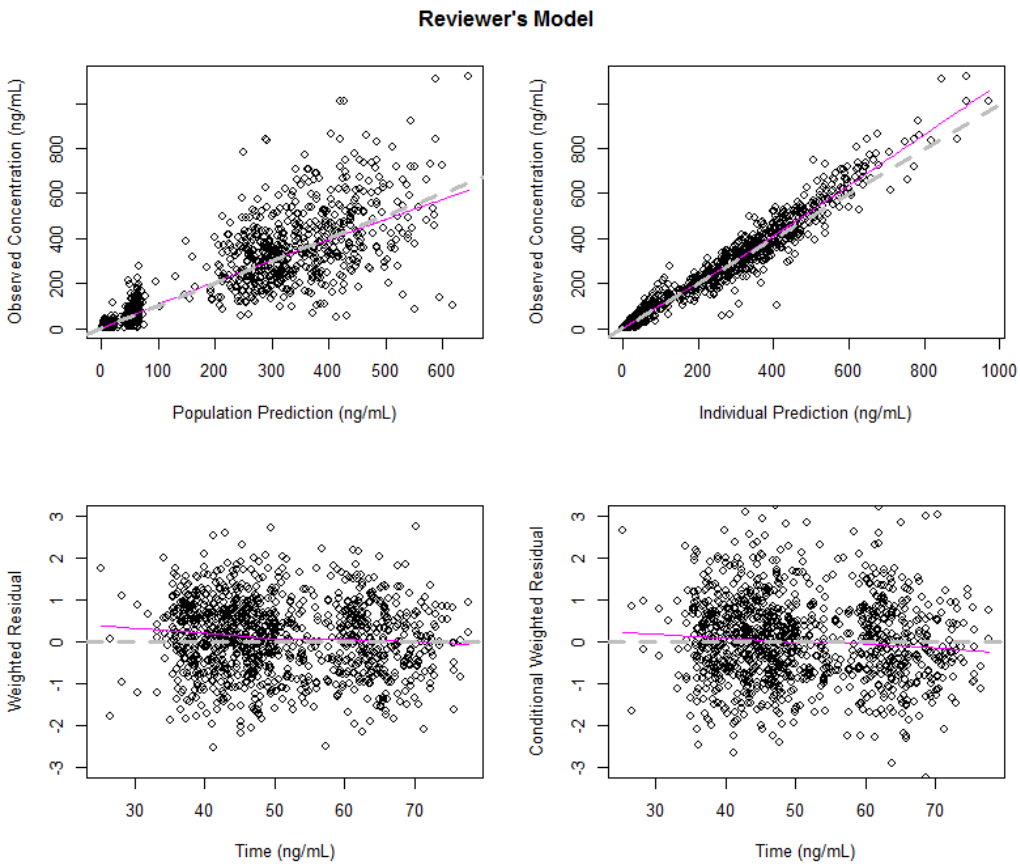
Population pharmacokinetics modeling was performed with NONMEM (version 7.2) and graphical, statistical analysis and simulation were performed with R (version 2.13.1)

4.3.3 Population PK modeling

The sponsor's final model used fixed values of power 0.75 and 1 for allometric scaling with body weight for clearance (CL) and volume of distribution (V). In the reviewer's alternative analysis, modeling was attempted to estimate the power values instead of fixing those values. The estimated power values allometric scaling with body weight for clearance and volume of distribution were 0.92 and 1.07, respectively. Although the objective function value decreased from 9240.676 to 9236.429 with the reviewer's model, the difference (ΔOBF=4.247) was not substantial to impact the ultimate analysis results. The plots for goodness of fit (Figure 6) also show that the model with estimated power for the allometric scaling for CL and V does not improve the model significantly. Thus the sponsor's final model is retained.

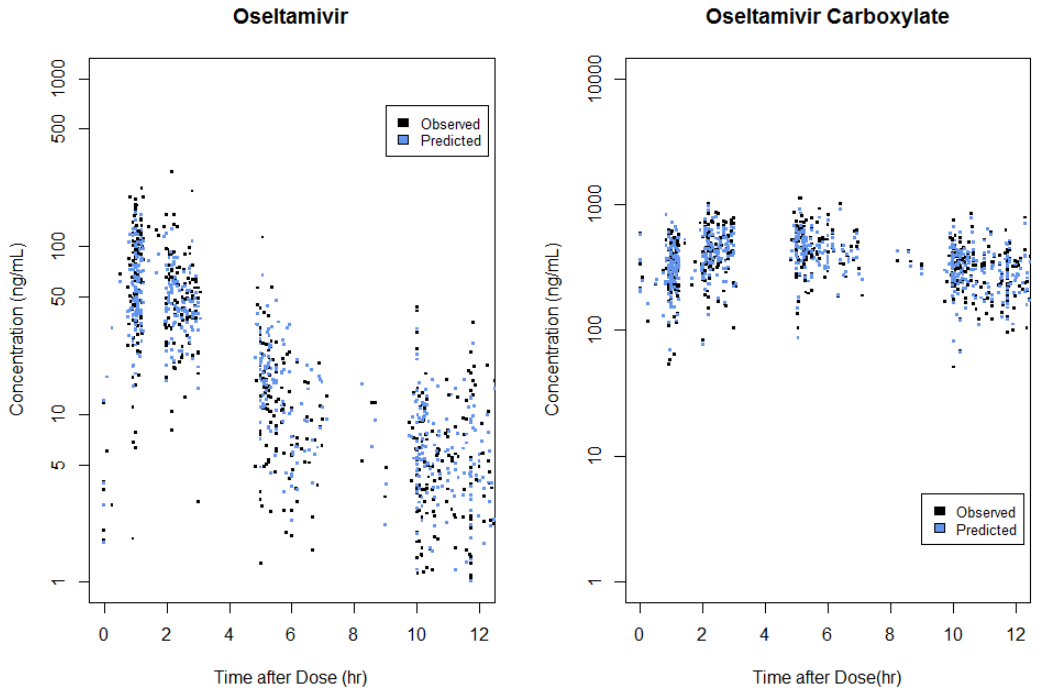
Figure 6. Goodness of fit comparison between the sponsor's model and the reviewer's model (*Source: reviewer's analysis using the sponsor's final model and the reviewer's alternative model***)**





The model predicted concentration profiles of oseltamivir and oseltamivir carboxylate generated with the sponsor's final model were in good agreement with observed concentration (Figure 7). The sponsor's analysis with other model evaluation techniques including visual predictive check (VPC) indicated that the sponsor's model is adequate to describe the data (figures are not shown).

Figure 7. Observed concentration vs. population PK model predicted concentrations (*Source: reviewer's analysis using the sponsor's final model***)**



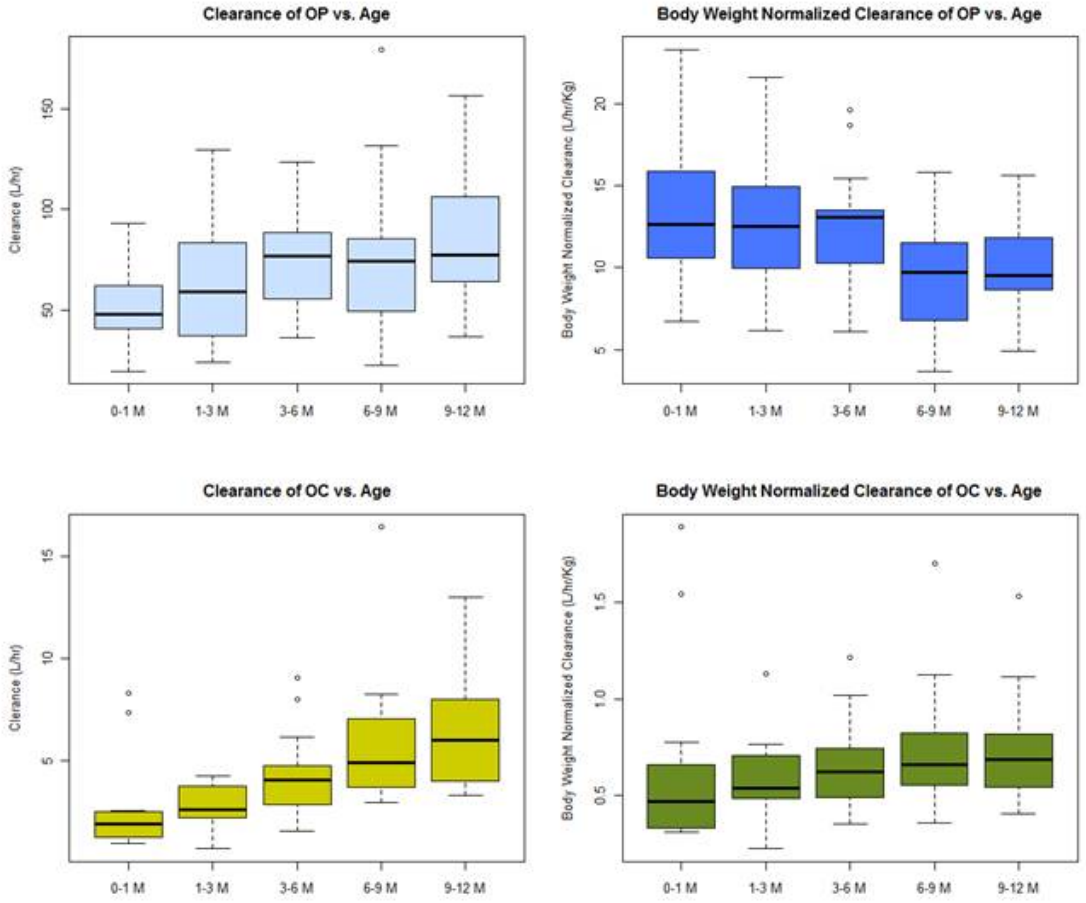
It is notable that the clearance increases as age increases in infants younger than 1 year of age. As shown in Table 9 and Figure 8, both total apparent clearance (CL/F) and body-weight normalized apparent clearance (CL/F/kg) of oseltamivir carboxylate increase as renal function rapidly mature until an infant reaches 1 year of age. These clearance values estimated from the sponsor's population PK analysis are in good agreement with the estimated values by noncompartmental analysis from CASG114 CSR (see Figure 14). The clearance of oseltamivir carboxylate in infants 0-3 months of age is less than half of the clearance of oseltamivir carboxylate in infants 9-12 months of age.

Table 9. Total clearance and body weight-normalized clearance of oseltamivir and oseltamivir carboxylate by age group (*Source: reviewer's analysis using the sponsor's final model, median and range are reported***)**

	Parameter	**0-1 Months**	**1-3 Months**	**3-6 Months**	**6-9 Months**	**9-12 Months**
Oseltamivir	CL/F (L/hr)	47.8 (19.5-93.2)	58.9 (24.0-129.6)	77.0 (36.3-123.6)	74.3 (22.2-179.6)	77.3 (36.6-156.7)
	Weight normalized CL/F (L/hr/kg)	12.6 (6.72-23.3)	12.5 (6.13-21.6)	13.1 (6.07-16.6)	9.7 (3.69-15.9)	9.5 (4.94-15.6)
Oseltamivir carboxylate	CL/F (L/hr)	1.89 (0.98-8.32)	2.61 (0.70-4.25)	4.08 (1.58-9.04)	4.91 (2.98-16.4)	6.01 (3.29-13.0)
	Weight normalized CL/F	0.47 (0.31-1.89)	0.54 (0.23-1.13)	0.63 (0.35-1.22)	0.66(0.36-1.70)	0.68 (0.41-1.53)

	(L/hr/kg)					

Figure 8. Clearance and body weight-normalized clearance of oseltamivir and oseltamivir carboxylate by age group (*Source: reviewer's analysis using the sponsor's final model***)**



Effect of Age on PK volume of distribution of oseltamivir carboxylate (V_M/F)

According to the sponsor, the impact of age on apparent volume of distribution may be explained by alteration in hepatic volume and effectiveness of intra-hepatic trapping as well as broader changes in total body water during the first year of life. The model suggests that the apparent volume of distribution increases with age in a linear way (within 1 year of age) even after the effect of body weight is accounted for. This observation is not common. A literature search on this topic identified one case where volume of distribution for paracetamol decreases with age after the effect of body weight is taken into consideration[1]. The bodyweight normalized volume of distribution (L/70kg) decreased exponentially and reached the adult level by 2 weeks of age. The authors

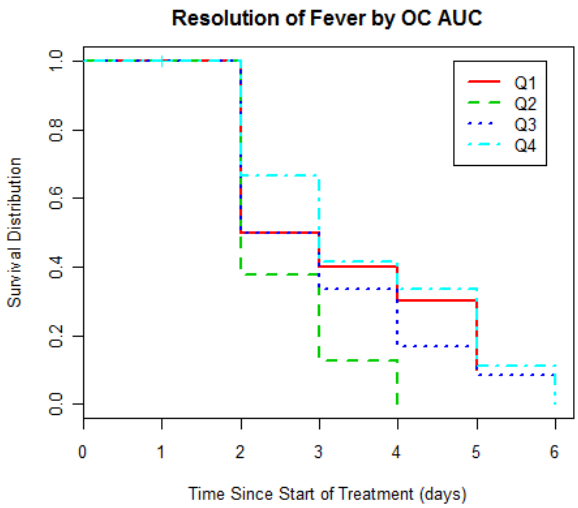
[1] Anderson B, Woollard GA, Holford NHG, A model for size and age changes in the pharmacokinetics of paracetamol in neonates, infants and children. *Br J Clin Pharmacol* 1999, 50: 125-134

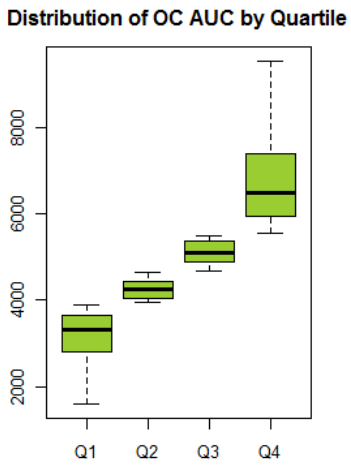
explained that "this dramatic change in distribution volume probably reflects neonatal body composition and the rapid changes in body water distribution in early life". These two apparently opposite cases both used changes in body water as one of the reasons to explain the observation. A possible alternative explanation for the observed relationship between oseltamivir carboxylate's apparent volume of distribution and age may be that the age effect is through F, the bioavailability of the oseltamivir. With increasing age and more mature hepatic function, F may decrease due to an increased first-pass effect on oseltamivir. As a result, the apparent volume of distribution, V_M/F, may increase even if V_M may not increase with age after the effect of body weight on V_M is accounted for.

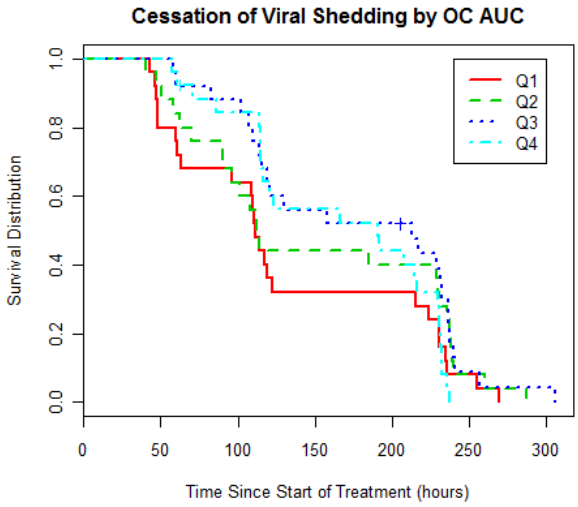
4.3.4 Evaluation of relationship between PK/PD

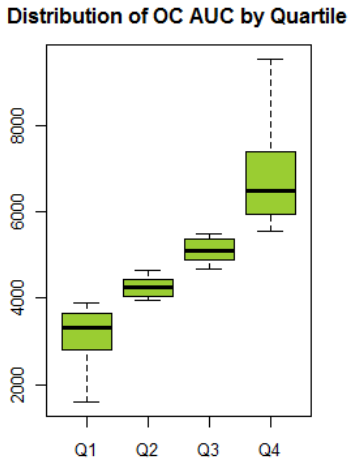
Analysis for correlation between PK exposures and PD endpoints was conducted using dataset that includes estimated PK exposures for individual patients including additional 11 subjects whose data were not submitted in the interim analysis dataset for WP22849 (n=105 of intent-to-treat infected patients (ITTI) of the original dataset + 11 from additional data). Similar to the sponsor's conclusion, the reviewer did not identify obvious relationships between exposure and any PD endpoint. The plots in Figure 9 and Figure 2 show the lack of PK-PD relationship for the primary PD and viral response endpoints: Time to resolution of fever and time to cessation of viral shedding. Since the range of doses administered to the patients was very narrow and those doses were chosen to target the effective exposure, no distinctive relationships between PK-PD within the studied exposure range was not surprising. However, the tendency of longer time to cessation of viral shedding for the patients with higher exposure was unexpected.

Figure 9. Kaplan-Meier plot of time to resolution of fever and time to cessation of viral shedding vs. AUC of oseltamivir carboxylate (*Source: reviewer's analysis***)**









Additional analysis was conducted to account for other risk factors such as time from onset of symptoms to first dose and age. As shown in Table 10, among patients who received the treatment within 2 days of onset of symptoms, patients with higher exposure of oseltamivir carboxylate needed longer time before the viral shedding stopped. As indicated in the approved labeling, the efficacy for the patients who begin therapy after 48 hours of symptoms was not established (*Tamiflu® labeling: Tamiflu® treatment of 2 mg/kg BID started within 48 hours of onset of symptoms, significantly reduced the total composite time to freedom of illness by 1.5 days compared to placebo*). Since there is no placebo group to compare, it is challenging to draw definitive conclusions on the impact of exposure and various risk factors on efficacy. However, heterogeneity in the responses is clearly seen from the subgroup analysis. As shown in Table 10, the median age of the highest exposure group (Q4 for AUC quartile) was relatively younger (35 days old and 78 days old for group of patients who spent 1 day or 2 days from onset of symptoms to first dose, respectively). The youngest infants who tend to show higher exposure also tend to need longer time to stop viral shedding. Due to their immature immune system,

neonates and younger infants may need longer time to stop viral shedding even with higher exposure compared to older infants. This observation supports that higher exposure following 3 mg/kg BID in younger infants (< 3 months of age) may be necessary owing to their slower response to antiviral agents as well as higher susceptibility to resistance. In addition, the results in Table 10 also suggest that older infants with longer time from onset of symptoms to first dose tend to need shorter time to stop viral shedding.

Table 10. Time to cessation of viral shedding by subgroups of Time from onset of symptoms to first dose and exposure quartile

		Time from onset of symptoms to first dose (Days)			
AUC quartile		1	2	3	4
Q1	number of patients	7	11	5	2
	number of events	7	11	5	2
	number of censored	0	0	0	0
	Median time to cessation of viral shedding (hrs)	111.4	117	114.1	78.5
	Median age (days)	168	195	152	268
	Median AUC (ng*hr/mL)	3402	3301	3259	3048
Q2	number of patients	5	9	4	7
	number of events	5	9	4	7
	number of censored	0	0	0	0
	Median time to cessation of viral shedding (hrs)	184.4	113.7	101.2	112.2
	Median age (days)	101	182	151	187
	Median AUC (ng*hr/mL)	4247	4233	4211	4242
Q3	number of patients	6	15	1	3
	number of events	6	14	1	3
	number of censored	0	1	0	0
	Median time to cessation of viral shedding (hrs)	237.8	212.6	118.7	102
	Median age (days)	138	188	118	206
	Median AUC (ng*hr/mL)	5075	4995	5383	5112
Q4	number of patients	5	11	7	3
	number of events	5	11	7	2
	number of censored	0	0	0	1
	Median time to cessation of viral shedding (hrs)	213.9	215.9	86.1	113.8
	Median age (days)	34	78	230	264
	Median AUC (ng*hr/mL)	5942	6625	6355	8113

4.3.5 Simulation

The reviewer's simulation was conducted for two dosing regimens: 3.0 mg/kg and 2.5 mg/kg to evaluate the adequacy of dosing regimens for younger infants (infants < 3 months of age in whom lowers clearance of oseltamivir carboxylate was observed).

The majority of simulated AUCs of oseltamivir carboxylate following 3.0 mg/kg BID were above the target exposure (Figure 10). As shown in Figure 10, the central tendency (visualized by orange lowess line in the plot) was higher than the 'average' target exposure. There is a general tendency of decreasing exposure as age and body weight increases, which is consistent with the notion that renal clearance increases as age and body weight increase in this age group due to the rapid maturation and increasing body size.

As shown in Figure 3, the simulated AUC of oseltamivir carboxylate following 3.0 mg/kg BID in infants 0-1 years of age are above the target AUC derived from AUC_{inf} in 1-2 years of age following 30 mg BID. Most of the age groups show AUC values between the observed AUC values in adults following 75 mg BID and those following 150 mg BID. However, due to the lower clearance, the lowest age group (0-1 months of age) show higher exposure compared to exposure in adults following 75 mg BID. Thus another simulation with 2.5 mg/kg BID was conducted by the reviewer. The simulated AUCs following 2.5 mg/kg BID show that lower dosing regimen can be sufficient enough to generate effective concentrations in infants younger than 6 months of age (Figure 11). The simulation results with a lower dosing regimen, 2.5 mg/kg BID showed slightly lower exposures (~17%) as expected. Although the simulated exposure in infants 0-3 months of age following 2.5 mg/kg BID was close to the target exposure, concerns over more frequent resistance and greater mortality associated with influenza in this youngest age group allow higher exposure of oseltamivir carboxylate than the target exposure.

Figure 10. Simulated AUC of oseltamivir carboxylate following 3.0 mg/kg BID (*the orange line represents the lowess line and the three horizontal lines represent the targets: mean, mean minus one standard deviation and minimum***; *Source: reviewer's simulation using the sponsor's final model***)**

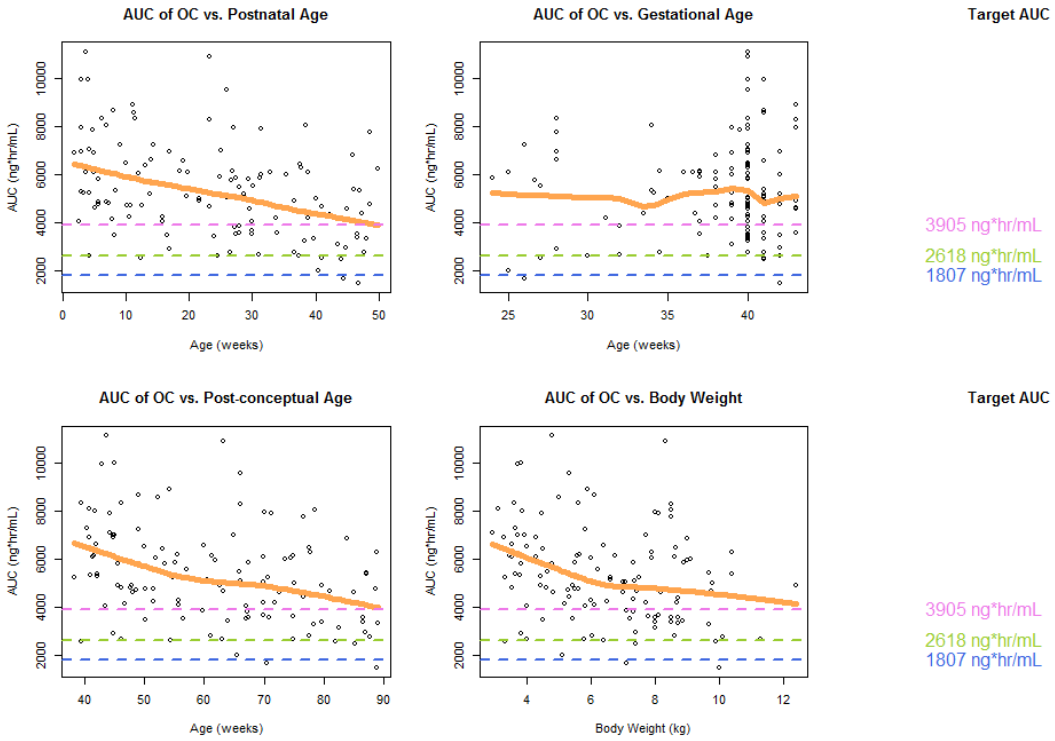
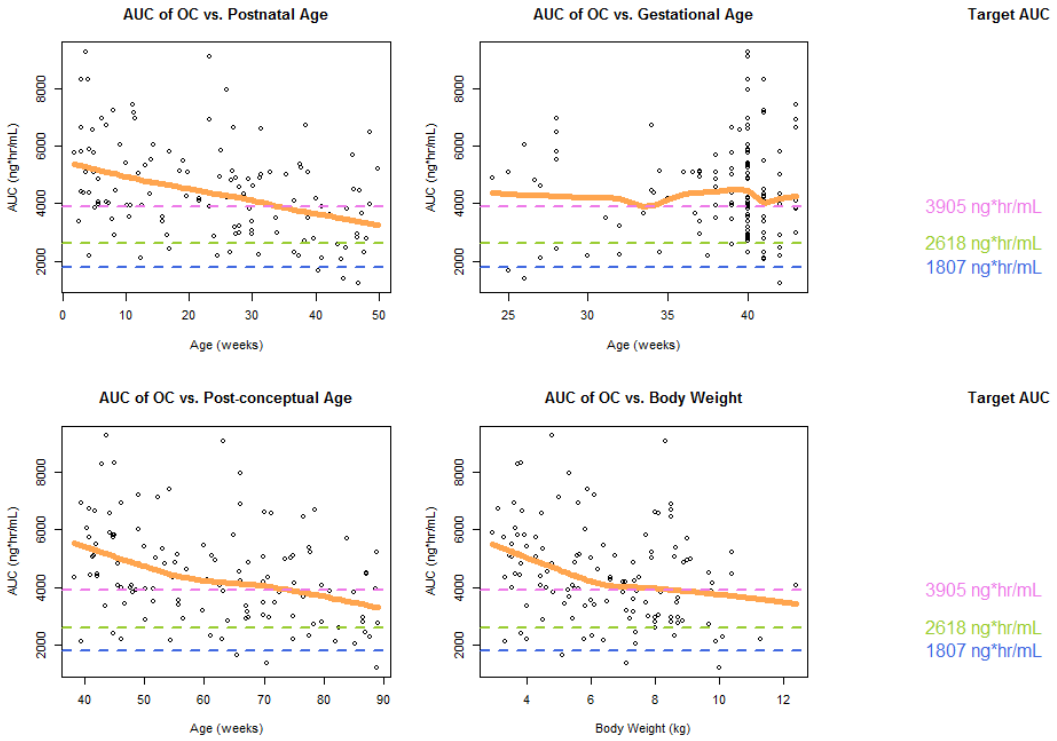
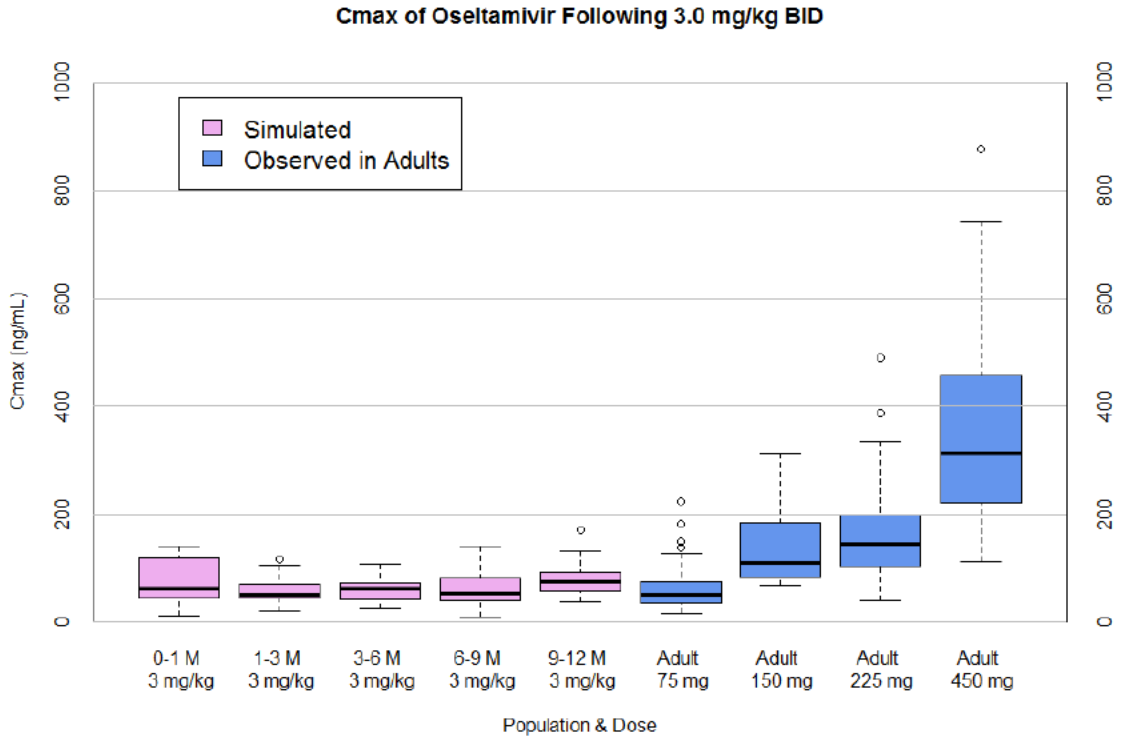


Figure 11. Simulated AUC of oseltamivir carboxylate following 2.5 mg/kg BID (*the orange line represents the lowess line and the three horizontal lines represent the targets: mean, mean minus one standard deviation and minimum***; *Source: reviewer's simulation using the sponsor's final model***)**



Moreover, the simulated Cmax of oseltamivir following 3.0 mg/kg BID in infants 0-1 years of age was similar to the Cmax in adults following 75 mg BID and less than that following 150 mg BID, which could be supportive evidence that alleviates safety concerns primarily associated with the prodrug.

Figure 12. Simulated AUCs of oseltamivir in infants 0-1 years of age following 3.0 mg/kg BID of Tamiflu in comparison with adults (*Source: reviewer's simulation using the sponsor's final model***)**



4.4 Listing of analyses codes and output files

File Name	Description	Location in \\cdsnas\pharmacometrics\
104-ctl.txt 104.ctl 105.ctl	Population PK analysis for oseltamivir and oseltamivir carboxylate	Reviews\Ongoing PM Reviews\ Tamiflu_NDA21246_JEL\PPK Analyses
NDA21246_PKPD.R NDA21246_PK.R	PKPD analysis	Reviews\Ongoing PM Reviews\Tamiflu_NDA21246_JEL\ER Analyses

5 Labeling

12.3.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

6 Appendix

Individual study reports except reports for Population Pharmacokinetics and Modeling and Simulation are summarized.

6.1 Individual Clinical Study Review

6.1.1 Study CASG114

A total of 87 infants younger than 24 months of age with confirmed influenza infection were enrolled in this prospective, age-stratified, open-label PK/PD study from 16 centers (all in US) Seventy-six (87%) of the 87 subjects completed the protocol-mandated follow-up. All subjects received at least two doses of study medication (except one subject who did not return for follow-up after administration of one dose). Three subjects received at least seven doses.

The summary of dosing regimens in each age cohort is provide in Table 1 except cohorts of infants 1 to 2 years of age who received 3.5 mg/kg BID or 30 mg BID. The formulation used in the study was supplied as a powder blend for constitution to a suspension. The oral dispenser device supplied by the sponsor for administration of oseltamivir suspension was marked to deliver 30 mg, 45 mg, and 60 mg of oseltamivir suspension. This oral dispenser device was developed to compensate for a foaming issue with oseltamivir suspension after mixing. During reconstitution some air bubbles are incorporated which made an overage adjustment on the oral dispenser necessary (marking on the dosing device). In effect the volume required to deliver a given dose of oseltamivir is greater than the actual volume calculated. The average overage was between (b) (4) as shown in Table 11.

Table 11. Oral disp

(b) (4)

Dose (oseltamivir)	
30 mg	
45 mg	
60 mg	

The PK exposure estimates obtained from a noncompartmental analysis for the data from CASG114 are provided in Table 12**.**

Table 12. Summary of PK exposures in CASG114

Cohort	Age (months)	Enrollment (for PK)	Mean PK Parameters + SE	
			Cmax (ng/mL)	AUC (ng.h/mL)
I	12 - 23 (30 mg)	9	OP – 132 ± 38 OC – 297 ± 42	OP – 427 ± 99 OC – 2809 ± 382
IIa	9 – 11 (3 mg/kg)	6	OP – 85 ± 14 OC – 384 ± 77	OP – 279 ± 32 OC – 3709 ± 679
IIb	9 – 11 (3.5 mg/kg)	3	OP – 194 ± 78 OC – 475 ± 73	OP – 734 ± 270 OC – 4073 ± 588
III	6 – 8 (3 mg/kg)	16	OP – 142 ± 30 OC – 440 ± 36	OP – 445 ± 59 OC – 4163 ± 331
IV	3 – 5 (3 mg/kg)	4	OP – 59 ± 12 OC – 410 ± 16	OP – 261 ± 50 OC – 4001 ± 217
V	<3 (3 mg/kg)	1	OP – 90 OC – 545	OP – 279 OC – 5204

The target exposure was derived from predicted mean estimates of exposure in subjects from studies (JV16284 and WV15758) in whom resistance was observed (but in whom no exposure data are available) using pooled data from 3 pediatric studies (WV15758, NP15826, PP16351). Predicted AUC_{0-12} following 2 mg/kg or 3 mg/kg was 2800 ng*hr/mL or 3800 ng*hr/mL, respectively. Thus the target exposure was determined to be 3800 ng*hr/mL, assuming 30% CV, the target standard deviation was 1140 ng*hr/mL. Therefore, the target lower limit of AUC_{0-12} was determined to be 2660 ng*hr/mL (3800 ng/mL – 1 SD) and the target upper limit of AUC_{0-12} was determined to be 7700 ng_hr/mL which was 2 standard deviations above the mean exposure following 150 mg BID in adults. This target exposure was within the range of exposure demonstrated as safe and efficacious in the adult phase III pivotal trials, in which regimens of 75 mg and 150 mg BID were investigated (AUC_{0-12} 2700 ng*hr/mL and 5500 ng*hr/mL, respectively).

Children from birth through 8 months of age achieved targeted oseltamivir carboxylate concentrations following 3.0 mg/kg BID. For infants 9 through 11 months of age, a higher dose of 3.5 mg/kg administered BID was needed to achieve the targeted exposure. In children 12 through 23 months of age, the approved dose of 30 mg BID achieved lower oseltamivir carboxylate exposures than targeted in the protocol. The results showed a strong correlation between age and oseltamivir carboxylate AUC12, with higher exposures in younger infants. Likewise, oseltamivir carboxylate clearance is higher in older infants and is lower in younger infants. Since oseltamivir carboxylate is mainly eliminated by the kidney, the decreased clearance in younger infants is not surprising.

Figure 13. Oseltamivir carboxylate exposure vs. Age cohorts (*Source: CASG114 CSR page 157***)**

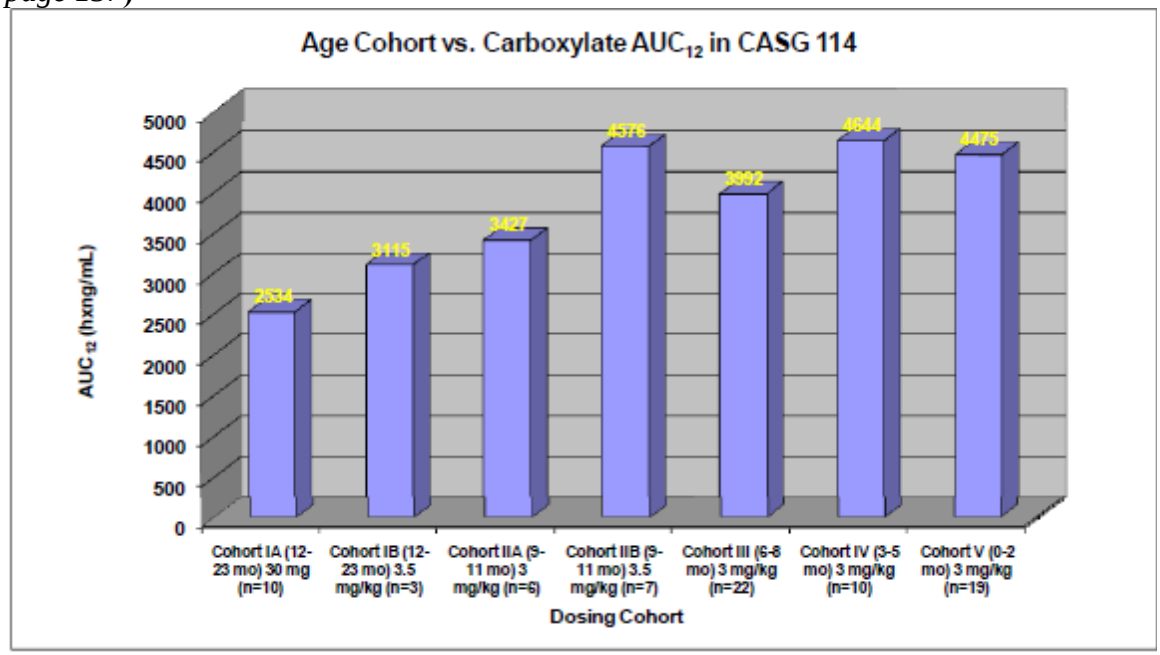
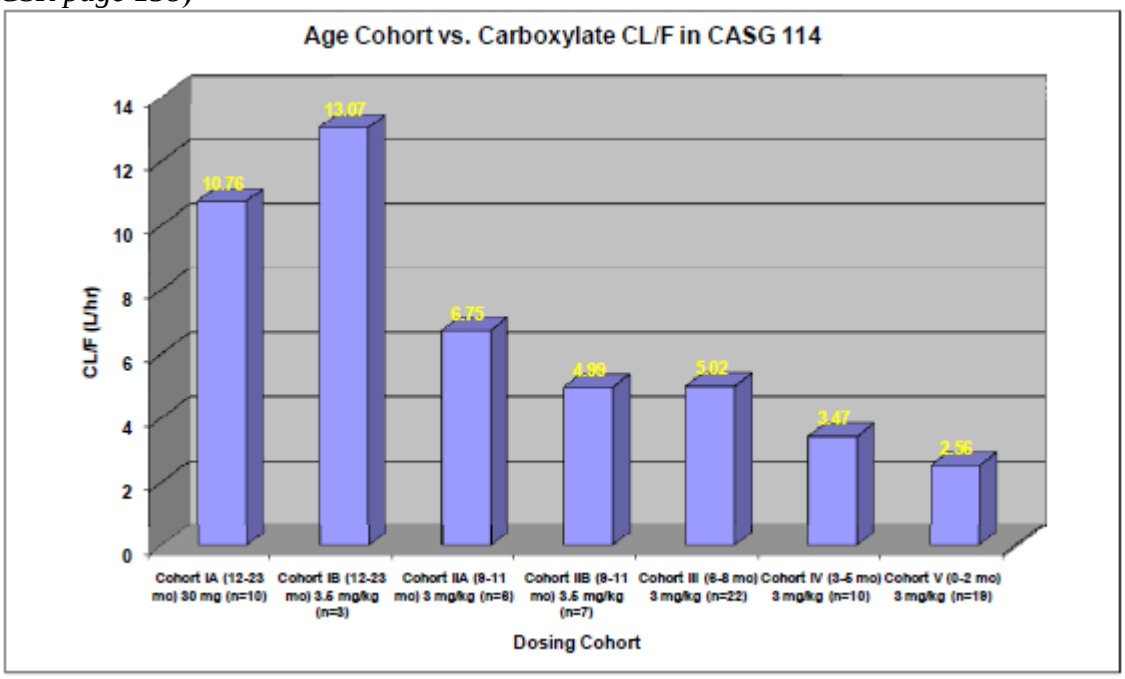
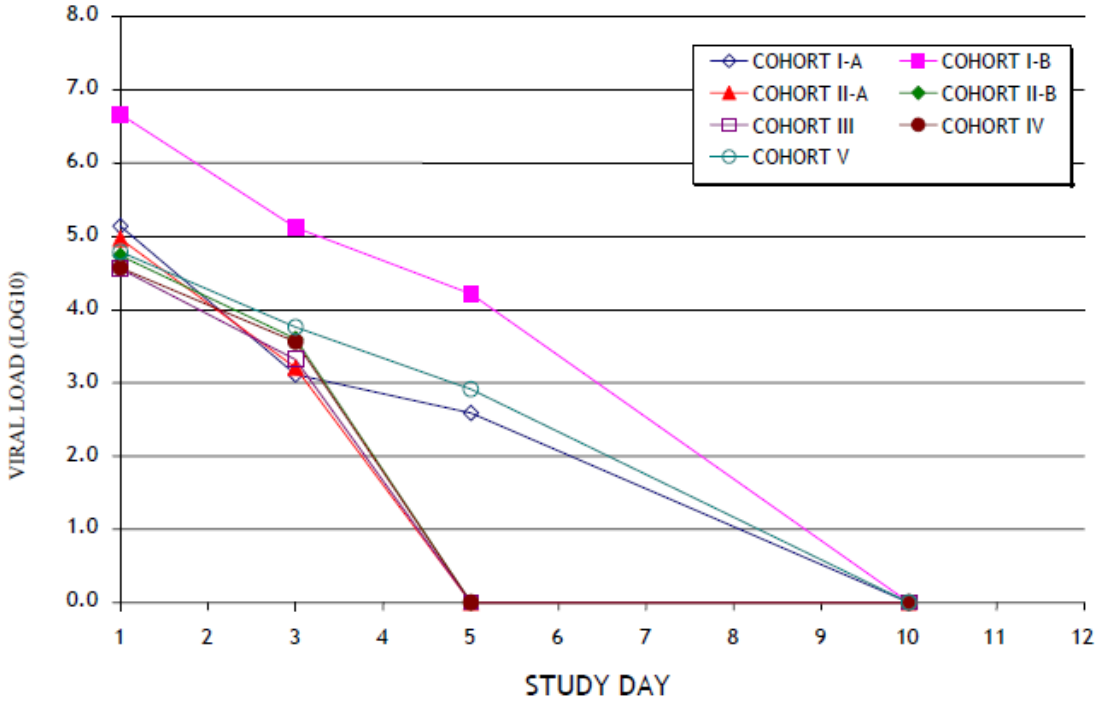


Figure 14. Clearance of oseltamivir carboxylate vs. Age cohorts (*Source: CASG114 CSR page 158***)**



As one of the PD endpoints, viral load change over study days is described in Figure 15.

Figure 15. Viral load (log_{10}) across study days (*Source: CASG114 CSR page 156*)



Spearman correlation coefficients of the PK parameters for oseltamivir carboxylate with age cohort, baseline log viral load, time to no flu symptoms, $TCID_{50}$ and days to no viral load were computed along with the p-values for the null hypothesis of no association. The summary of results is provided in Table 13.

Table 13. PK/PD correlation (Spearman) (*Source: CASG114 CSR page 118*)

Oseltamivir PK Parameters	Age Cohort	Baseline log VL	Time to No Flu Symptoms	$TCID_{50}$	Days to -VL for Subjects + at Baseline
C_{max} (ng/mL)	-0.23 (p=0.04)	-0.24 (p=0.04)	0.17 (p=0.14)	-0.24 (p=0.05)	-0.17 (p=0.19)
T_{max} (hr.)	0.14 (p=0.23)	-0.14 (p=0.21)	-0.07 (p=0.55)	-0.02 (p=0.87)	-0.07 (p=0.61)
AUC_{0-12} (hr*ng/mL)	-0.36 (p=0.002)	-0.21 (p=0.07)	0.17 (p=0.13)	-0.26 (p=0.04)	-0.18 (p=0.16)
$T_{1/2}$ (hr.)	0.07 (p=0.56)	-0.04 (p=0.72)	0.09 (p=0.43)	-0.21 (p=0.09)	-0.07 (p=0.63)
CL/F (L/hr/kg)	0.36 (p=0.002)	0.24 (p=0.04)	-0.15 (p=0.19)	0.34 (p=0.006)	0.23 (p=0.08)
V/F (L/kg)	0.31 (p=0.008)	0.11 (p=0.36)	0.07 (p=0.58)	0.04 (p=0.77)	0.07 (p=0.60)

Carboxylate PK Parameters	Age Cohort	Baseline log VL	Time to No Flu Symptoms	$TCID_{50}$	Days to -VL for Subjects + at Baseline
C_{max} (ng/mL)	0.39 (p=0.0004)	-0.17 (p=0.14)	-0.10 (p=0.41)	-0.17 (p=0.17)	-0.11 (p=0.40)
T_{max} (hr.)	0.22 (p=0.06)	-0.03 (p=0.78)	-0.11 (p=0.36)	-0.12 (p=0.32)	0.11 (p=0.40)
AUC_{0-12} (hr*ng/mL)	0.37 (p=0.0008)	-0.18 (p=0.12)	-0.10 (p=0.40)	-0.19 (p=0.13)	-0.11 (p=0.40)
$T_{1/2}$ (hr.)	0.23 (p=0.05)	-0.03 (p=0.81)	0.09 (p=0.47)	0.05 (p=0.67)	-0.16 (p=0.24)
CL/F (L/hr/kg)	-0.69 (p=<0.0001)	0.16 (p=0.16)	0.22 (p=0.06)	0.23 (p=0.07)	0.01 (p=0.94)
V/F (L/kg)	-0.37 (p=0.001)	0.08 (p=0.49)	0.17 (p=0.15)	0.20 (p=0.12)	-0.05 (p=0.69)

Oseltamivir: Carboxylate	Age Cohort	Baseline log VL	Time to No Flu Symptoms	$TCID_{50}$	Days to -VL for Subjects + at Baseline
AUC_{12} (µM*h)	0.63 (p=< 0.0001)	0.003 (p=0.98)	-0.22 (p=0.05)	0.05 (p=0.67)	0.06 (p=0.65)
C_{max} (µM)	0.54 (p=<0.0001)	0.0002 (p=1.0)	-0.25 (p=0.03)	0.001 (p=0.94)	0.05 (p=0.68)

From the analysis with a non-parametric Spearman correlation coefficient without assuming normality, there was no correlation between PK and PD endpoints, except the correlation of the PK parameters with age cohort.

The study targeted a narrow range of oseltamivir and oseltamivir carboxylate systemic exposure and all subjects received the same antiviral treatment so it is difficult to find correlation between PK and virology PD endpoint. Determination of amount of virus detected by PCR correlated highly with amount of virus detected by culture ($TCID_{50}$). The sponsor takes physiology associated with influenza into account for this lack of positive relationship between PK and PD. Influenza is cytokine-mediated disease, with viral replication tending to remain localized to the lungs but extent of illness being the result of the host response to the infection. Furthermore, the sponsor discuss that the sampling procedure have variability, as young children may not be cooperative with nasal swabs – especially after having the first one obtained and knowing what the procedure entails.

Reviewer's comments: Both PK data indicate that 30 mg fixed dose for children 1-2 years of age may not be sufficient to achieve effective concentration. However, the decrease in viral load for the infants who received 3.5 mg/kg (Cohort 1B, dose was

modified based on lower exposure observed from 9 subjects who received 30 mg) did not seem to be better than the cohort 1A who received 30 mg. Furthermore, the sample size is too small (n=9) to make a definitive conclusion.

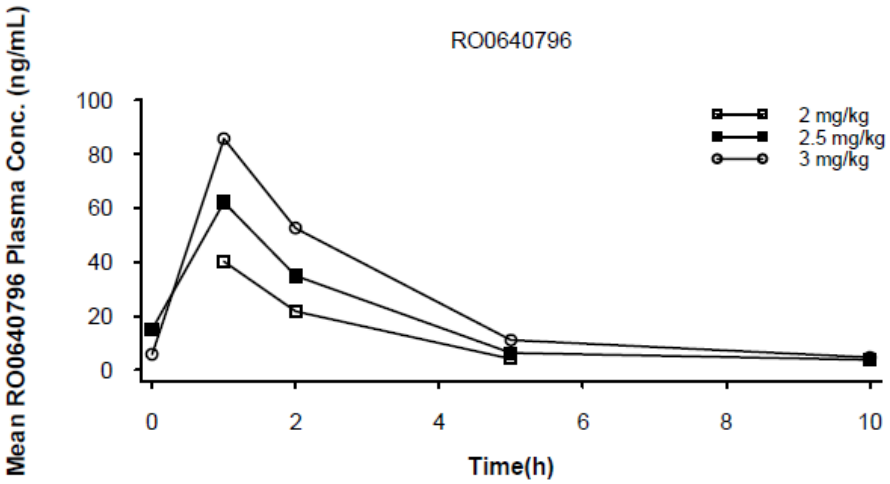
6.1.2 Study WP22849 (Interim CSR)

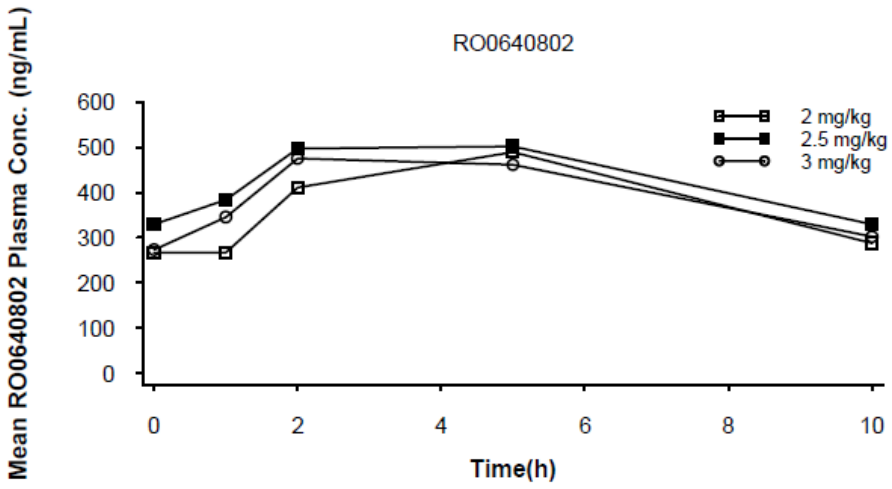
A total of 54 infants 0 to 12 months of age with confirmed influenza infection were enrolled in the first flu season (2010-2011) this open label, prospective, PK/PD study. Doses given to these infants are summarized in Table 1. Additional 11 subjects enrolled in the 2011-2012 flu season were not included in this interim study report and individual PK-PD data were submitted upon request. The updated CSR was not submitted as the sponsor indicated originally. Thus the summary only includes 54 patients and those additional data were included in the reviewer's analysis for PK-PD.

Influenza was confirmed in 48 patients by culture ($TCID_{50}$ test) or by viral load (PCR), and these patients comprised the intent-to-treat infected (ITTI) population.

The 5 PK blood samples were taken from 52 (96%) of the 54 enrolled patients. The mean concentration profiles of oseltamivir and oseltamivir carboxylate are shown in Figure 16.

Figure 16. Arithmetic mean plasma concentration vs. time profile of oseltamivir and oseltamivir carboxylate following multiple oral doses of 2-3 mg/kg oseltamivir (*Source: WP22849 CSR page 54***)**





The summary of PK parameters of oseltamivir and oseltamivir carboxylate are provided in Table 14 and Table 15.

Table 14. Geometric mean (CV %) PK parameters of oseltamivir following multiple oral doses of 2-3 mg/kg oseltamivir (*Source: WP22849 CSR page 55***)**

Dose (mg/kg)	N	C_{max} (ng/mL)	t_{max}[a] (h)	$t_{1/2}$ (h)	Css, min (ng/mL)	AUC_{0-12} (h*ng/mL)
2 (Cohort III, Age 0-30 days)	5	25.2 (211.6)	1.08 (1.00-3.00)	1.66[b] (41.5)	2.56 (90.0)	142[b] (48.8)
2.5 (Cohort II, Age 31-90 days)	13	62.3 (66.7)	1.00 (0.00-2.08)	2.05[c] (52.9)	2.19 (63.0)	181[c] (49.3)
3 (Cohort I, Age 91 to <365 days)	36	84.2 (45.2)	1.08 (0.90-3.08)	1.99[d] (39.9)	2.82 (64.5)	282[d] (34.5)

[a] Median values (Min-Max)
[b] N=4
[c] N=11
[d] N=33

Table 15. Geometric mean (CV %) PK parameters of oseltamivir carboxylate following multiple oral doses of 2-3 mg/kg oseltamivir (*Source: WP22849 CSR page 56***)**

Dose (mg/kg)	N	C_{max} (ng/mL)	t_{max}[a] (h)	$t_{1/2}$ (h)	Css, min (ng/mL)	AUC_{0-12} (h*ng/mL)
2 (Cohort III, Age 0-30 days)	5	501 (22.2)	5.83 (2.58-6.67)	NC[b] NC	169 (96.4)	NC[b] NC
2.5 (Cohort II, Age 31-90 days)	13	524 (38.1)	2.67 (0.00-6.67)	14.6[c] (110.6)	266 (49.9)	5290[c] (43.4)
3 (Cohort I, Age 91 to <365 days)	36	468 (38.3)	4.04 (2.08-7.00)	9.44[d] (55.2)	234 (44.9)	4970[d] (28.2)

a Median values (Min-Max)

b N=2

c N=7

d N=17

The association between PK parameters (AUC_{0-12}, Cmax, and Cmin) and the exploratory PD endpoints (time-to-event endpoints and maximum fold change in IC_{50}) was explored as a post-hoc analysis. From the analysis no definitive conclusions could be made. The summary of correlation between PK and PD parameters is summarized in Table 16.

Table 16. Pearson correlation between PK and PD parameters (ITTI) (*Source: WP22849 CSR page 65*)

PD Parameters	Cmax	Cmin	AUC0-12
Time to resolution of Fever*			
Pearson Correlation Coefficients	0.2232	0.1584	0.6374
P-value	0.2446	0.4119	0.0106
Number of Observations	29	29	15
Time to cessation of Viral Shedding			
Pearson Correlation Coefficients	0.0634	0.3139	0.3659
P-value	0.6722	0.0317	0.0940
Number of Observations	47	47	22
IC50 maximum fold change from baseline			
Pearson Correlation Coefficients	-0.2618	-0.3325	-0.2013
P-value	0.1478	0.0630	0.4719
Number of Observations	32	32	15

Oseltamivir treatment was generally well tolerated following BID dosing for 5 days or 10 days in infants younger than 1 year of age. The safety profile was similar among age cohorts with vomiting and diarrhea being the most frequently reported AEs. Six patients had serious AEs, none of which was treatment related. There were no deaths and no withdrawals due to AEs.

6.1.3 Population PK Model Report

Not summarized since the summary of main body of the report is included in Section 3.

6.1.4 Integrated PK/PD and PK-PD Analysis Report

A retrospective analysis with pooled data for infants younger than 1 year of age was performed. Studies WP22849 and CASG114 were included in the analysis. Due to the small sample size, any association between PD endpoints (i.e., time to resolution of fever, time to cessation of viral shedding, development of secondary illness, development of treatment-emergent resistance) and drug exposure was difficult to assess. Virology assessments by PCR and culture were performed in both studies with swab samples on Days 1, 3/4, 5/6, 10/11 for WP22849 and Days 1, 3, 5, 10 for CASG114. Both studies reported viral titer results in $\log_{10}$ ($TCID_{50}$) unit but assays used for each study was different. The PCR results were also reported in different units; in (b) (4) for WP22849 and in $\log_{10}$ (copies/mL) for CASG114.

The analysis was performed after the PK population analysis was done and the predicted oseltamivir carboxylate $AUC_{0\text{-}12}$, Cmax, and Cmin were available. No PK thresholds or cutoff values for each derived PK parameters were found from exploratory analyses, so quartiles of predicted PK parameters were used for the analysis. Gestational age category (≤37 and ≥37 weeks), duration of symptoms (≤48 and ≥48 hours), viral type (type A or non-A), and sex (F or M) were used as covariates. The dependent variables for the analysis were time to event in resolution of fever and cessation of viral shedding by culture results, slope of decline in temperature and viral titer, maximum fold change greater than or equal to 5 folds in post baseline IC_{50}, and emergence of genotypic resistance.

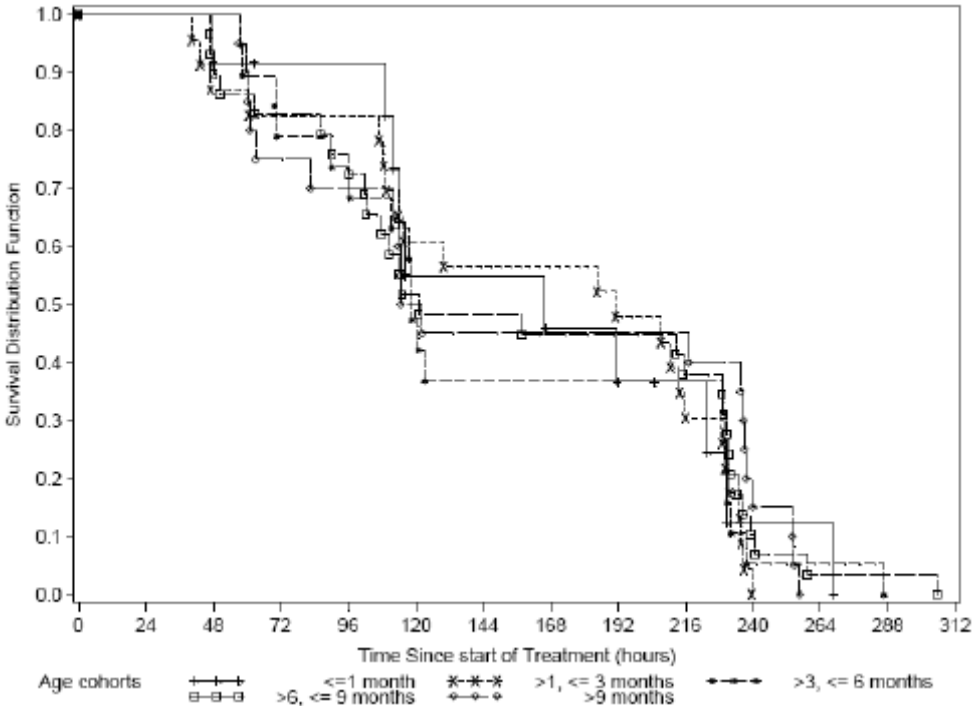
There were no treatment differences among all age cohorts on time to resolution of Fever. The univariate Chi-squared test indicated that the gestational age category (p=0.018) and viral type at baseline (p=0.076) might have an impact on the time to resolution of fever.

Table 17. Time to cessation of viral shedding by age cohort (culture) (*Source: Integrated PK-PD Analysis Report page 36*)

Time-to-Event (a) (days) Age Cohort (days)	I (≤ 30)	II (31-90)	III (91-180)	IV (181-270)	V (≥271)
Test of Equality over Age Cohorts (unstratified Kaplan-Meier Method)					
N	6	9	7	15	9
Number of Censored	1	1	0	2	1
Median (b)	3.00	3.00	2.00	2.50	3.00
(95% CI)	(2.00, 6.00)	(2.00, 5.00)	(2.00, 3.00)	(2.00, 5.00)	(2.00, 4.00)
Wilcoxon Test(c)					p_value = 0.5434
Test the Association of time to resolution of fever with Covariates (Univariate Chi-squared for Wilcoxon Test (d)					
Gestational Age Category (<=37 or >37 weeks)					P_value = 0.018
Duration of Symptoms (<=48 or > 48 hours)					0.552
Viral Type at Baseline (Type A or non-type A)					0.076
Sex (F or M)					0.332

There was no evidence of difference in rate of decline in body temperature among age cohorts (p=0.335). No age-related increase in the percentage of patients who developed secondary illness (i.e., otitis media) was identified. Although two youngest age cohorts (I and II) had longer median time to cessation of viral shedding than the older age cohorts, there were no treatment differences among all age cohorts (p=0.098). The univariate Chi-squared test indicated that only duration of influenza symptoms prior to initiation of oseltamivir treatment might have an impact on the time to cessation of viral shedding. (p=0.002).

Figure 17. Kaplan-Meier Plot for cessation of viral shedding by age cohort (ITTI) (*Source: Integrated PK-PD Analysis Report page 37***)**



Phenotypic analysis was measured by IC_{50} and percentage of patients with a ≥ 5-fold increase from baseline during treatment period is summarized in Table 18, after excluding 11 outliers identified at baseline.

Table 18. Percentage of patients with a ≥ 5-fold increase in IC_{50} from baseline (*Source: Integrated PK-PD Analysis Report page 35*)

Age Cohort	I	II	III	IV	V
	≤30 Days n=12	31–90 Days n=24	91–180 Days n=19	181–270 Days n=30	≥270 Days n=20
No. of patients. with IC50 at baseline [a]	12	24	19	29	19
<5	9 (75.0%)	13 (54.2%)	15 (78.9%)	21 (72.4%)	15 (78.9%)
≥5	2 (16.7%)	5 (20.8%)	1 (5.3%)	2 (6.9%)	0

The relationship between PK and PK parameters was explored by calculating Pearson correlation coefficients. Additionally, the univariate Chi-squared Wilcoxon test for testing the association between time to event data and PK parameters was performed, and the results are summarized in Table 19.

Table 19. Pearson Correlation Coefficient between PK and PD Parameters (*Source: Integrated PK-PD Analysis Report page 40*)

	Time to		Rate of decline		
PK	Cessation of Viral Shedding	Resolution of Fever	Body Temperature	Log_{10} (TCID50)	Maximum IC50 Fold Change
AUC_{12}	–0.033 (0.830)	0.069 (0.496)	0.297 (0.056)	0.107 (0.285)	–0.18 (0.107)
C_{min}	–0.024 (0.875)	0.06 (0.553)	0.329 (0.034)	0.060 (0.554)	–0.234 (0.036)
C_{max}	–0.041 (0.789)	0.064 (0.522)	0.262 (0.094)	0.132 (0.187)	–0.136 (0.225)

The sponsor found no associations between PK and time to event endpoints for resolution of fever, cessation of viral shedding. Although the correlation was weak, there was a positive correlation between PK exposure and rate of decline endpoints. The sponsor interpreted the positive correlation between rate of decline endpoints as following: Infants who had high PK exposure had their body temperature and viral titer log_{10} ($TCID_{50}$) decline faster. However, additional analysis of covariance with the model included log_{10} (PK Parameter), gestational age category, duration of symptoms prior to start of treatment, viral type and sex as covariates. Both adjusted and unadjusted p-values for covariate log_{10} (PK Parameters) did not show any evidence that the PK parameters could affect the rate of decline in body temperature or rate of decline in log_{10} ($TCID_{50}$). The negative correlations between maximum IC_{50} fold change and PK parameters were also as expected.

Reviewer's comments*:* Although the sponsor's univariate analysis did show any correlation between PK and PD endpoints, subgroup analyses show a positive relationship between PK exposure and time to cessation of viral shedding. Young infants who tended to show higher exposure also tended spend longer time to stop viral shedding. It seems to be associated with intrinsic characteristic of youngest infants including neonates, thus it still lacks PK-PD relationship. See Table 10.

6.1.5 Modeling and Simulation

Not summarized since the summary of main body of the report is included in Section 3.

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

/s/

JEE E LEE
11/27/2012

HUIMIN ZHENG
11/27/2012

SHIRLEY K SEO
11/27/2012

YANING WANG
11/27/2012

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	021246/S045 021087/S062 (cross-ref) Pediatric efficacy supplement	Brand Name	Tamiflu
OCP Division (I, II, III, IV, V)	DCP IV, DPM	Generic Name	oseltamivir phosphate
Medical Division	DAVP	Drug Class	antiviral-anti-influenza
OCP Reviewer	Jenny Zheng, Ph.D.	Indication(s)	Treatment of influenza in infants with a post-conceptional age of at least (b) (4) weeks to less than 1 year of age
OCP Pharmacometrics Reviewer	Jee Eun Lee, Ph.D.	Dosage Form	Powder for suspension 6 mg/mL upon reconstitution
OCP Team Leader	Shirley K. Seo, Ph.D., Yaning Wang, Ph.D.	Dosing Regimen	3 mg/mL BID
Date of Submission	6/21/2012	Route of Administration	oral
Estimated Due Date of OCP Review	11/15/2012	Sponsor	Hoffmann La Roche
PDUFA Due Date	12/22/2012	Priority Classification	P
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**	**2**		Stability report for CASG114 study is included but not the BA report. The BA reports for WP22849 was submitted
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				

fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vitro effects of primary drug:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**X**	**2***		PK/PD studies in pediatrics
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**2**		

Filability		
	"X" if yes	**Comments**
Application filable?	**X**	
Submission in Brief: See the details below.	**Reviewer's Comments (to the project manager):** 1. In anticipation of a need for site inspections, please provide the full bioanalytical report(s) for plasma samples analyzed in trial CASG114 along with complete site information. 2. Please provide the number of subjects under 1 year of age at each clinical site for trial CASG114 along with complete site information. 3. Provide all data included in your population PK database used for Simulation (Report titled "Population PK Analysis of Oseltamivir in Infants Less Than One-Year Old", dated March 13, 2012) • *Adult patients administered 75 mg BID doses: 93 subjects from Study WP16263* • *Adult patients administered 150 mg BID doses: 20 subjects from Study WV15670* • *Adult patients administered 225 mg BID doses: 94 subjects from Study WP16263* • *Adult patients administered 450 mg BID doses: 99 subjects from Study WP16263* • *1-2 year old patients administered 30 mg single doses: 12 subjects from Study PP16351* • *3-5 year old patients administered 45 mg single doses : 12 subjects from Study PP16351* 4. Provide all other available PK/PD data including children 1-2 years of age. These should include data from Studies JV16284 and WV15758 where significant number of patients developed resistance following 2 mg/kg dose. **Please send the comments to the sponsor.**	

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

	Content Parameter	Yes	No	NA	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in			X	CSAG114 used previously marketed

	the pivotal clinical trials?				formulation and WP22849 used currently marketed formulation. Interchangeability has been addressed
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a matter to allow substantive review to begin	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			Raw datasets provided as SAS transport files and analysis datasets were provided as ASCII files.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			**CSAG114:** pre-determined starting doses • 12-23 months: 30 mg BID • 0-11 month: 3 mg/kg BID Doses were adjusted to achieve target AUC **WP22849:** • 3-12 months 3 mg/kg BID for 5 days • 1-3 months 2.5 mg/kg BID for 5 days

					• 0-1 month 2 mg/kg BID for 5 days
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	X			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	X			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		x		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES_____

If the NDA/BLA is not fileable from the clinical pharmacology 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.

Jee Eun Lee, Ph.D. / Jenny H Zheng , Ph.D. 8/1/2012

Reviewing Clinical Pharmacologists Date

Yaning Wang, Ph.D. / Shirley Seo, Ph.D. 8/1/2012

Team Leaders Date

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

/s/

JEE E LEE
08/03/2012

HUIMIN ZHENG
08/03/2012

YANING WANG
08/03/2012

SHIRLEY K SEO
08/03/2012